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Discussion

The role of Korean Medicine in the post-COVID-19 era: an online panel discussion part 2 – basic research and education



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ABSTRACT

Background: Experiencing difficulties and challenges though COVID-19 pandemic, there are voices that it needs to be discussed to seek direction of basic research and college education of Korean Medicine (KM) so that KM community can play a significant role in the future infectious disease outbreaks.

Methods: This paper summarizes the edited highlights of an online video meeting by Google meet on May 19, 2020, organized by the Korean Medicine Convergence Research Information Center. Five researchers specialized in immunology, microbiology, virology, preventive medicine, and herbology, respectively, presented what KM community should prepare for the future acute infectious disease outbreaks by learning from the previous research on antiviral effect of herbs for coronavirus and the experiences of the present COVID-19 pandemic.

Results: There are a lot of herbs or natural products with potential anti-coronavirus effects reported from in vitro experiments and despite criticism, many clinical trials on traditional herbal medicine for COVID-19 are being conducted. In addition to establishing research evidence, KM community should train and produce public health professionals among Korean Medicine Doctors (KMDs) and official participation in public healthcare system should be ensured in terms of regulation and policy. Newly developed KM treatments can be interpreted by the KM theories and also should be allowed by regulations for KMDs to utilize them.

Conclusion: The present online discussion suggested directions of basic research for acute viral infections diseases utilizing KM and how to enforce relevant education and regulations in the post-COVID-19 era.

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1. Introduction

In contrast to Korea's proactive responses to the Coronavirus Disease 2019 (COVID-19) pandemic, Korean Medicine (KM) community was not able to take part in any stage of responses to COVID-19 including testing or screening, epidemiological investigation, quarantine, treatment or prevention due to various reasons including political and regulatory barriers. Because Korean

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Medicine Doctors (KMDs) had no way to participate or volunteer in any activities by the Central Disease Control Headquarters, the Association of Korean Medicine, by self-help, opened a KM teleconsultation center for COVID-19 which was operated by KMD volunteers. As of April 22, 2020, approximately 20% of confirmed cases of COVID-19 in Korea who were self-isolated because they could not be admitted to a hospital or quarantine facility received KM treatment via phone calls to KM teleconsultation center.

As experts predict epidemics of infectious diseases will be occurring more often, Korean Medicine Convergence Research Information Center (KMCRIC), a KM research information center funded by the Korean government held a series of discussions for KM community to come up with future measures against infectious disease outbreaks. Discussions were held online with

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Table 1Information of Speakers in the Present Discussion

Speakers (in order of appearance)	Affiliation	Clinical expertise and/or role in the discussion
Prof. Hyangsook Lee	KMCRIC	Organizer of the event
	Kyung Hee University	
Prof. Dae-Hyun Hahm	College of Medicine	Host
	Kyung Hee University	
Prof. Myungsoo Joo	School of Korean Medicine	Immunology/virology
	Pusan National University	
Prof. Kyongmin Kim	School of Medicine	Virology
	Ajou University	
Dr. Sunoh Kwon	Korea Institute of Oriental Medicine	Research on herbal medicine for infectious diseases
Prof. Sunju Park	College of Korean Medicine	Preventive medicine
	Daejeon University	
Prof. Hoyoung Choi	College of Korean Medicine	Herbology
	Kyung Hee University	

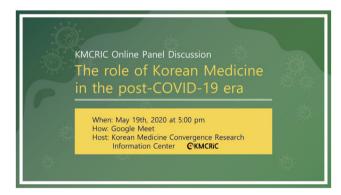




Fig. 1. Flyer of KMCRIC online panel discussion.

KMCRIC, Korean Medicine Convergence Research Information Center.

Google meet and this article provides summarized and edited presentations of the KMCRIC 2nd online panel discussion on directions of basic research for viral infectious diseases using herbal medicine and how to improve KM college education programs for future infectious disease outbreaks by the 5 experts in immunology, microbiology, virology, preventive medicine, and herbology (Table 1).

2. Online panel discussion

Lee: In an ongoing pandemic of COVID-19 across the globe, the KMCRIC organized two online panel discussions to address what and how to prepare in the post-COVID-19 era in the KM community. Following a previous online panel discussion on clinical research in KM in post-COVID-19 era, this is our 2nd online event wherein we are going to talk about the challenges and directions for basic research and education in KM in the COVID-19 pandemic and beyond (Fig. 1). Below is an edited summary of presentations by experts in immunology, virology, preventive medicine, and herbology to suggest what basic research on infectious diseases is needed and what further contents should be incorporated in the university education of KM.

2.1. Introducing current status of basic research on COVID-19 and presenting issues for discussion

Joo: In 2015, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection was a great challenge for us. The last time the MERS epidemic occurred, the medical community seemed to function in great chaos, but fortunately, this time they seem to be coping well. The KM community is also contributing significantly to the struggle of overcoming COVID-19. Before starting the main discussion, I would like to discuss the current situation briefly and facilitate a discussion about the role of KM in basic research and

education in overcoming a potential future outbreak of COVID-19 or similar viral diseases. The severe acute respiratory syndrome coronavirus (SARS-CoV) first emerged in 2002. Before that, it was simply thought of as a benign virus, causing a common cold. In 2002, it was identified as a virus causing SARS. It peaked mostly around April-May, and 8000 people around the world were infected. The case fatality rate (CFR) was 11%, and there were three confirmed cases in Korea but no deaths.⁴ In 2015, MERS-CoV, a different species of coronavirus, emerged. It peaked mostly around May-July, and the disease broke out only in Korea, where 186 people were infected, with about 20% CFR.⁵ Five years later, last December, SARS-CoV-2 emerged for the first time. Unlike the previous two beta viruses, this coronavirus has spread worldwide. It caused a pandemic, and as of the 30th of April, the CFR prediction interval is 0.82–9.64% – the lowest end of the current prediction is 0.82% and in line with several other estimates. 6 As I said earlier, coronaviruses were not highly dangerous in the past. This pattern changed in the late 2000s when a coronavirus infection started causing SARS. There are no specific treatments or vaccines. China reported that the combination of traditional Chinese medicine (TCM) and Western medicine (WM) and CheongPyeBaeDok decoction (QingFeiPaiDutang in Chinese, Seihaihaidokuto in Japanese) was effective in treating SARS in 2002 and influenza later. They reported that it was also effective for COVID-19. In Korea, unfortunately, there are no reports of effective coronavirus or influenza infection treatment applying KM. As of March 2020, there are ongoing clinical trials on about 20 drugs, mainly in the U.S. and China, and it is impressive that a considerable number of TCM herbal medications are included in the list.

Today discussion topics are as follows:

- The need for basic research on infectious diseases in KM and its direction;
- The need for improving the university education of KM.

The KM community could not participate in prevention measures related to the recent outbreak of COVID-19. KMDs were not allowed to participate, but they still contributed a lot to help patients overcome the COVID-19 via teleconsultation center. Looking at the current situation, I pose questions like: "Why are Korean people largely not interested in that KMDs are not officially allowed by the government to participate in treating COVID-19 patients?", "Why do people talk about vaccines and antiviral treatments, but not about KM treatments?" I think it is, probably, because of the common notion that KM and infectious diseases are not entirely related.

Therefore, why not address infectious diseases in terms of KM in the first place? More specifically, although there is a treatment for infectious diseases in KM, I think it would be great if we design and perform a study, providing guidelines on a specific treatment, effective against influenza virus, and likewise against coronavirus infection. I think it would be essential if there were studies presenting a specific KM treatment that is effective for viral diseases critical to public health. Then, people's perspective and view on KM, as well as the notion that KM is irrelevant to viral infections, might change.

Second, I think we need to take this opportunity to change education programs on infectious diseases in the colleges of KM. For one, the proportion of infectious diseases in KM university programs is not high. I hope today's discussion includes directions for some basic research that can provide the basis for KM treatment for infectious diseases. And, I also see the need for KM education to transform the conventional notion about the importance of KM in viral infection. It would be nice to exchange thoughts with you on these two topics. Thank you.

2.2. In vitro inhibition of coronavirus replications by herbal medicine

Hahm: Thank you for your presentation on the current status of viral infectious diseases and the need for further research and education as topics for discussion. I suggest changing the order slightly. Now Prof. Kyongmin Kim will be presenting the previous and ongoing basic research on herbal medicine for coronavirus first.

Kim: In the past, coronaviruses causing common cold symptoms were not considered important. It became highly critical with the 2003 SARS, 2012 MERS, 2015 Korean MERS, and 2019 SARS-CoV-2 pandemic. SARS-CoV-2 of the current outbreak, was named so because it was most similar to SARS-CoV. The name of the disease is COVID-19, and the name of the virus is SARS-CoV-2.⁸ This is the virus with the highest homology and SARS and MERS both originated from bats.

Here is our data from an *in vitro* experiment. We created a cell culture, infected it with the virus, and found that Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, and Phellodendron cortex inhibit replications of mouse hepatitis virus (MHV) and coronavirus.⁹

We evaluated the virus titer wherein the baseline is 100, and a decrease below 10 is considered effective as an antiviral treatment. As you can see, Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, and Phellodendron cortex showed values much lower than 10, demonstrating a marked inhibition of viral replication to the point where there was almost no RNA expression. Sophora subprostrata radix also had an antiviral effect (\leq 10, meaning that it was effective) and we assume that they inhibit RNA basically by inhibiting RNA polymerase, protease, or replication.

Our 2nd paper was published in 2010. There, we reported on our *in vitro* experiments wherein Sophorae radix, Acanthopanacis cortex, Sanguisorbae radix, and Torilis fructus inhibited replication of the coronavirus. Ribavirin is a commonly used drug against RNA viruses. We observed that Sophorae radix, Acanthopanacis

cortex, Sanguisorbae radix, and Torilis fructus markedly inhibited replication of the coronavirus as much as ribavirin. In the end, we completed the paper hypothesizing that while Sophorae radix, Acanthopanacis cortex, and Torilis fructus inhibit RNA dependent RNA polymerase replication, Sanguisorbae radix inhibits viral replication by inhibiting not RNA synthesis but later steps of the viral replication.¹⁰

2.3. Development of antiviral agents from natural products

Hahm: Next, I understand that Dr. Sunoh Kwon of the Korea Institute of Oriental Medicine (KIOM) is also conducting basic research on herbal medicine for viral infectious diseases even now. Please give us a brief introduction to your research.

Kwon: Our team use the human coronavirus OC43 (HCoV-OC43) strain from the same beta coronavirus genera to investigate the antiviral effects of natural products. These substances are alkaloids from the root of *Stephania tetrandra* S. Moore (Menispermaceae) and other related species. *S. tetrandra* is known for analgesic and anti-inflammatory effects in patients with arthritis and edema. ¹¹ We could confirm the antiviral effect by concentration, using the cell-survival rates and the levels of viral M-protein RNA have decreased post-treatment of *S. tetrandra*. The release of inflammatory cytokines has also decreased post-treatment. ¹²

Researchers at the University of Wisconsin demonstrated in a translocation assay using a MERS pseudovirus, ¹³ dose-dependent inhibition of viral gene expression by tetrandrine and fangchinoline, which are the same compounds that our team used. These compounds are known as calcium channel blockers, and for the viral gene to be expressed, calcium channels must be working properly to allow Ca²⁺ signaling. According to this study, treatment with these compounds reduced the signaling and, thus, inhibited viral gene expression.

A trial of tetrandrine tablets which were used in our research, for COVID-19 treatment, is registered at ClinicalTrials.gov (https://www.clinicaltrials.gov/) and it focuses on reduction of inflammations, including pneumonia, due to the anti-inflammatory effect of tetrandrine, rather than the antiviral effect itself.¹⁴

In contrast to the findings above, recently, articles criticizing that TCM products whose efficacy and safety have not been sufficiently verified, are being applied in clinical practice and even exported to Europe, were published in *Nature* (https://www. nature.com/articles/d41586-020-01284-x) and Science (https:// www.sciencemag.org/news/2020/05/unproven-herbal-remedyagainst-covid-19-could-fuel-drug-resistant-malaria-scientists) on the same day, May 6th, 2020, 15,16 followed by the newspaper article in the JoongAng Ilbo on May 7th, 2020, discussing whether traditional medicine has therapeutic effects in COVID-19 treatment and whether there is scientific evidence for it (https://news.joins. com/article/23771276).¹⁷ In the Science Translational Medicine blog by an expert in drug discovery (https://stm.sciencemag.org), the author criticized it is unfortunate that there are so many clinical trials of TCM therapy registered at ClinicalTrials.gov (https://www. clinicaltrials.gov/).¹⁸

Under these circumstances, let me tell you my opinion on the future direction of the development of a preventive treatment based on KM for novel and mutant virus infections. With regards to KM for prevention and treatment of not only COVID-19 but also new mutant viral infections that may emerge in the future, KM may have potential in increasing herd immunity and vaccine adjuvants for prevention of adverse effects, on the prevention side. On the treatment side, it has the potential for preventing complications, providing immunomodulators that improve resilience and therapeutics for the management of complications. Unlike China, Korea is rarely using KM for infectious disease management. In the future, we should enhance the research infrastructure and our capacity

To-be As-is [Prevention] Need for drugs for prevention of infectious [Prevention] Lack of approved vaccines for COVID-19 diseases that enhance vaccine efficacy Prevention Vaccine adjuvants for increasing the chances of achieving Only way to achieve herd immunity Intense competition among global pharmaceutical companies and for development of vaccines Increasing ability to prevent infections diseases in vulnerable treatment Need to secure neutralizing antibody with confirmed efficacy population Minimizing adverse events associated with vaccines for novel and [Treatment] Remdesivir - US FDA emergency use authorization [Treatment] Need for broad-spectrum treatment of viral mutant Limited to severe cases and cannot be used to inhibit transmission in early stages Safe drug that alleviates symptoms, prevents complications viral Antiviral effect verified but limited clinical efficacy and increases the recovery rate Drugs for boosting innate immunity and suppressing infection Discontinuation due to adverse events Direction: drug repurposing - emergency clinical trial hyperimmune response Drugs for management of complications and adverse events [China] Active utilization of TCM in responding to infectious (Strengthening the national capacity in response to Inclusion of TCM treatment plan in the clinical practice infectious diseases using KM] guidelines for infectious diseas Establishing evidence by expanding research infrastructure Reporting results of basic/clinical research of TCM on Response and capacity infectious diseases KM adjuvants for enhancing vaccine efficacy to Secured leading position in infectious disease research after Personalized, broad-spectrum KM treatment for infectious infectious diseases Establishing and utilizing KM clinical practice guidelines for disease [Koreal Exclusion of KM in response to infectious diseases infectious diseases usina KM National information service for KM health preservation No KM utilization plan in the government guarantine (yangsheng) for infectious disease prevention 20% of confirmed cases received KM treatment via COVID-19 Proposing KM utilization plan to be included in the national teleconsultation center infectious disease control system Insufficient evidence due to lack of research infrastructure

Fig. 2. Suggestions for future basic research on infectious diseases utilizing KM by Dr. Sunoh Kwon. FDA, Food and Drug Administration; KM, Korean Medicine; TCM, Traditional Chinese Medicine.

to obtain scientific evidence and quickly reflect it in the clinical practice guideline, to provide information via public promotion, while continuing to request to include KM in the national policy on infectious diseases (Fig. 2).

Hahm: Thank you. As far as I know, Dr. Kwon is a responsible researcher for infectious disease research in Korea Institute of Oriental Medicine, and there are new findings that have not been published yet. That's why *JoongAng Ilbo* interviewed him. He explained various issues and suggested future directions as well.

2.4. Contribution of KM to public healthcare system in the post-COVID-19 era

Hahm: Next, Prof. Park will discuss how KM can contribute to the public health system in the future via changes in university education and in legal and regulatory barriers.

Park: Although the KM community has made significant progress by putting a lot of efforts in the current COVID-19 pandemic, compared to the past, I hope that we make more regular and systematic contributions to the public healthcare system in the future. David Quammen, the author of "Spillover: Animal Infections and the Next Human Pandemic," mentions 4 things that are essential to managing infectious diseases in the future: science, technology, public health, and politics. ¹⁹ I would also like to talk about the public health aspect.

I have been thinking that not just the efforts of the KM community alone, but also the government and academia must collaborate, in a joint effort, towards establishing the basis and strengthening our capabilities. In the end, the goal is to develop the role of KM in managing infectious diseases and secure our expertise so that the KM community can play an active role in the infectious disease management.

I have divided this presentation into three parts, i.e., establishing research evidence, education, and regulations (Fig. 3). As research directions were already addressed, I would just add to that; there were cases in which the KM community has contributed to emergency situations, as in a recent teleconsultation center.⁷ Thinking

back, we need to establish in advance a data collection/utilization system that works even in emergencies. If there is a system that is designed with an expert researcher participating from early on and evaluated post hoc for improvement, I think those data would be useful in the future. I will skip the part about claims and claims data utilization since it was explained well in the 1st KMCRIC online panel discussion.² Others also addressed the role of infectious disease research and accumulating relevant knowledge. As the president Moon mentioned in his 3rd inaugural anniversary speech establishing a national research center for infectious disease, I hope that the KM community can take part in it as well. And lastly, we should continue to explore ways for the KM community to participate in public healthcare and think about our role in it.

Next, in terms of education, students of colleges of KM are educated and trained in epidemiology and medical statistics, but they are not well-aware of their importance, and thus, engagement is rather limited. I think we should focus on education to emphasize the importance of these subjects and reinforce the utilization plan. Of course, they are already included in the curriculum and taught in colleges, but I think education, related to the public sector, must also be reinforced. Students should fully grasp the characteristics and role of public healthcare in their undergraduate studies, and their sense of commitment to society should be nurtured as well.

Next, I think it is also essential to train KMD public health professionals and strengthen the competence and professionalize the KM community. In terms of upbringing KMD public health professionals, I hope that the number of professionals in preventive KM increases. Also, they should be allowed to work as epidemiological investigators by law, which I will mention again in part about regulations. I also think that education on infectious diseases should be added and reinforced for KMDs serving the army in the public health centers.

After all these things are achieved, they should be supplemented in terms of regulation and policy. The Infectious Disease Prevention Act and related laws should be enhanced, and, as the activities of epidemiological investigation teams increase, the application

Establishing research evidence

- Establishing a data collection and utilization system in disaster situations
- Utilization of claims data
- Research on infectious diseases to accumulate relevant knowledge
- Exploring ways for the KM community to participate in public healthcare system

Education (Empowerment and securing expertise)

 Development of KM university education programs for upbringing public healthcare professionals

Regulations (promoting participation of KMDs)

- Supplementing relevant laws and regulations
- Promoting KMD participation in public healthcare
- Including KMDs in public health professionals in the infectious diseases response taskforce
- Engaging KMDs in specialized educational institutions and curriculum-development of public health professionals training

Fig. 3. Directions for future research evidence, education, and regulations in KM by prof. Sunju Park.

KM, Korean Medicine; KMD, Korean Medicine Doctor.

requirements should be modified so that KMDs can apply as well. Next, we should continue to establish measures to expand the participation of KMDs in public healthcare, such as increasing recruitment in national and public hospitals, health centers and the task force on infectious diseases. Finally, I think the plan should be expanded to include KMDs in specialized educational institutions and create a curriculum for training public health professionals to strengthen their competences and achieve professionalization.

2.5. KM education and development of herbal treatment for infectious diseases in the post-COVID-19 era

Choi: According to a recently published paper by Luo et al.,²⁰ there are about 19 medicinal herbs, which are commonly used to prevent COVID-19. We know most of them, and some of them are widely used in Korea. Why aren't there any new ones other than these? If you look at the formula in the guideline/recommendation for COVID-19,²¹ most of the prescriptions are familiar, and even the ones we have not heard of, like CheongGeumGangHwa decoction (QingJinJiangHuo-tang in Chinese, Seikinkokato in Japanese) and CheongPyeBaeDok decoction (QingFeiPaiDu-tang in Chinese, Seihaihaidokuto in Japanese), can be thought of as a combination of commonly used herbs that we know. There are about 602 different herbs, according to the Korean Pharmacopoeia and the Korean Herbal Pharmacopoeia^{22,23} and 8980 according to the Chinese Materia Medica.²⁴ Among them, 186 kinds, including Equiseti herba and Phytolaccae radix, have already been reported to have antiviral effects. If you look at the definitions of herbal medicine and medicinal herbs, they are mostly of animal, plant, and the mineral origin and then dried, cut and purified in its original form. In practice, there are indeed many mineral-based medicines besides plants and animals such as single element minerals of Gold foil and sulfur. So, the most important thing in the definition of herbal medicine and medicinal herb is that it is defined by the principles of KM. Aside from the ones used in the past, newly discovered or developed ones, whether it be a medicinal herb, an extract, or a single component, if it can be analyzed based on the principles of KM, then it can certainly be used in clinical practice. In other words, are Western herbs, plant-based remedies commonly used in the lay community, medicinal herbs because they are all plants? Not really. It can only be defined as medicinal herb after it has been analyzed in terms of KM on the type, specifications, and dryness or dampness pattern it can be used for. Therefore, the 4

properties and 5 flavors of herbs are present in not only natural products, but all medicines, even the ones chemically synthesized. For example, many herbs such as Olibanum, Myrrha, Styrax, Benzonium, Croci Stigma, Sennae Folium, Panacis Quinquefolii Radix, Rhinoceri Cornu, and Draconis Sanguis are not from China. Some were imported even from Africa to China and are used as medicinal herbs today. New herbs have been established as herbal medicines over time, and similarly, in Korea, various herbs, surely including Western herbs, may be used as herbal medicines.

Now on KM education, various courses on infectious diseases should be reinforced. Most importantly, students must realize that the knowledge and training experience acquired through such courses should be part of their work as KMDs in the future so that they are motivated to study hard in colleges. They will study even harder at school and work harder after graduation if these topics are reflected in the national examination. If not, then I think students will not be as persistent or interested, even if the courses are provided.

Research on herbal medicine treatment is accomplished by the various efforts of researchers, trained and working in the field of KM, so the findings must be applied in human health for sure, as well as KM clinical practice. Currently, however, various research findings cannot be used in KM clinical practice due to legal or regulatory barriers. For example, Shinbaro tablet (GCSB-5), which was developed by the Jaseng Hospital of KM, cannot be used by KMDs, and only WM doctors are allowed to use it. While it is beneficial for human health, the KM community is facing many difficulties, as the results of KM community's hard work and large investment are not permitted to be applied to the field of KM. For the COVID-19, it is a crucial factor whether KMDs can use research findings in their practice to treat various symptoms of the COVID-19. Therefore, research is essential, but I think legal and regulatory improvements are also necessary.

To conclude, we need to reinforce education and courses on infectious diseases, and I think, linking it to the work of KMDs will be quite crucial. I think we should create a system in which KMDs can participate in the treatment of infectious diseases. In terms of research, we should advise on developing herbal medicine treatment for infectious diseases that can be used by the KMDs via legal and regulatory improvements.

Hahm: Thank you. Prof. Hoyoung Choi gave us a full lecture on herbal medicine and things to be supplemented, and he explained that education and research must be expanded to cover infectious

diseases, but definitely there are regulatory barriers to be improved. I thank all the panel members who presented earlier.

Lee: Thank you so much for sharing your valuable experiences and opinions. There were many good comments, and no one expects the answers to be found in this one encounter. The world is rapidly changing amidst many other problems and I think the most critical task is to establish the basis so that we can argue for the role of KM in academics and clinical practice, and of KMDs as health-care professionals. And as prof. Hahm said, such a task should begin with education. I also believe that although the work in each field is different, the evidence from each area will eventually accumulate to establish the supporting background. There should still be many more discussions in each field, and I hope that even more sound evidence be established through our efforts. Thank you.

3. Summary

Many in vitro experiments reported anti-coronavirus effects of traditional herbs or natural products and clinical trials on traditional herbal medicine for COVID-19 are currently ongoing. In addition to establishing research evidence, KM community should train and produce public health professionals among KMDs by improving KM college education programs and official participation in public healthcare system should be ensured in terms of regulation and policy. In the post-COVID-19 era, it also should be allowed by regulations for KMDs to utilize newly developed herbal medicine/natural products for viral infectious diseases so that such research and relevant education can be motivated in KM community.

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Author contribution

Conceptualization: HL. Methodology: HL. Data Curation: SP and HL. Writing – Original Draft: SP, D-HH, MJ, KK, SK, HC, and HL. Writing – Review & Editing: SK and HL. Supervision: HL. Project Administration: HL. Funding Acquisition: HL.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical statement

This work did not require an ethical approval as it does not involve any human or animal experiment.

Data availability

The full recording of this online panel discussion can be accessed at https://www.kmcric.com/education/speciallecture/view_seminar/42922.

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