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ORIGINAL PAPER

Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: randomized control trial in Singapore

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Abstract

Purpose One of the key approaches to minimize the risk of COVID-19 transmission would be to reduce the titres of SARS-CoV-2 in the saliva of infected COVID-19 patients. This is particularly important in high-risk procedures like dental treatment. The present randomized control trial evaluated the efficacy of three commercial mouth-rinse viz. povidone–iodine (PI), chlorhexidine gluconate (CHX) and cetylpyridinium chloride (CPC), in reducing the salivary SARS-CoV-2 viral load in COVID-19 patients compared with water.

Methods A total of 36 SARS-CoV-2-positive patients were recruited, of which 16 patients were randomly assigned to four groups—PI group ($n=4$), CHX group ($n=6$), CPC group ($n=4$) and water as control group ($n=2$). Saliva samples were collected from all patients at baseline and at 5 min, 3 h and 6 h post-application of mouth-rinses/water. The samples were subjected to SARS-CoV-2 RT-PCR analysis.

Results Comparison of salivary Ct values of patients within each group of PI, CHX, CPC and water at 5 min, 3 h and 6 h time points did not show any significant differences. However, when the Ct value fold change of each of the mouth-rinse group patients were compared with the fold change of water group patients at the respective time points, a significant increase was observed in the CPC group patients at 5 min and 6 h and in the PI group patients at 6 h.

Conclusion The effect of decreasing salivary load with CPC and PI mouth-rinsing was observed to be sustained at 6 h time point. Within the limitation of the current study, as number of the samples analyzed, the use of CPC and PI formulated that commercial mouth-rinses may be useful as a pre-procedural rinse to help reduce the transmission of COVID-19.
ISRCTN (ISRCTN95933274), 09/09/20, retrospectively registered

Keyword COVID-19 · SARS-CoV-2 · Mouth-rinses · Saliva · Clinical trial · Antiseptics

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic caused by novel beta-coronavirus has infected more than 24 million people with 841,335 deaths globally as of 31

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August 2020 [1]. At present, therapeutic strategies and preventive vaccines for SARS-CoV-2 have not been developed. Infection control strategies targeted at individuals as well as public health measures are key to curb the spread of SARS-CoV-2 infection.

Human-to-human transmission of SARS-CoV-2 has been reported to occur via droplets or contact transmission [2]. Hence, to prevent cross-contamination, infection prevention practices such as hand hygiene, wearing mask and social distancing have been the mainstay of public infection control. A previous study has detected the presence of SARS-CoV-2 in the saliva of 91.7% COVID-19 patients, with a median viral load of 3.3×10^6 copies/ml [3]. SARS-CoV-2 RNA in saliva from infected individuals has been found to be stable at 4 °C, room temperature (~ 19 °C), and 30 °C for prolonged periods [4]. Moreover, the detection rate of SARS-CoV-2 has been reported to be partially higher in saliva than nasopharyngeal swabs [5]. Thus, saliva can carry a risk of transmission of COVID-19, either via direct contact or indirect contact with contaminated objects. Since the beginning of the pandemic, there has been a growing concern on the risk of SARS-CoV-2 transmission in dental practice [6]. Dental care professionals are exposed to aerosols from the oral cavity of patients, which might be a potential hazard to auxiliary staff and perhaps other patients [7]. According to the World Economic Forum analysis, dental hygienists, dental assistants and dentists are among the occupations with highest COVID-19 risk [8]. Thus, besides stringent protection measures, reducing the salivary viral titers in COVID-19 patients could be one of the key approaches to prevent transmission of COVID-19, particularly in the dental settings.

The use of antiseptic mouth-rinsing has been suggested as a pre-procedural infection control measure by international as well as local health authorities. For instance, during the early stage of COVID-19 pandemic, Chinese health authorities recommended the use of povidone–iodine (PI) and hydrogen peroxide-based mouth-rinses as a pre-procedural preventive measure [9], while National Dental Centre Singapore has advocated the use Cetylpyridinium chloride (CPC) mouth-rinse. However, the foregoing recommendations were not evidence-based as no clinical or in vitro data are currently available on the effect of mouth-rinse on SARS-CoV-2 concentration or viral load. The first case report on efficacy of mouth-rinses in reducing the SARS-CoV-2 viral load in the saliva was reported in Korea [10]. Subsequently, Martínez Lamas et al., 2020 in a case-series of four patients suggested that PI mouth-rinse could reduce the saliva viral load of SARS-CoV-2 in patients with higher viral loads [11]. A recent in vitro study has shown the efficacy virucidal activity of certain commercially available mouth-rinses against SARS-CoV-2 [12]. Given that there are no clinical trials in the literature that have examined the efficacy of mouth-rinses to reduce the SARS-CoV-2 viral load in saliva, we evaluated the efficacy of three commercially available mouth-rinses, namely PI, CHX and CPC, on the salivary SARS-CoV-2 viral load in a cohort of SARS-CoV-2-positive patients in Singapore.

Methods

Patient cohort

A total of 36 COVID-19 patients, whose nasal swabs were positive for SARS-CoV-2 based on reverse-transcription polymerase chain reaction (RT-PCR) assay, were recruited from Singapore General Hospital (SGH) from June 2020 to August 2020. History of allergy to PI, CPC or CHX and its relevant excipients, all forms of thyroid disease or current radioactive iodine treatment, lithium therapy, known pregnancy, and renal failure were considered as exclusion criteria. Ethics approval was obtained from SingHealth Centralized Institutional Review Board (CIRB Ref No: 2020/2537). The trial has been registered with ISRCTN (ISRCTN95933274). All patients provided informed consent upon recruitment in the study. The demographic characteristics of the subjects are depicted in Table 1.

Sample collection

The enrolled patients were randomized using Robust Randomization App (RRApp) using block randomization technique [13] and were allocated to four groups accordingly— PI, CHX, CPC and water control group. Prior to saliva collection, patients were asked to refrain from eating, drinking, or performing oral hygiene procedures for at least 30 min. Three milliliters of saliva was collected by passive drool technique from all the enrolled COVID-19 patients at four time points as described previously [14]. First, baseline saliva sample was collected prior to intervention of the mouth-rinse. Immediately after this, patients were requested to rinse their mouth with the allocated mouth-rinse for 30 s. Commercial mouth-rinses were prepared at the dilution and dosage recommended by respective manufacturers. In brief, PI group patients rinsed their mouths with 5 ml of PI mouthwash (commercially available as Betadine Gargle and Mouthwash 10 mg) diluted with 5 ml of water (0.5% w/v) whereas the CHX group patients used 15 ml of undiluted CHX mouthwash (commercially available as Pearly White Chlor-Rinse, 0.2% w/v). The CPC group and water control group patients rinsed their mouths with 20 ml of 0.075% CPC (commercially available as Colgate Plax mouthwash) and 15 ml sterile water, respectively. Three milliliters of saliva were collected again from all subjects 5 min after

Table 1 Demographic characteristics of subjects

	PI ($n=4$)	CHX ($n=6$)	CPC ($n=4$)	Water ($n=2$)
Age (years ± SD)	40.7 ± 11.5	43.6 ± 8.6	35.7 ± 8.5	36 ± 14.1
Gender				
Male	4 (100%)	6 (100%)	4 (100%)	1 (50%)
Female	0 (0%)	0 (0%)	0 (0%)	1 (50%)
Ethnicity				
Indian	3 (75%)	4 (66.6%)	3 (75%)	2 (100%)
Chinese	0 (0%)	2 (33.3%)	1 (25%)	0 (0%)
Others	1 (25%)	0 (0%)	0 (0%)	0 (0%)
Comorbidities				
Present	1 (75%)	1 (16.6%)	2 (50%)	1 (50%)
Absent	3 (25%)	5 (83.3%)	2 (50%)	1 (50%)
Time lapse between COVID-19 diagnosis and sample collection (days ± SD)	2.2 ± 1.2	3.5 ± 0.8	2.5 ± 1.7	2 ± 0

the use of mouth-rinse. To evaluate the duration of the efficacy of mouth-rinses, salivary samples were collected at the 3 h and 6 h post-rinsing using the methodology described earlier [14].

RT-PCR assay for SARS-CoV-2

Collected salivary samples of COVID-19 patients were immediately transported to the Molecular Laboratory, Singapore General Hospital (SGH). The SGH Molecular Laboratory performs routine diagnostic testing of COVID-19 using a validated SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) assay. NUCLISENS easyMAG was used to extract total nucleic acids from 200 µL of saliva following manufacturer's protocol. The in-house RT-PCR method used primers and probe from the protocol by Corman V et al. 2020 released by the World Health Organization (WHO) as well as Chu et al. 2020 protocol from the University of Hong Kong [15, 16]. This assay involves a single-step RT-PCR targeting the E gene of SARS-CoV-2. An internal spiked-in Bioline control (Bioline RNA Extraction Control 670 Kit #BIO-38040) or bovine-diarrhea disease virus (BVDV) is added to the assay prior to total nucleic acid extraction. These internal controls serve as extraction and amplification control. A run is considered valid if the positive control yields positive detection and negative controls remain negative. The in-house assay was estimated to have a limit of detection of 40.8 (95% confidence interval 30.3–104.7) E gene copies/reaction. We did not observe any inhibitory effect of the antiseptics on the action of the polymerase in our samples. However, to exclude inhibition-related false-negative result, for each test sample, the internal control spiked during extraction process and Ct reading were within ± 3 of run extraction control.

Data analysis

From the total of 36 SARS-CoV-2-positive recruits, saliva from 16 patients were RT-PCR positive for SARS-CoV-2, while saliva from 19 patients were RT-PCR negative and hence were excluded from the study. In addition, one patient was excluded due to non-compliance with study protocol. Thus, a total of 16 subjects comprising of PI group ($n=4$), CHX group ($n=6$), CPC group ($n=4$) and water as control group ($n=2$) were analyzed in this study. A longitudinal comparison of the absolute Ct values among all the time point within each group was carried out using Analysis of Variance, followed by post hoc tests to compare the differences between the groups. Relative fold change analysis was carried out after transforming the data on a scale of 1–5. Fold change was then estimated on the transformed data by calculating the ratio between Ct values at each time point versus the Ct value at baseline (at 0 min) for each patient ($Ct_{timepoint}/Ct_{baseline}$). The average fold change values thus obtained at 5 min, 3 h and 6 h time points for each of the mouth-rinse groups were compared with fold change value at corresponding time points of water group patients using Independent t test. The p value threshold for significance was set at < 0.05.

Results

The Ct values detected in all 16 patients were within the range of 15.6–34.5, with a mean value of 27.7 ± 4.8. The mean Ct values for the three mouth-rinses and water control group patients are depicted in Fig. 1. Whilst the trend looks

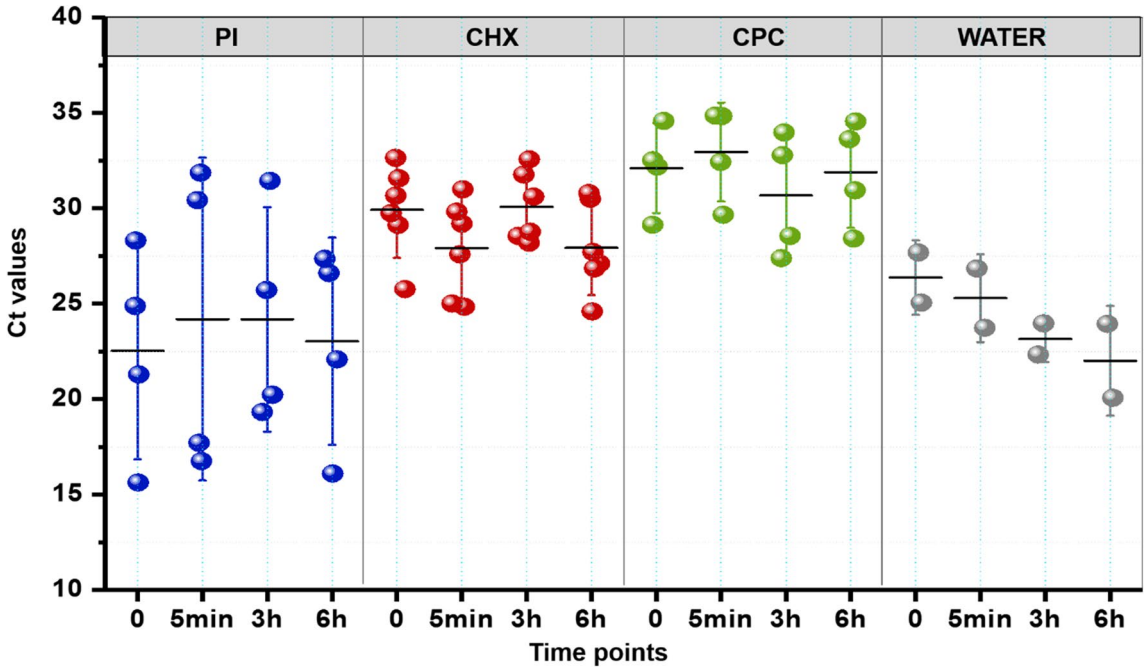

Fig. 1 Cycle threshold (Ct) profile in saliva of SARS-CoV-2-positive patients treated with mouth-rinses. Dots represent Ct value for each patient. Horizontal bar represents the mean value and vertical bar represents the 95% confidence interval

promising, no statistical differences were obtained in the Ct values with regards to any time points in all the group patients.

To compare the efficacy of the three mouth-rinses, first, the fold change of Ct value at each time point with respect to its baseline Ct value was estimated. Then, the fold changes at 5 min, 3 h and 6 h in all the three mouth-rinse groups' patients were compared with the Ct value fold change at the respective time points of water group patients (Fig. 2). A statistically significant increase in fold change of Ct value at 5 min (1) and 6 h (0.9) was observed post-rinsing with CPC mouth-rinse compared to the water group patients ($p < 0.05$). Although the fold changes in Ct values were higher at 3 h (0.9) in CPC group patients, no statistical significance was achieved ($p = 0.20$). Similarly, the PI group patients also showed higher fold changes in Ct value post 5 min (1.1) and 3 h (1.2) of post-rinsing, compared to the water group patients. However, statistically significant increase in fold change was obtained only at 6 h (1) post-rinsing with PI in comparison with water ($p < 0.01$). The CHX group patients demonstrated a varied effect among saliva Ct values after 5-min rinsing and hence further studies with a larger sample size are required to determine its significance. Although calculation of fold change is a mathematical means to identify the difference between of mouth-rinse groups compared to water control group, it cannot be supported by the data obtained in saliva Ct (Fig. 1). Nevertheless, the trends at 3 h and 6 h post-rinsing with CHX were consistent with other mouthwashes. Ct values are considered inversely related to viral load, and therefore, may serve as an indirect method of arbitrarily quantifying the viral load in the sample [17]. Hence, it can be postulated that CPC mouth-rinse decreased the salivary SARS-CoV-2 levels within 5 min of use, compared to water rinsing. The effect size of decreasing salivary load with CPC and PI mouth-rinsing was observed to be sustained at 3-h and 6-h time points compared to the control group patients.

Discussion

This is to our knowledge the first randomized clinical study to examine the efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in COVID-19 patients. In fact, only a single clinical trial is available in the literature that has evaluated the effect of essential oil containing mouth-rinses on Herpes simplex virus [18]. In the aforementioned clinical trial, effectively zero recoverable virions were found at 30 s post-rinse and the reduction in virus in saliva sustained significantly for 60 min, which was the last time point recorded. Hence, despite limitations, the present study will provide a novel insight on the quantity of SARS-CoV-2 in saliva. This is especially important as significant amounts of aerosols are generated in a relatively closed setting during dental treatments [19]. Health authorities such as, Centres for Disease Control

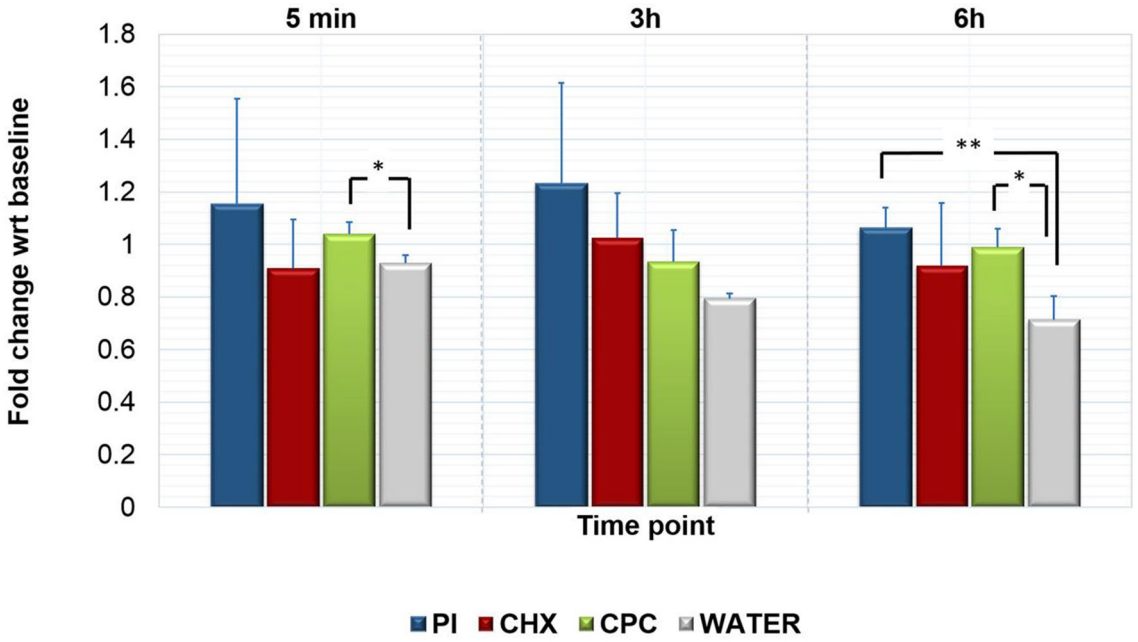

Fig. 2 Relative fold change of Cycle threshold (Ct) values in mouth-rinse and water group patients. The column size represents the mean of fold change of Ct value at each time point with respect to its baseline Ct value and the bars represents the standard deviation. Each mouth-rinse group patients—povidone–iodine (PI), chlorhexidine gluconate (CHX) and Cetylpyridinium chloride (CPC) were compared with water group patients using Independent *t* test. **Represents $p < 0.01$ and *represents $p < 0.05$.

and Prevention (CDC) and Australian Dental Association (ADA) have recommended the use of pre-procedural mouth-rinses for dental treatment, even without robust clinical evidence [20, 21]. Therefore, the present study provides the much-needed evidence on the efficacy of commercial mouth-rinses for salivary viral load reduction in a group of COVID-19 patients in Singapore.

It was observed that CPC and PI mouth-rinses have sustained effect in reducing viral load in saliva compared to water control patients in our study (Fig. 2). Previously, CPC has been shown to have antiviral activity against influenza viruses in in vitro with a half maximal effective concentration (EC50) of 5–20 µg/ml and in vivo, through direct attack on the viral envelope [22]. The virucidal spectrum of PI has been reported to be against both enveloped and non-enveloped viruses [23]. An in vitro study has shown the antiviral effectiveness of a 0.12% CHX mouth-rinse on several viruses associated with the oral cavity [24]. Moreover, a recent in vitro study evaluated the virucidal activity of commercial mouth-rinses against SARS-CoV-2 [12]. This in vitro study found that three mouth-rinses containing different active components, namely dequalinium chloride/benzalkonium chloride, polyvidone-iodine and essential oil could significantly reduce the SARS-CoV-2 viral load to undetectable level. However, chlorhexidine-based mouth-rinse failed to reduce the viral load significantly [12]. O'Donnell et al. (2020) also suggested that chlorhexidine could only weakly inactivate coronavirus strains [25]. In our study, we observed highly varied efficacy of CHX mouth-rinse on SARS-CoV-2 in saliva. Hence, we recommend further studies to establish the clinical efficacy of CHX in COVID-19 patients.

CPC is a quaternary ammonium compound which exerts its antiviral effect through disruption of the viral lipid envelope through physicochemical interactions. Coronaviruses including SARS-CoV-2 are surrounded by lipid membrane as envelop [26]. The spike glycoprotein responsible for the infection is inserted into this lipid envelop. Therefore, destruction of the lipid membrane by ethanol has been one of the main infection control measurements against SARS-CoV-2 transmission by hand disinfection. As CPC and PI are able to destroy the lipid membrane of the SARS-CoV-2, mouth-rinsing could be a safe, effective strategy to reduce the viral transmission through oral route. Interestingly, previous randomized clinical trial has shown that oral topical administration of ARMS-I, that contains CPC, was effective in reducing severity and duration of upper respiratory tract infections in patients infected with viruses such as influenza, coronavirus or rhinovirus. [27].

It has been suggested that the angiotensin-converting enzyme 2 (ACE2)-positive epithelial cells that line the salivary gland ducts are early target cells of SARS-CoV and a likely source of the virions found in patients' saliva droplets, especially early in infection [28]. Moreover, mucosa of

oral cavity could also express the ACE2 receptors and was observed to be higher in tongue cells than other oral sites [29]. Therefore, it is possible that oral epithelial cells may also contain the virus and the virus-infected oral epithelial cells may desquamate as a salivary component. Thus, it is postulated that virucidal activity of mouth-rinses may collectively reduce the viral presence in saliva as well as aerosolised viral particles from the oral route.

Although the evidence of the current study is encouraging, several limitations should be noted. The study was intended to recruit a larger cohort of COVID-19 patients based on the sample size calculation. However, recruitment was concluded after 36 patients due to drastic decrease in COVID-19 cases by late August, 2020 in Singapore. Moreover, we were not able to detect SARS-CoV-2 in 19 of 36 saliva samples, which may be possibly due to the SARS-CoV-2 variant with a 382-nucleotide deletion (Δ382) detected in Singapore cases [30]. The availability of only 2–4 patients in each group may cause bias in the results and the relevance of significant difference obtained with the such small number of patients needs to be further confirmed. In addition, inter-individual variation can also account for the varied Ct values. While the SARS-CoV-2 RT-PCR employed in this study was performed using a standardized protocol to enable viral load estimation, the assay was not designed to be a quantitative test. Moreover, the current testing method (RT-PCR) has the limitation of not being able to determine the viability of viruses. Given the difficulties in culturing SARS-CoV-2 virus from clinical specimens, using viral RNA load as a surrogate remains plausible at this moment [31]. Therefore, more studies are warranted with a larger sample size and viral culture to arrive at a definitive conclusion on the efficacy of mouth-rinses on the SARS-CoV-2 viral load in saliva. In addition, a homogenized population should be analyzed so as to delineate severe form of COVID-19 cases from asymptomatic cases. This would provide us information on the efficacy of mouth-rinses on the severity of disease and whether any modification in dosages or concentration of mouth-rinses can circumvent the issues, if any.

Conclusions

Within the limitations of the present study, it can be postulated that CPC and PI formulated commercial mouth-rinses may have a sustained effect on reducing the salivary SARS-CoV-2 level in COVID-19 patients. These mouth-rinses could be a useful pre-procedural transmission reduction strategy in clinical dental settings, where aerosol generation is unavoidable. Also in asymptomatic COVID-19 patients, the routine use of antiseptic mouth-rinsing could be a cost effective approach in reducing viral outspread, with potentially low health risk. Considering that mouth-rinses are available over the counter, it holds potential as a strategy with high public health impact to minimize the transmission of SARS-CoV-2 through oral route. However, it is important to mention that our study advocate the use of surgical masks as a control measure. In addition, during any aerosol-generating procedures in dental clinic, it is necessary to don appropriate personal protection equipment, use four-handed dentistry, high evacuation suction and dental dams to minimize droplet spatter and aerosols.

Author contributions CJS, PB, KKKK, and JSXY contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. NU, DL, DNHL, IV and GBT contributed to design and data acquisition, drafted and critically revised the manuscript. JLKS, LML, and LO contributed to data acquisition and interpretation, drafted and critically revised the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials The dataset used in the study is available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest with respect to the authorship and/or publication of this article.

Ethics approval Ethics approval was obtained from SingHealth Centralized Institutional Review Board (CIRB Ref No: 2020/2537).

Consent to participate. All the patients provided informed consent upon recruitment in the study.

Consent for publication All the authors have provided consent for publication.

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