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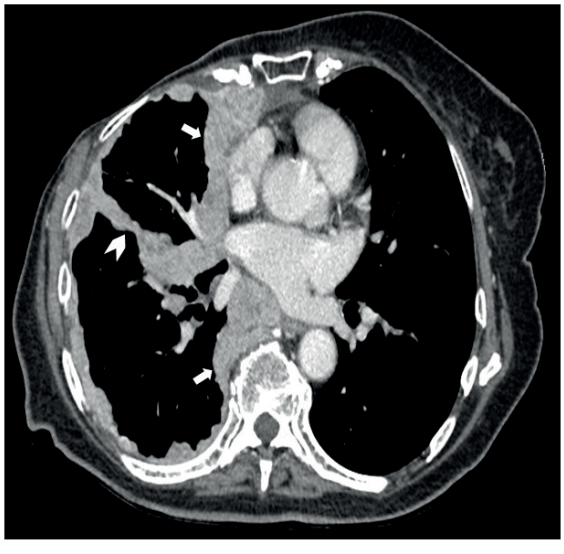

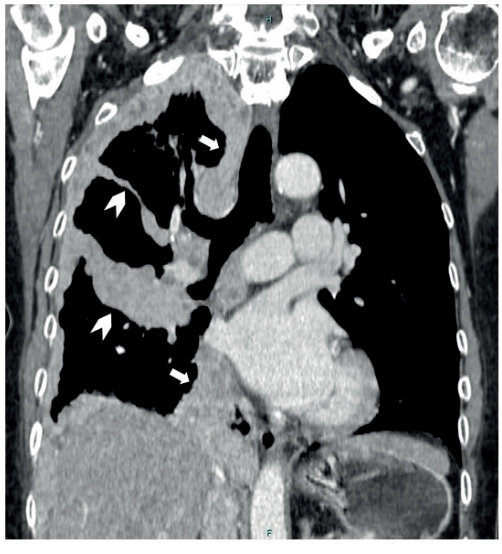

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Human Travelling and COVID-19 Pandemic

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ABSTRACT

Objective: To determine whether there is a relationship between the extent of human travel and the number of COVID-19 cases in Thailand.

Materials and Methods: The data set on monthly COVID-19 in Thailand between January and July 2020 were retrieved from the Ministry of Public Health, Thailand. Data regarding people's travel in Thailand during the COVID-19 pandemic and for the same period of 2019 were retrieved from Open Government Data of Thailand. A paired t-test was used to compare the differences between the number of journeys made in each mode of transport in 2019 (January - July) and 2020 (January - July). Pearson's product-moment correlation coefficient was used to examine the relationships among studied variables.

Results: A Paired Samples t-test showed that from January until July 2020, the number of journeys made by public buses, ships, and airplanes declined by more than 50% from the previous year ($p < 0.05$). Pearson correlation coefficients showed that the mean monthly number of COVID-19 cases was significantly and inversely correlated with the number of public bus journeys made ($r = -0.897$, $p < 0.01$), the number of train journeys ($r = -0.834$, $p < 0.05$), ship journeys ($r = -0.890$, $p < 0.01$), and airplane journeys ($r = -0.911$, $p < 0.01$). There was no significant relationship between the number of COVID-19 cases and private car journeys ($r = -0.405$, $p = 0.367$).

Conclusion: During the pandemic, the number of journeys has been decreased. Moreover, the correlation between the number of journeys and COVID-19 cases has been shown in our analysis.

Keywords: Environment, travel, COVID-19, nationwide (Siriraj Med J 2021; 73: 562-569)

INTRODUCTION

The first primary pneumonia cases from an unknown source were identified in Wuhan, Hubie province, China, in December 2019.[1] The symptoms were designated COVID-19[2] caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[3] The World Health Organization (WHO) has formally proclaimed that COVID-19 is a public health emergency of international concern.[4] By the end of December 2020, COVID-19 had taken around 1.7 million people's lives from all over the world, with about 81 million accumulated verified cases of the disease.[5] On January 13, 2020, Thailand announced the first COVID-19 case after China.[6] This country recently (December 29, 2020)

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had 6,440 confirmed COVID-19 cases with 61 deaths; 4,184 cases have recovered.[5] Simultaneously, various universities, healthcare institutions, and companies from several countries have developed COVID-19 vaccines to prevent this disease.[7]

Previous research has reported a number of general signs and symptoms of COVID-19 infection including, cough, sore throat, high body temperature, diarrhoea, headache, muscle or joint pain, weakness, and loss of sense of smell and taste. The average incubation period is 5-6 days, with the most prolonged incubation period being 14 days.[8-9] Restriction on travel, either international or domestic, has been established in several countries[10] including prevention of travel from high risk areas.[11] This limitation affects ordinary people's lives and those of vulnerable groups, such as those who have pre-existing health problems.[11] However, some experts have stated that there is no justification for measures that unnecessarily interfere with worldwide travel and commerce.[12]

A modelling exercise has suggested that, with original transmissibility (r =1) not reduced, a reduction in the travel of 90% to and from mainland China would only modestly affect the epidemic's trajectory.[13] Nevertheless, it can decrease the transmission of COVID-19 within the community by at least 50 %.[13] Accordingly, in addition to climatic conditions (temperature and humidity) and population density, it seems that people's travel is one factor that affects the spread of COVID-19.[14] However, there is a lack of evidence in Thailand regarding the association between human travelling and the spread of COVID-19. The current research, therefore, aimed to determine the relationship between human travelling and COVID-19 in that country. It is hoped that the results of the current study will contribute to efforts to prevent the spread of COVID-19 both in Thailand and elsewhere.

MATERIALS AND METHODS

Study area and data collection

In this correlational study, the data was obtained in Thailand, a country located in Southeast Asia, with a population of roughly 69 million, whose capital city is Bangkok.[15] The computerised data set on monthly COVID-19 cases in Thailand between January and July 2020 were retrieved from the Ministry of Public Health of Thailand (https://data.go.th/dataset/covid-19-daily).[16] Data regarding people's travel during the COVID-19 pandemic (January – July 2020) and during the same period of the previous year (January – July 2019) were retrieved from Open Government Data of Thailand (https://data.go.th/dataset/psgcovid19),[17] (Data ID: 54d62466-58ef-408c-bded-46f78103d6ae, Contact person: motoc@mot.go.th, License: DGA Open Government License). The right to use the data is subject to the terms and conditions for DGA Open Government License. Since the authors identified and reviewed data from open government data resources and did not involve human participants, therefore, Institutional Review Board approval is exempted.

The data consist of five main categories, and each category consists of different subcategories, as follow:

Category 1: The number of bus journeys made between January - July 2019 and January - July 2020, with four subcategories: 1) using public bus in Bangkok and suburbs, 2) using public bus between Bangkok and provincial cities, 3) using public bus between provinces, and 4) using public bus within a province.

Category 2: The number of private car journeys between January - July 2019 and January - July 2020, with two subcategories: 1) the number of private car journeys on main highways or roads and 2) the number of journeys on the expressway.

Category 3: The number of train journeys made between January - July 2019 and - July 2020, with two subcategories: 1) using the electric train in Bangkok and 2) using the intercity train in provincial towns and cities.

Category 4: The number of journeys made by ship between January - July 2019 and January - July 2020, with two subcategories: 1) using the ship in Bangkok and 2) using a ship in the provinces.

Category 5: The number of airplane journeys between January - July 2019 and January - July 2020 with three subcategories: 1) the number of passengers to and from Suvarnabhumi International Airport (for most long-haul international flights to and from Thailand), 2) the number of passengers to and from Don Mueang International Airport (for some international flights and a high volume of domestic flights), and 3) the number of passengers to and from regional airports.

Data analysis

In this study, the total number of journeys made within each transport category during the seven months January-July in each of the years 2020 to 2019 was averaged to give the mean number of journeys made per month in each mode of transport in each year. These means, along with standard deviations has shown in Table 1. A Paired Samples T-Test was utilised to test the differences between the number of journeys made in each mode of transport in 2019 (January - July) and 2020 (January - July). The value of t, degree of freedom (df), and significant value (p) was reported in Table 2. Furthermore, since data is a continuous level variable, the Pearson's product-

TABLE 1. The total number of journeys made within each category of transport during the seven months (January-July in each of the years 2020 to 2019)

Variables	January 2019 – July 2019		January 2020 – July 2020	
	Mean	SD	Mean	SD
The number of bus journeys made	64,318,906	3,380,337.69	31,245,393	14,054,263.18
The number of private car journeys	78,809,542	5,383,276.17	63,978,446	12,689,774.19
The number of train journeys made	34,863,981	1,708,978.44	23,928,388	12,459,165.70
The number of journeys made by ships	7,818,674	863,470.57	3,738,552	2,784,879.05
The number of airplane journeys	2,978,254	200,765.68	1,385,565	1,191,167.61

TABLE 2. The differences between the number of journeys made in each mode of transport in 2019 (January - July) and 2020 (January - July)

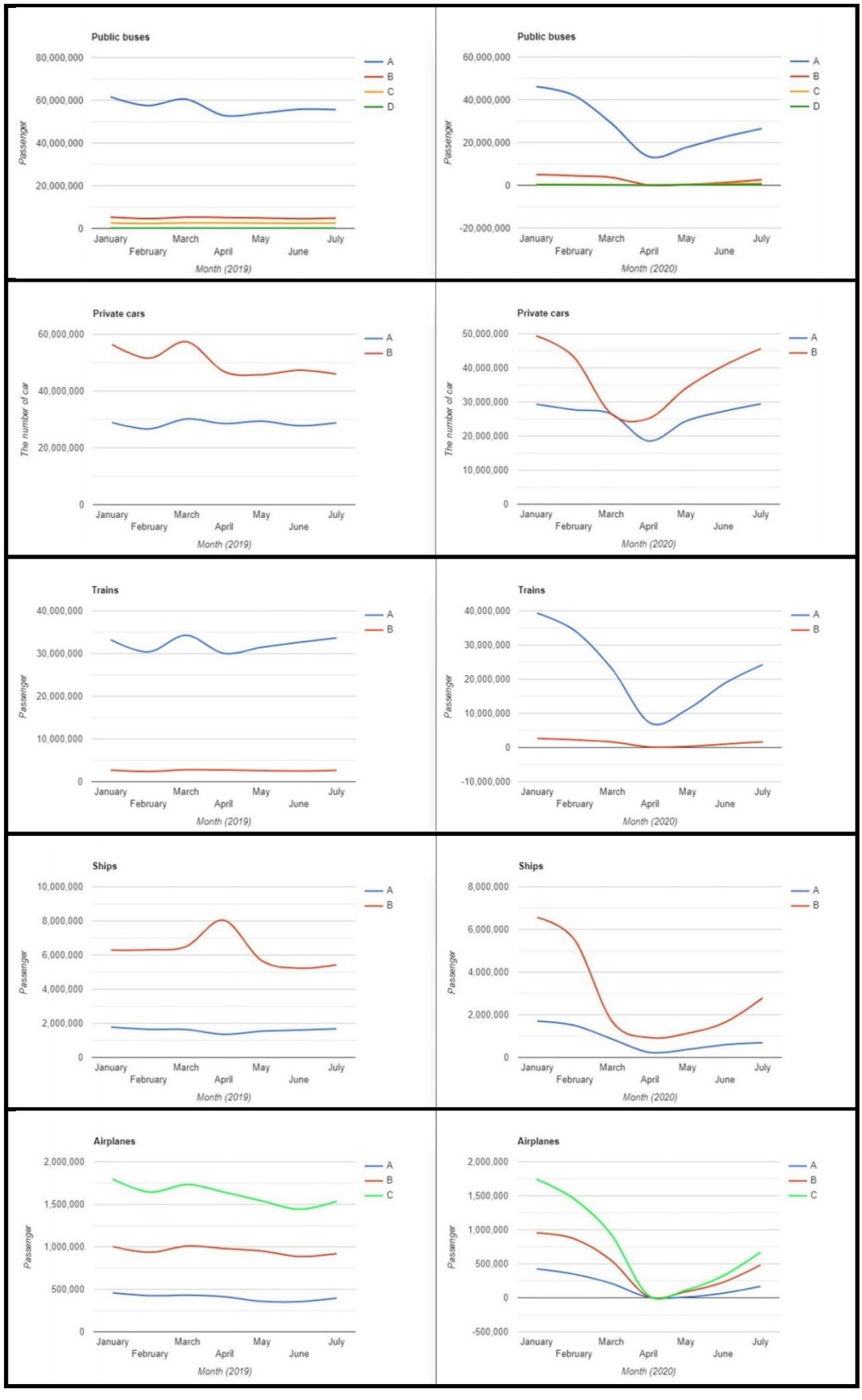
	Paired Differences					t	df	p
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1*	33,073,512.57	11,569,288.88	4,372,780.18	-43,773,320.20	-22,373,704.94	7.563	6	0.000
Pair 2**	14,831,096.14	13,446,020.74	5,082,118.14	-27,266,591.26	-2,395,601.03	2.918	6	0.027
Pair 3***	10,935,593.71	12,027,993.12	4,546,154.08	-22,059,632.02	188,444.59	2.405	6	0.053
Pair 4****	4,080,121.86	2,907,542.92	1,098,947.93	-6,769,150.57	-1,391,093.15	3.713	6	0.010
Pair 5*****	1,592,689.14	1,077,301.40	407,181.65	-2,589,026.76	-596,351.53	3.911	6	0.008

Note. *The number of bus journeys made in 2020 compared to 2019. **The number of private car journeys in 2020 compared to 2019. ***The number of train journeys made in 2020 compared to 2019. ****The number of journeys made by ships in 2020 compared to 2019. *****The number of airplane journeys in 2020 compared to 2019

moment correlation coefficient was used to examine the relationships between the number of journeys by each mode of transport made in the period January – July in 2020 and the monthly number of cases of COVID-19 (Table 3). The author followed Ratnasari and colleagues[18] regarding the correlation report's direction and strength. Statistical analyses were performed using IBM SPSS Statistics V. 20.0.

RESULTS

The number of journeys undertaken in each category (mode of transport) and subcategory (location of travel) in each of the months from January to July in the two years 2019 and 2020 is shown graphically in Fig 1. Overall, it can be seen that there is a pronounced dip for almost all modes of transport in April 2020. This was the month in which the government of Thailand imposed travel restrictions.



(1)

(A) Using public bus in Bangkok and suburbs
(B) Using public bus between Bangkok and provincial cities
(C) Using public bus between provinces
(D) Using public bus within a province

(2)

(A) The number of private car journeys on main highways or roads
(B) The number of journeys on the expressway

(3)

(A) Using the electric train in Bangkok
(B) Using intercity train in provincial towns and cities

(4)

(A) Using the ship in Bangkok
(B) Using a ship in the provinces

(5)

(A) The number of passengers to and from Suvarnabhumi International Airport
(B) The number of passengers to and from Don Mueang International Airport
(C) The number of passengers to and from regional airports

Note. (1) The number of bus journeys made ***(2)*** The number of private car journeys ***(3)*** The number of train journeys made ***(4)*** The number of journeys made by ships ***(5)*** The number of airplane journeys

Fig 1. The comparison between the number of journeys undertaken in each category (mode of transport) and subcategory (location of travel) in each of the months from January to July in the two years 2019 and 2020

Within each category of transport, the data for the subcategories were combined. The total number of journeys made within each category of transport during the 7-month period January-July in each of the years 2020 to 2019 was averaged to give the mean number of journeys made per month in each mode of transport in each year. These means, along with standard deviations, are shown in Table 1. It can be seen that the average monthly number of journeys made in each mode of transport was reduced in 2020 compared with 2019. The reduction is most marked for public transport; private car journeys declined relatively little (19%) in contrast with other modes of transport (over 50% for bus, ships, and airplanes, 31% for trains). In general, then, there was an apparent reduction in travel during the first half of 2020 as compared with 2019, thus indicating that government measures were effective in reducing the number of journeys made.

The data for the corresponding month of each year (e.g., January 2019 and January 2020) can be regarded as paired. Related t-tests were therefore utilised to test the differences between the number of journeys made in each mode of transport in 2019 (January - July) and 2020 (January - July). Table 2 shows the difference between each pair of means and the standard deviation of the difference, along with 95 percent confidence intervals, the value of t, degree of freedom (df), and p-value. Accepting the conventional level of statistical significance as $p < 0.05$, the reduction is significant for all modes except for transport by train, which just misses significance.

Fig 2 presents a comparison between the total number of travellers from all transportation forms from January until July 2020 and the number of COVID-19 cases and death in Thailand. The total number of journeys (summed across subcategories) made in each mode of transport during each month of the period January - July in 2020 is shown in the upper half of this figure, and the lower half shows the total 3,310 cases of COVID-19 and 58 deaths recorded in Thailand during each month of the same period. The result reveals that the number of travellers remains stable at the beginning of January, correspondingly with the number of COVID-19 cases and death. Nonetheless, as the number of travellers starts to decline from the beginning of February 2020, the number of COVID-19 cases drastically spike approximately 2-3 weeks later and continues to increase until July 2020. However, the number of deaths slightly changes along with the graph.

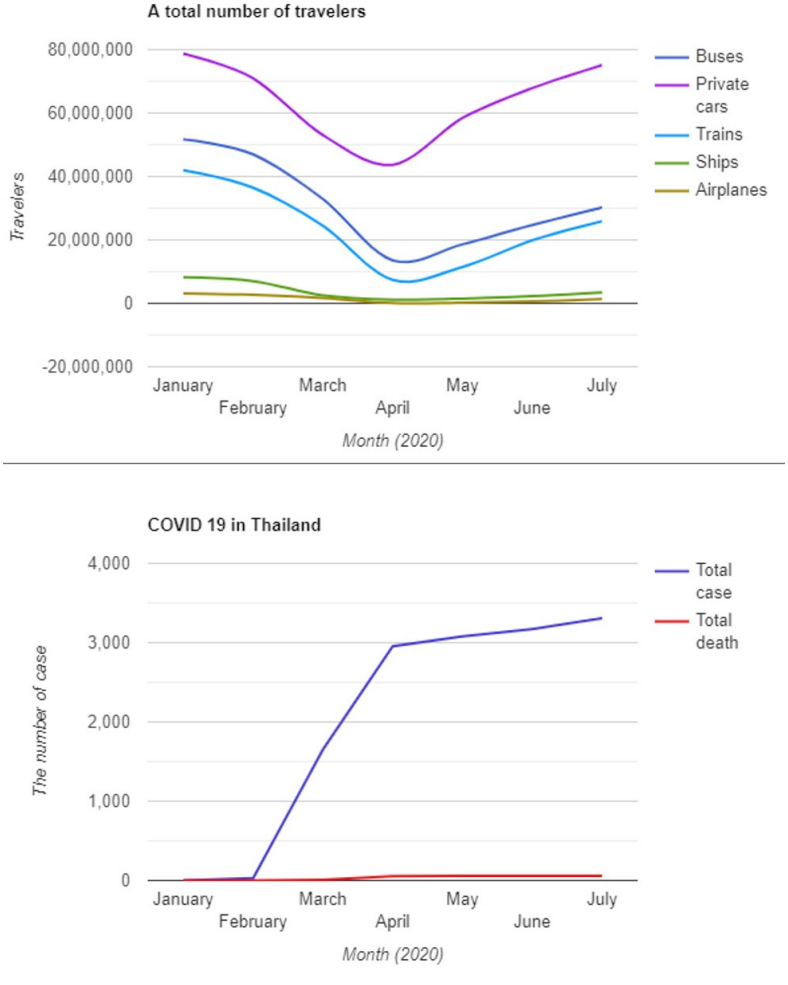


Fig 2. The comparison between the total number of travellers from all transportation forms from January until July 2020 and the number of COVID-19 cases and death in Thailand

To examine the relationships between the number of journeys by each mode of transport made in the period January – July in 2020 and the monthly number of cases of COVID-19, the Pearson correlation coefficient was used. The correlations between the monthly number of cases of COVID-19 and the total number of journeys made in each month by each mode of transport are shown in the correlation matrix of Table 3. It can be seen that there are strong correlations between each of the different modes of public transport, with coefficients almost all above 0.90 and significance levels above $p < 0.001$. The correlations between the number of car journeys and the number of journeys made by ships and the number of car journeys and the number of airplane journeys, however, are lower and generally not significant. Moreover, the mean monthly number of COVID-19 cases was significantly and inversely correlated with the number of public bus journeys made ($r = -0.897$, $p < 0.01$), the number of train journeys ($r = -0.834$, $p < 0.05$), ship journeys ($r = -0.890$, $p < 0.01$), and airplane journeys ($r = -0.911$, $p < 0.01$). In addition, there was no significant relationship between the number of COVID-19 cases and private car journeys ($r = -0.405$, $p = 0.367$).

DISCUSSION

It is suggested that postponing travel and staying home is the best way to protect people from exposure to COVID-19.[19] However, there is a lack of evidence in Thailand regarding the association between human travelling and COVID-19 exposure. Since public transport vehicles are relatively closed settings conducive to the transmission of COVID-19[20-21], several countries have reported that many clusters of cases with infections caused by respiratory viruses, including SARS-CoV-2, took place in public transport vehicles.[20] The Thai government has enforced travel restrictions since March 2020.[6], which more likely to be the main reason for the sharp reduction of the overall use of public transportations.

The fall of private cars' use is possible due to the forced closure of risk transmission areas such as shopping malls, schools, and universities, thus lessen the necessity of being out of the neighbourhood and driving private cars to other places. Moreover, as the awareness of the higher risk of infection via public vehicles as well as the fear of dying of COVID-19 is rising.[6], when people have to travel, they would prefer using private cars over public vehicles, leading to a relatively less reduction of

TABLE 3. The correlations between the monthly number of cases of COVID-19 and the total number of journeys made in each month by each mode of transport in the period January – July in 2020

Variables		(1)	(2)	(3)	(4)	(5)	(6)
The number of	Pearson Correlation	1	0.734	0.991**	0.962**	0.993**	-0.897**
bus journeys made	Sig. (2-tailed)		0.060	0.000	0.001	0.000	0.006
The number of	Pearson Correlation		1	0.800*	0.749	0.673	-0.405
private car journeys	Sig. (2-tailed)			0.031	0.053	0.098	0.367
The number of train	Pearson Correlation			1	0.950**	0.979**	-0.834*
journeys made	Sig. (2-tailed)				0.001	0.000	0.020
The number of	Pearson Correlation				1	0.950**	-0.890**
journeys made by ships	Sig. (2-tailed)					0.001	0.007
The number of	Pearson Correlation					1	-0.911**
airplane journeys	Sig. (2-tailed)						0.004
The monthly number	Pearson Correlation						1
of cases of COVID-19	Sig. (2-tailed)						

Note. **Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

the use of private cars in comparison with that of public vehicles.

In respect of why April 2020 is the lowest point of the numbers of all passengers, the most likely reason is that since the number of new cases continued to increase, the Thai government took further action on April 3, including a nationwide curfew from 10 PM to 4 AM, a travel ban for all international flights entering Thailand, suspending intercity public transport, a ban on the sale of alcohol to reduce the risk of social gatherings and so forth[6], resulting prevented people from travelling to a great extent. Besides, the sharp increase of the infected cases in Thailand may lead to a greater degree of fear and caution in public, bringing about reduced travelling.

A substantial proportion of COVID-19 cases are asymptomatic, which may also have high viral loads similar to those in symptomatic patients.[22] An increasing number of reports indicated that SARS-CoV-2 might be transmitted from infected people, but asymptomatic.[23] Furthermore, since the incubation period of COVID-19 is variable and sometimes may take a long time (2-14 days)[20], the virus's transmission may have already begun before people can realise it. Simultaneously, the disease outbreak takes some time, thus explaining the sudden spike in the number of infected cases in February 2020 even after people had stopped travelling. This can possibly contribute to the rising number of infected cases in March 2020 despite of the restrictions and reduced travelling too, since it took time to make a definite diagnosis of the COVID-19, and during this period, the virus may have infected people around the host, resulting in an increase in infection rate.

The growth of the number of COVID-19 cases has been relatively slow since April 2020, on account that the government stepped up its efforts in almost every aspect to battle with COVID-19, such as quarantine, active case detection, physical distancing, and travel restrictions, which are quite efficient in hindering COVID-19 transmission in Thailand.[6] These drastic measures, along with people's increasing notion of how to take appropriate precautions against COVID-19 (e.g., high usage of face masks (93.3%) in Thailand)[24], prevented the rapid rise of the infected cases even when the number of travellers picked up substantially since April 2020.

This study has numerous limitations. Firstly, acknowledging that this is secondary data analysis, the authors are less able to correct the source's errors through data collection. Nevertheless, the authors handled the data from the government organisation with caution. Furthermore, given the retrospective nature of the data, inherent biases to such a study exist. Therefore, a further prospective study investigating the association between human travelling and COVID-19 transmission to develop an efficient procedure in preventing COVID-19 is recommended.

CONCLUSION

During the pandemic of COVID-19 from January until July 2020, the number of journeys made by public buses, ships, and airplanes has been reduced. Furthermore, our correlational analysis showed that the association between the number of public bus journeys made, the number of train journeys, ship journeys, and airplane journeys, and COVID-19 cases exist.

ACKNOWLEDGEMENT

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Conflict of interests

There are no conflicts of interest to declare.

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Randomized Controlled Trial Evaluating the Efficacy and Cost Effectiveness of a Ready-to-Use Applicator Containing Iodine Povacrylex and Isopropyl Alcohol Compared with Conventional Skin Scrubbing and Painting in Patients Undergoing Colorectal Surgery

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ABSTRACT

Objective: The aim of this study was to evaluate the efficacy and cost-effectiveness of a ready-to-use applicator containing iodine povacrylex and isopropyl alcohol (IPIA) for the prevention of surgical site infection (SSI) following colorectal surgery.

Materials and Methods: The IPIA was randomly used in patients who underwent colorectal surgical procedures. The control group for comparison was a group of patients who underwent colorectal surgical procedures using conventional skin scrubbing and painting with antiseptic solutions without IPIA. In total, 100 patients were included in the study, randomized into 2 groups: IPIA was applied in study group and convention skin preparation was applied in control group.The outcome measurements included ease-of-use as assessed by a questionnaire, preparation time comparison, estimated skin preparation expense, adverse reactions, and rate of SSI. All the patients were visited daily up to 7 days postoperation or until discharge, and then 14 and 30 days postoperatively for monitoring the occurrence of SSI.

Results: Of the 100 patients undergoing elective colorectal surgery enrolled in the study, 51 were males and 49 females, with the mean age of 63.5 ± 11.3 years. The majority of the patients had colorectal cancer undergone colectomies or rectal resections. There was no mortality. Seven patients (7%) had postoperative SSI (4 patients in the control group and 3 patients in the IPIA group, 8% vs. 6%, $p = 0.45$). The bacterial cultures revealed Gram negative-bacilli in all of the patients with SSI. The preparation time for the skin preparation was 5.48 ± 2.49 min in the control group and 2.65 ± 1.55 min in the IPIA group ($p = 0.002$), without statistical significance of expenses.

Conclusion: IPIA was demonstrated to be as safe and effective as conventional antiseptic solutions as a skin preparation to prevent SSI following colorectal surgery. With good ease of use, IPIA proved more convenient than a scrubbing preparation as well as offered better cost effectiveness by significantly reducing the time and cost of the skin preparation.

Keywords: Surgical site infection; Skin preparation; Colorectal surgery; A ready-to-use applicator containing iodine povacrylex and isopropyl alcohol (IPIA) (Siriraj Med J 2021; 73: 570-575)

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INTRODUCTION

Surgical site infection (SSI) is an infection of the tissues, organs, or spaces exposed to contaminated environment, surgical equipment or personnel, or even to a patient's own flora during performing of invasive clinical procedures or operations. SSI occurs when endogenous flora are translocated to a sterile site. Up to 5% of patients undergoing clean extra-abdominal operations and up to 20% of patients undergoing intra-abdominal operations develop SSI.[1] SSI is associated with considerable morbidity and mortality as well as substantial health-care costs and patient dissatisfaction.[2] In addition to a good surgical technique, the use of appropriate antiseptics at the surgical site with antibiotic prophylaxis can reduce the incidence of SSI rates during certain types of procedures. The antimicrobial activity of such antiseptics should be effective against the types of bacteria that are likely to be encountered during the particular types of operation performed in clinic and should certainly be safe for patients. For this reason, in May 2004, the US National Surgical Infection Prevention Project announced a consensus on antimicrobial prophylaxis for surgery. They concluded that infusion of the first antimicrobial dose should be administered within 60 min before surgical incision. In addition, prophylactic antimicrobials should be discontinued within 24 h after the end of surgery.[3] The appropriate antiseptics and antibiotics should contain antibacterial activity against the intestinal flora and common pathogens. Nowadays, various antiseptic solutions have been used with a prophylactic intention for SSI. Concerning mixed aerobic and anaerobic bacterial domination, broad-spectrum antiseptics, such as povidone–iodine, have been commonly used as the first-line agent. The application of antiseptics in conventional theaters involves preparing sterile containers, applicators (i.e., sponge holder forceps), and packs of sterile gauzes. The antiseptics have to be poured out of the container, during which, most of the time, the excess solution has to be discarded. However, if the complexity of administration is an issue of concern, or due to a busy workload or lack of nursing staff, the use of ready-to-use antiseptics is certainly favorable. One of the most widely used antiseptics preparation for SSI prophylaxis is a ready-to-use applicator containing iodine povacrylex and isopropyl alcohol (IPIA). Excellent efficacy and safety of IPIA for SSI prophylaxis have been reported in the literature. Also, IPIA solution has been shown to require significantly less time to apply than a traditional scrub and paint preparation.[4] Alcohol-based solutions are quick, can be sustained, and are durable, with a broader spectrum of antimicrobial activity. These agents seem ideal for longer open surgeries with the potential for irrigation or surgical spillage.[5] However, most studies in the literature have been conducted with Western populations, whose responses to antiseptics and adverse reactions may be different from Thai patients. Consequently, the aim of the present study was to evaluate the efficacy and safety of IPIA for the prevention of SSI following abdominal surgery in a Thai population.

MATERIALS AND METHODS

After obtaining ethical approval from our institute's ethical committee, an open prospective controlled randomized comparative trial was conducted in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand between December 1, 2011, and November 30, 2012.

In total, 100 patients were included and were randomized into 2 groups. Each group of patients was applied either a ready-to-use applicator containing iodine povacrylex and isopropyl alcohol (IPIA) or a conventional skin preparation (skin scrub and paint) with antiseptic solutions without IPIA. DuraPrep™ (3M Corporate Headquarters, Minnesota, US) is a ready-to-use cylinder containing 26 ml of an alcohol-based surgical skin preparation solution with an applicator at one end. Its active ingredients are iodine povacrylex (0.7% available iodine) and isopropyl alcohol 74% (w/w). Patients were enrolled with the following inclusion criteria: aged between 18 and 80 years old; ASA class I–III; and undergoing an intra-abdominal operation for elective endorectal surgery.

Patients were excluded by one of the following criteria: previous history of hypersensitivity or allergy to seafood, iodine or its derivatives; women with pregnancy or lactation; renal insufficiency; hepatic impairment; APACHE II score more than 15; and consent refusal.

All the patients underwent colorectal operations under balanced general anesthesia. The details of the operative procedures depended on diagnosis and the intra-operative findings. The appropriate intravenous prophylactic antibiotics were given to all patients by anesthesiologists at the time of anesthetic induction (approximately 30 minutes before skin incision). Subsequently, the skin antiseptics were applied after a randomized label was attached (open code in the theater). The subjects were randomized into two groups given either the conventional technique as a skin preparation or a ready-to-use applicator containing iodine povacrylex and isopropyl alcohol solution.

The conventional technique was based on a

skin preparation with water-based or alcohol-based antiseptics. Basically, chlorhexidine (alcohol-based) or povidone–iodine (water-based) were used as the active antiseptic ingredient. We followed the standard regulations established by US-CDC and WHO. The steps were the following: 1) the affected skin was scrubbed with soap-based chlorhexidine for 5 minutes; 2) the skin was then dried with sterile clothes; 3) the water-based or alcohol-based antiseptic was applied thoroughly to the skin twice using the antiseptic refilled in a stainless cup and soaked onto a prepared sponge-stick (typically, 3 pieces of 4 x 4 gauze were used for each case); 4) the skin was then ready for sterile draping.

IPIA was applied as per the manufacturer's instructions. Briefly, the following steps were carried out: 1) the sponge was held parallel to the floor to touch the affected skin; 2) a lever was snapped to allow all the fluid to flow into the sponge; 3) the cap end of the applicator was pressed to the skin; 4) a single uniform coat of solution was painted onto the skin; 5) the solution was allowed to dry thoroughly on the skin for 3 minutes.

Additional antibiotics were prescribed as appropriate if the patients bore certain risks or later developed symptoms and signs of SSI. SSI was diagnosed following the US Centers for Disease Control and Prevention (CDC) criteria 1992.[6]

Health economic data were collected, including the ease-of-use questionnaire results, preparation time comparison, estimated skin preparation expense, adverse reactions, and rate of SSI. All the patients were visited daily up to 7 days postoperation or until discharge, and then 14 and 30 days postoperatively for monitoring the occurrence of SSI.

The patients were discharged from the hospital if they had no fever, had normal bowel function, good ambulation, and no sign of infection. All the patients were scheduled for follow-up at 14 and 30 days postoperatively.

Outcome measures

The primary outcome would be that IPIA is as safe and effective as conventional antiseptic solutions as a skin preparation to prevent SSI following colorectal surgery. The secondary outcome would be that, with good ease of use, IPIA proved more convenient than a scrubbing preparation as well as offered better cost effectiveness by significantly reducing the time and cost of the skin preparation.

Statistical analysis

The sample size was calculated for a two-sided test of 5%. Descriptive statistics, such as the number and percentage, of the categorical data were described in terms of the mean and standard deviation. For continuous variables with the normal distribution, student t-tests were conducted. If nonparametric tests were required, Mann-Whitney U tests were used. Inferential statistics, including the chi-square test or Fisher's exact test, were used to compare the diseases, results of surgical site infection and mortality between patients within the two groups. Here, p-values less than 0.05 were considered as indicating a statistically significant difference.

RESULTS

In total, 100 patients who underwent elective colorectal surgery were enrolled in the study. A summary of the results is given in Table 1. The 100 study population comprised 51 males and 49 females, with the mean age of 63.5 ±11.3 years old. Of these, 48 patients received a conventional skin preparation (control group), while 52 patients received a ready-to-use applicator containing IPIA as a skin preparation (study group). There were 26 males and 22 females with the mean age of 63.4 ± 13.0 years old in the control group, compared with 25 males and 27 females with the mean age of 63.6 ± 11.9 years old in the study group. The majority of patients with colorectal cancer underwent colectomies (30 patients in the control group vs. 32 patients in the study group, $p = 0.921$) or rectal resections (16 patients in the control group vs. 19 patients in the study group, $p = 0.737$). Three patients with benign diseases underwent colorectal resections (a colovesical fistula and a colovaginal fistula in the control group vs. a rectosigmoid polyp in the study group, $p = 0.606$). There was no mortality. Seven patients (7%) had postoperative SSI (4 patients (8%) in the control group vs. 3 patients (6%) in the study group, $p = 0.45$). The bacterial cultures revealed Gram negative-bacilli in all of the patients with SSI. The preparation times were 5.48 ± 2.49 minutes in the control group and 2.65 ± 1.55 minutes in the study group ($p = 0.002$). The expenses for the skin preparations were US$10.96 ± 1.20 in the control group compared to US$10.82 ± 5.02 in the study group ($p = 0.844$). The satisfaction scores in terms of ease of use for the control group and study group were 8.39±1.10 and 8.47±1.26 out of 10, respectively ($p = 0.754$).

DISCUSSION

Surgical site infection (SSI) is one of the risk burdens following major operations, such as intra-abdominal surgery, especially in patients with colorectal cancer.[7-8] Patients with SSI are more likely to stay longer in the hospital, pay more expenses (i.e., for expensive antibiotics), and subsequently have an increased mortality rate.[9-11]

TABLE 1. Results of the control group using a standard skin preparation vs. the study group using a ready-to-use applicator containing iodine povacrylex and isopropyl alcohol (IPIA).

Characteristics	Control Group (n = 48)	IPIA Group (n = 52)	*p*-value
Age	63.4 ± 13.0	63.6 ± 11.9	0.214
Sex : Male	26 (54%)	25 (48%)	0.543
Female	22 (46%)	27 (52%)	
Colon Cancer	30 (63%)	32 (62%)	0.921
Rectal Cancer	16 (33%)	19 (36%)	0.737
Benign Diseases	2 (4%)	1 (2%)	0.606
Mortality	0 (0%)	0 (0%)	-
Surgical Site Infection	4 (8%)	3 (6%)	0.450
Preparation Time (min)	5.48 ± 2.49	2.65 ± 1.55	0.002
Expense of Skin Preparation (US Dollars, US$)	10.96 ± 1.20	10.82 ± 5.02	0.844
Satisfaction Score in Terms of Ease of Use (1–10)	8.39±1.10	8.47±1.26	0.754

According to the practice guidelines for SSI prevention, an appropriate skin preparation with an effective antiseptic solution, and wound-edge protection, as well as an intravenous antibiotic prophylaxis could be an important combination to avoid SSI.[12] The incidence of SSI in both tested groups in the present study was in an acceptable and similar range to previous reports of elective colorectal surgery.[7,13-14] When we looked at the results of the bacterial cultures and sensitivity tests, *E. coli* was found in all seven specimens. This finding suggested that the contamination did not originate from the skin incision, but rather the contamination arose from intestinal flora during the operation. *Streptococcus epidermis* and *Staphylococcus aureus* are the pathologic organisms mostly involved in the majority of patients with SSI. This occurs if skin is not properly disinfected with applicable antiseptics. Basically, surgeries with colorectal resection are categorized as clean-contaminated procedures that can carry a risk of SSI developing, with an incidence rate of between 4.7 - 27.3 % according to the published literature.[13-16] Undoubtedly, one of the most important factors is the surgical technique, especially intraoperative soiling and insufficient wound-edge protection. In this study, most of the cases in both groups were reported to have wound-edge protectors, such as Alexis wound protectors and abdominal swabs. The rates of SSI in both groups were rather low compared to the rates of SSI reported in previous studies.[14-15] In addition, our better short-term postoperative outcomes including lower SSI rate have been achieved after the establishment of specific Colorectal Surgery and Minimally Invasive Surgery Units within the Division of General Surgery.[17-18]

The skin preparation time in the IPIA group was on average half that of the control group, with a saving of over 2.5 minutes. The authors did not put this time reduction in to the unit cost calculation. In addition, the reusable items included bowls and sterile towels as well as their depreciation costs and re-sterilization cost were not taken into consideration. Otherwise, a couple of dollars could have been credited to each case in the IPIA group. Nevertheless, the expenses for skin preparation in the IPIA group was only 14 cents cheaper when compared to the skin preparation costs in the control group. Definitely, this fractional saving money showed no statistically significant difference in costs. Regarding the satisfactory score in the ease of use, the staff who used the IPIA seemed to express fractional higher scores, but these were not statistically significant different. At least, from the economic evaluation perspective, it may be assumed that users might be able to switch from the conventional method to this new method without much difficulty.

In conclusion, we demonstrated that a ready-to-use applicator containing IPIA was as safe and effective as conventional antiseptic solutions as skin preparations to prevent SSI following colorectal surgery. With good

ease of use, IPIA provided more convenience for the scrubbing personnel as well as better cost effectiveness by significantly reducing the time and cost of skin preparation.

Limitation of the study

As this study was conducted in a single university hospital, it may be inapplicable for other institutes. Although the fractional saving cost could not demonstrate the statistically significant difference, this randomized study may indicate the cost-saving tendency depending on the economy of scale. From the hospital perspective, an individual cost-minimizing analysis should be conducted to compare the economic efficiency between an IPIA and conventional skin scrubbing and painting.

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Ethics approval and consent to participate:

Before its commencement, this research is eligible for exemption review by the Institutional Review Board of Siriraj Hospital, Siriraj Institutional Review Board (SIRB). This study conducted in established educational settings, involving normal educational practice such as research on regular and special education instructional strategies, research on the effectiveness of the comparison among instructional techniques, curricula, or classroom management methods. The need for consent for participation is deemed unnecessary according to the research nature without identifiable patient information. The requirement for informed consent was waived.

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Quality of Life in Postoperative Colorectal Cancer Survivors: A Structural Equation Model

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ABSTRACT

Objective: The present study has been aimed at constructing a causal model to determine factors affecting health-related quality of life (HRQoL) in postoperative patients with colorectal cancer (CRC) following discharge.

Materials and Methods: A cross-sectional study was conducted with 396 postoperative CRC cancer patients from ten tertiary hospitals representing each of the four Regions of Thailand. Data was collected through a standard questionnaire. Structure equation modeling (SEM) was applied to analyze data.

Results: The findings revealed that the majority of patients with CRC surgery had a moderate HRQoL. One hundred and twenty-three patients (31.1%) had complications. SEM showed a good fit with χ^2=40.347, df=28, p=0.062, GFI=0.980, CFI=0.959 and RMSEA=0.033. The final model showed that age, stage of cancer and healthcare service being received following CRC surgery had direct effects on HRQoL. Nutritional status and follow-up outpatient clinic had indirect effects on HRQoL during postoperative complications. Moreover, social support and primary family caregiver support had indirect effects on HRQoL through self-management capacity.

Conclusion: The findings of this study emphasized the importance of implementing effective strategies to improve quality of life among postoperative patients with CRC after discharge and indicated these strategies should focus on quality of healthcare service following CRC surgery, self-management capacity and prevention of postoperative complications. Postoperative complications can be reduced by providing effective follow-up in outpatient clinics and nutritional status management, consequently improving quality of life among this population.

Keywords: Quality of life; postoperative complications; healthcare delivery; colorectal cancer (Siriraj Med J 2021; 73: 576-586)

INTRODUCTION

Health-related quality of life (HRQoL) is an important indicator of a healthcare system. One of the main goals of caring of postoperative patients with colorectal cancer (CRC) is the achievement of a better HRQoL. However, survivors of CRC following surgery might experience a decrease in HRQoL owing to pain, diarrhea and physical and social functioning.[1-3] Such post-operative conditions impose great demands on follow-up models following discharge, thus making it difficult to improve the overall quality of life of patients.[4] Post-discharge follow-up visits should take place either in the home[5] or in an

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outpatient clinic[6], or take the form of a telephone visit[7] in order to promote continuity of care. Prompt follow-up of discharged patients has been related to reduced postoperative complications[8,9] and improved functional ability and quality of life.[10] Patients undergoing CRC surgery need continued healthcare service following discharge for symptom management[11], skill development[12], psychosocial support[13], access to health care[14], continuity of care[9] and effectiveness of healthcare services for the purpose of maintaining HRQoL and reducing postoperative complication rates.

Many studies have investigated the impact on HRQoL of self-management capacity, family caregiver support, social support and patients' dimensional factors in patients who undergo CRC surgery. The self-management of patients is a behavioral factor that makes patients healthy and directly affects their quality of life.[15] Successful self-management is the result of the use of knowledge, skills and confidence in dealing with the problem of illness, which can be achieved through postoperative symptom experience, social roles and stress-and-anxiety control at home, which can thus result in an improved quality of life.[16] Moreover, family caregiver support has a direct influence on patients' self-management ability.[17] Caregivers assist patients in managing their treatment plans and consistently keeping their appointments. Further, caregivers support patients in their daily-living activities and help them to monitor unusual symptoms after their surgeries and assist them in managing post-operative pain.[18] Social support from families, peers and other people in the community is critical for people living with CRC. Social support has been found to be positively correlated with quality of life in patients with cancer.[19] The influence of age, stage of cancer[20], co-morbidity[21] and nutrition status[22] on HRQoL has also been demonstrated in previous studies.

However, previous studies of postoperative quality of life following CRC surgery have focused on individual factors such as the physiological and psychological components of wellness.[23,24] This study explored the health service delivery system by using a more comprehensive causal model to explain HRQoL in patients with postoperative CRC following their discharge from the hospital. The factors that were considered included the model of follow-up care, healthcare service after CRC surgery, postoperative complications, primary family caregiver support, social support, self-management capacity and patients' dimensional factors (age, co-morbidity, nutrition status and stage of cancer). The aim of this study was to identify the relationships between these factors and HRQoL in patients who had been discharged following CRC surgery in a hypothesized model using structure equation modeling (SEM). The results from this study are expected to be useful in the application of information to formulate policy to develop models of care and health service systems for postoperative patients with CRC.

MATERIALS AND METHODS

Study design and setting

This study was based on a cross–sectional descriptive study design in ten tertiary hospitals from the four Regions of Thailand during from May 2018 to May 2019. The study was approved by the Siriraj Institutional Review Board (SIRB) (Si 318/2018) and Human Research Ethics Committee of each of nine tertiary hospitals.

Study participants

In structural equation modeling, sample sizes of 200-400 are usually recommended to test the model. Based on the recommendation that the ratio between sample size and free parameters should be 20:1.[25] The number of free parameters to be estimated in this study was 19. Thus, the study sample of 396 participants clearly satisfied the minimum sample size of 380. Then, the distribution of participants in each hospital setting was calculated based on the probability proportional to size sampling[26] that was appropriate for an unequal number of CRC population in each hospital. The participants were recruited from among the outpatients at the surgical and oncology clinic on the basis on the following inclusion criteria: (1) patients aged 18 years or older; (2) diagnosis with CRC and treatment with colon or rectal resection at least six weeks before the study; (3) stage I–IV cancer; (4) ability to understand and answer the questionnaires; and (5) knowledge of their diagnosis of cancer. In addition, the primary family caregivers were selected on the basis on the following inclusion criteria: (1) family caregivers aged 18 years or older; (2) identification as a family member; (3) duties as a primary family caregiver (the person who provided the majority of unpaid, informal care); (4) ability to communicate; and (5) provision of care for postoperative CRC patients who meet the inclusion criteria and are willing to participate in the study.

Data collection

The data were collected with standard questionnaires by the researcher. Approximately six weeks following discharge, the researcher was introduced to eligible participants and a) provided a written and verbal explanation of the project; b) obtained written consent for participation including consent to access the patients' medical record; and c) asked participants to identify a primary family

caregiver. Data collection took approximately 50 minutes for each participant. The instrument for data collection was a questionnaire consisting of the following seven parts:

Demographic characteristics were obtained, including age, sex, marital status and stage of cancer.

Health-related quality of life was measured by the Quality-of-Life Questionnaire C30, version 3.0 (EORTC QLQ-C30) of the European Organization for Research and Treatment of Cancer. This instrument was translated into Thai by Chatchawan Silpakit and Colleagues. Cronbach's alpha coefficient of the Thai version of the EORTC QLQ-C30 was 0.7.[27] This tool comprises 30 questions that correspond to five functioning scales, eight symptoms scales and the global health and financial impact of the disease and treatment. In the present study, the Cronbach's alpha of the reliability coefficient was 0.82.

Postoperative complications were measured on the basis of the Clavien–Dindo classification, which was developed by Clavien et al.[28] and translated into Thai by Chanutphorn Rattanamongkol and Colleagues. The content validity index (CVI) value of the Thai version of the Clavien–Dindo classification was 0.92. This tool was graded from I to V, which is based on the treatment required for any given postoperative complication. Severe complications were defined as those classified as Grade III or IV.[29] To improve reporting of postoperative complications, the comprehensive complication index (CCI) was designed by Slankamenac et al.[29] The CCI was calculated using the online with free access at www.assessurgery.com.[29] The CCI is thus a summation of all the postoperative complications in a continuous scale ranking from 0 (no complications) to 100 (death).

Healthcare service after CRC surgery was measured using the Healthcare Service after CRC Surgery Questionnaire. This tool was developed by the researchers. The instrument is composed of 39 items and focuses on symptom management support, skills-training service, psychosocial support, access to health care, continuity of information, continuity of management, continuity of the relationship and effectiveness of the service with scores ranging from 1 to 5; higher scores mean better services than lower scores. In the present study, the content validity index (CVI) value of this instrument was 0.92. In addition, the Cronbach's alpha of the reliability coefficient was 0.83.

The model of follow-up care was measured using the Model of Follow-up Care Questionnaire. This tool was developed by the researcher and covers the following three aspects: a) follow-up outpatient clinic, b) follow-up outpatient clinic and a telephone visit, and c) follow-up outpatient clinic and a home visit. The patients in this study received follow-up under one of several follow-up models. The questions are answered "received" or "not received". In the present study, the CVI value of this instrument was 0.80.

Self-management capacity was measured with the Patient Activation Measure (PAM), which was developed by Hibbard et al.[30] and translated into Thai by Choocherd and Wanitkun. The Content Validity Index (CVI) value of the Thai version of the PAM was 0.92. The PAM provides an assessment of the potential or capacity of patients to be engaged in health care from three aspects of disease self-management, including patient knowledge, skills and confidence. The response categories of the 13-item scale ranged from strongly disagree to strongly agree and "not applicable." This tool has a scoring range between 0 and 100, with higher scores indicating better self-management capacity. In the present study, the Cronbach's alpha of the reliability coefficient was 0.83.

Comorbidity was measured by the Charlson Comorbidity Index (CCI). This tool was translated into Thai version by Utriyaprasit.[31] The CCI score included 19 different medical conditions and each comorbid condition ranges from 1 to 6 points. The CCI was calculated as based on the total points for each comorbidity.

Nutritional status was measured by the nutritional risk screening tool (NRS-2002). This tool was developed by Kondrup et al.[32] This tool consists of a nutritional status score based on weight loss, food intake, body mass index (1-3 points), a severity of disease score (1-3 points) and an age adjustment for patients older than 70 years (+1). The total NRS 2002 score ranges from 0 to 7, and a score of ≥3 denotes nutritional risk.

Social support was measured with the Multidimensional Scale of Perceived Social Support (MSPSS), which was developed by Zimet et al.[33] and translated into Thai by Tinakon Wongpakaran and Colleagues, while a trial with 152 psychiatric patients had a Cronbach's alpha of the reliability coefficient was 0.87.[34] This tool consists of a 12–item scale that assesses the perception of social support from family, friends and a significant other. Each of the three subscales was assessed with four items. Each item was based on a 7–point Likert–type response format ranging from one (very strongly disagree) to seven (very strongly agree). High scores indicated better social support. In the present study, the Cronbach's alpha of the reliability coefficient was 0.80.

The researcher collected data from the primary family caregiver at outpatient clinics. The instrument for data collection was a questionnaire consisting of

two parts as described below. Demographic of primary family caregivers were obtained and included age, sex, marital status and relationship status.

Primary family caregiver support was measured by the Primary Family Caregiver Support Questionnaire. This instrument was developed by the researcher and covers the following five aspects: physical care, symptom management support, psychosocial support, advocating role and health resource accessibility. Scores range from 1 to 5 points, in which high scores indicate that the activity is more consistent than lower scores. In the present study, the CVI value of this instrument was 0.95. In addition, the Cronbach's alpha of the reliability coefficient was 0.93.

Data analysis

Data analyses were conducted by using SPSS software (Version 18, SPSS, Chicago, IL) and AMOS statistical package (version 26.0) and were based on an iterative process of adding significant pathways and removing variables that did not add significantly to the model's fit. The path coefficient and the causal relationship between the variables were tested by SEM.

RESULTS

Patient dimensional factors

The total number of postoperative CRC patients in this study was 396. More than half of the participants (51.1%) were male. The mean age was 60.58±11.13 years (ranging from 20 to 86 years). Pathological reports classified 3.5% of tumors as Stage I, 14.9% as Stage II, 44.7% as Stage III and 36.9% as Stage IV. Comorbidities were present for 180 participants (45.5%) and mild levels of comorbidity severity were common (36.7%). According to the NRS 2002, there were 265 participants (66.9%) at nutrition risk.

Health-related Quality of Life (HRQoL) of CRC patients

In the EORTC QOL–C30, the overall HRQoL mean score was 49.0±21.9 for the respondents, indicating that the majority of the patients with CRC surgery had a moderate HRQoL. In addition, for the functional scales of the EORTC QOL–C30, the mean score was highest for role functioning (95.3±16.48), followed by cognitive functioning (90.7±15.81), physical functioning (82.3±18.11), emotional functioning (78.6±23.27) and social functioning (67.9±31.37). On the symptom scales, the participants had lower median-symptom scores on fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhea. Scores for these symptoms were in contrast with financial difficulties, for which the scale showed a higher score in HRQoL with a median score of 33.3 (IQR: 0.0–66.6) (Table 1).

TABLE 1. Health–related quality of life characteristics of CRC patients as based on EORTC QOL–C30 assessment (N=396)

Domains	Range	Mean±SD	Median(IQR)
Global health status/QOL	0-100	49.0±21.9	50.0(33.3-66.6)
Functional scales*			
Physical functioning	0-100	82.3±18.11	86.7(73.3-93.3)
Role functioning	0-100	95.3±16.48	100(100-100)
Emotional functioning	0-100	78.6±23.27	83.3(66.6-100)
Cognitive functioning	0-100	90.7±15.81	100(83.3-100)
Social functioning	0-100	67.9±31.37	75.0(50.0-100)
Symptom scales/items**			
Fatigue	0-100	24.4±17.8	22.0(11.1-33.3)
Nausea and vomiting	0-100	8.3±18.3	0.0(0.0-0.0)
Pain	0-100	11.9±17.5	0.0(0.0-16.6)
Dyspnoea	0-100	12.4±19.3	0.0(0.0-33.3)
Insomnia	0-100	27.7±34.2	0.0(0.0-33.3)
Appetite loss	0-100	24.1±32.9	0.0(0.0-33.3)
Constipation	0-100	12.5±24.2	0.0(0.0-33.3)
Diarrhea	0-100	15.5±27.6	0.0(0.0-33.3)
Financial difficulties	0-100	42.1±39.0	33.3(0.0-66.6)

IQR, inter-quartile range

* Higher score on functional scale indicates a better level of functioning

** Higher score on symptom scale indicates a higher degree of symptoms

Postoperative complications

One hundred and twenty-three participants (31.1%) had one or more of the complications. Among these participants, 102 (25.8%) had less severe complications (grade I to II), whereas 21 participants (5.3%) had severe complications (grade ≥ III). The mean CCI of participants with the complication severity was 20.8±9.5. In the complications group, postoperative complications were highest in the first week after discharge 66 (55.5%) and declined steadily by the second, third and fourth weeks to 27 (22.7%), 11 (9.2%), and 4 (3.4%) respectively. The most frequent complications were wound infections (12.6%).

Description of the study variables

The mean score for self-management capacity was 60.61±0.71. Most of the participants (66.6%) reported a Level ≥3 self–management capacity at six weeks following hospital discharge. Each factor in healthcare service following CRC surgery was analyzed, and it was found that the mean scores for symptom management support, skill-training service, psychosocial support, treatment accessibility, continuity of information, continuity of management, continuity of relationship and service effectiveness were 2.90±0.90, 1.48±0.83, 2.15±0.89, 3.80±0.65, 4.06±0.80, 3.93±0.81, 3.98±0.79 and 4.06±0.55, respectively. Moreover, the total mean score of social support was 60.04 ± 12.18. Participants had the highest degree of support from their families (25.73±3.41). The primary family caregiver support score was frequently measured in terms of five domains, namely, the mean scores on the physical care, symptom management support, psychosocial support, advocate role and health resource accessibility domains. Scores in these domains were based on frequently performed activities and were evaluated as 3.51±0.80, 3.45±1.11, 3.81±0.91, 3.29±1.61, and 3.67±0.98, respectively (Table 2).

Model of follow-up care following CRC surgery

Following discharge, 80.1% of the participants received follow-up at the outpatient clinic only. The participant visits (40.4%) at the clinic tended to occur 8-to-14 days after their discharge. The median number of follow-up appointments within a sixweek period was 3 (IQR, 2 to 4). As regards clinic follow-up visits, participants (48.6%) received follow-up care from a general surgeon, a medical oncologist and a registered nurse, inclusively. In addition, thirty-two participants (8.1%) received both outpatient-clinic visits and telephone follow-up calls. The median time to the telephone follow-up calls was 22.5 days (IQR, 22.5 to 30.7). Of 32 participants, 19 (59.4%) received a telephone call from their oncology specialist nurses and follow-up care by a general surgeon, a medical oncologist and a registered nurse. Forty participants (10.1%) received home visits, in addition to outpatient-clinic follow–up. The majority of the first home visits (62.5%) occurred within 1 to 7 days, and the median time to first home visits was 7 days (IQR, 7 to 14). Most home visits were provided by a registered nurse from the local sub-district health promotion hospital (42.5%). In addition, the majority of participants (90%) received a follow–up care model from their general surgeons, medical oncologists and registered nurses.

Relationship between study variables and HRQoL

The structure equation model was implemented to examine the effects of follow-up care, healthcare service after CRC surgery, postoperative complications, primary family caregiver support, social support, self-management capacity and patients' dimensional factors (age, co-morbidity, nutrition status and stage of cancer) on HRQoL in a hypothesized model by using the AMOS statistical package (version 26.0). Table 3 presents the hypothesized model which did not fit with the empirical data and the poor goodness-of-fit coefficient. Therefore, the hypothesized model (Fig 1) was revised by deletion of non-significant paths between variables and the addition of paths, as indicated by modification and GFI indices. Fig 2 shows the paths leading from co-morbidity, social support, follow-up outpatient clinic, follow-up outpatient clinic and telephone visit, follow-up outpatient clinic and a home visit to both HRQoL and postoperative complication, which were deleted in the final model. Inspection of the modification indices suggested that the path of nutrition status to social support would lead to an improvement of the model with a better fit than the hypothesized model. In addition, the covariance parameters should be placed between e3 and e5, and between healthcare service after CRC surgery and the follow-up outpatient clinic. The final modified model has an adequate fit (χ^2=40.347 (df=28, p=0.062), GFI=0.980, CFI=0.959, RMSEA=0.033) without the input of correlated error measurements of observed variables (Table 3).

The final model is shown in Fig 2 and Table 4. Age (ß =–0.12, P<0.05), stage of cancer (ß = 0.13, P<0.01), self-management capacity (ß =–0.12, P<0.05), healthcare service after CRC surgery (ß =–0.14, P<0.01) and postoperative complication (ß =0.23, P<0.01) had direct effects on HRQoL. Nutritional status (ß = 0.04, P<0.01), creation of stoma (ß = 0.03, P<0.01), healthcare service after CRC surgery (ß = -0.07, P<0.01) and follow-up outpatient clinic (ß =–0.03, P<0.01) had indirect effects on HRQoL

TABLE 2. Self–management capacity, healthcare service, social support and primary family caregiver support after CRC surgery of patients with CRC surgery (N=396)

Scale items	Number (%)	Range	Mean (SD)
Self–management capacity			
Level 1 (score ≤47.0)	74(18.7)		
Level 2 (score 47.1–55.1)	58(14.7)		
Level 3 (score 55.2–67.0)	132(33.3)		
Level 4 (score ≥67.1)	132(33.3)		
Mean=60.61, SD=0.71, range=25.70–100			
Healthcare service after CRC surgery			
Symptom management support		1-5	2.90 (0.90)
Skills training service		1-5	1.48(0.83)
Psychosocial support		1-5	2.15(0.89)
Treatment accessibility		1.75-5.00	3.80(0.65)
Continuity of information		1-5	4.06(0.80)
Continuity of management		1-5	3.93(0.81)
Continuity of the relationship		1-5	3.98(0.79)
Effectiveness of the service		2.20-5	4.06(0.55)
Social support			
Family		4-28	25.73(3.41)
Friends		4-28	15.16(8.11)
Significant other		4-28	19.16(5.18)
Total score of social support		24-84	60.04(12.18)
Level of perceived social support			
Low		75(18.9)	
Moderate		201(50.8)	
High		120(30.3)	
Primary family caregiver support			
Physical care		1.17-5.00	3.51(0.80)
Symptom management support		1-5	3.45(1.11)
Psychosocial support		1-5	3.81(0.91)
Advocate role		1-5	3.29(1.61)
Health resources accessibility		1-5	3.67(0.98)

SD, standard deviation

TABLE 3. Statistical fitted index values of hypothetical model and final modified model (N=396)

	χ^2(df)	χ^2/df	GFI	CFI	RMSEA	SRMR
Hypothetical model	1056.991 (df = 58,	18.22 P<0.001)	0.842	0.194	0.209	3.670
Final modified model	40.347 (df = 28,	1.44 P=0.062)	0.980	0.959	0.033	3.570

Abbreviations: df degree of freedom; GFI goodness of fit index; CFI comparative fit index; RMSEA root mean square error of approximation; SRMR standardized root mean square residual

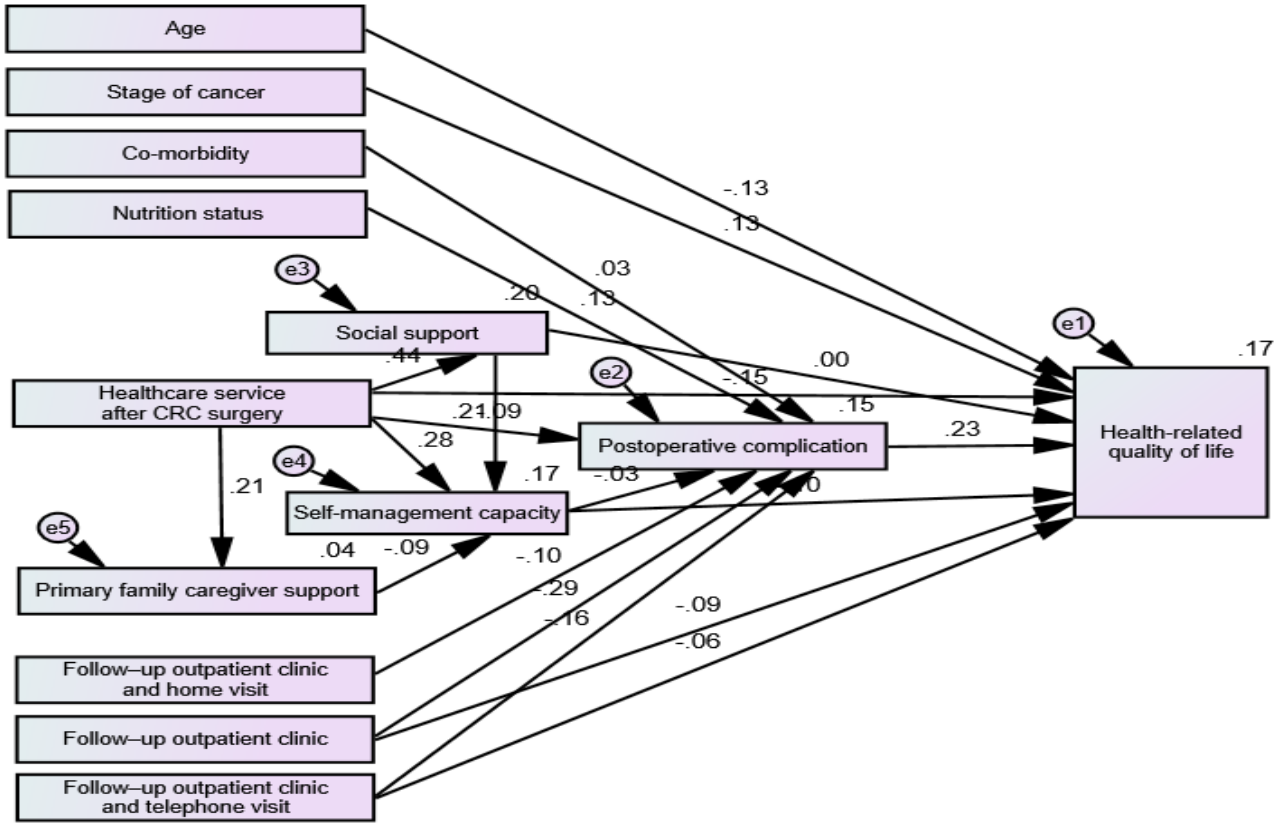

Fig 1. Hypothesized model: relationships between model of follow-up care, healthcare service after CRC surgery, postoperative complication, primary family caregiver support, social support, self–management capacity, patients' dimensional factors and HRQoL in hypothetical model.

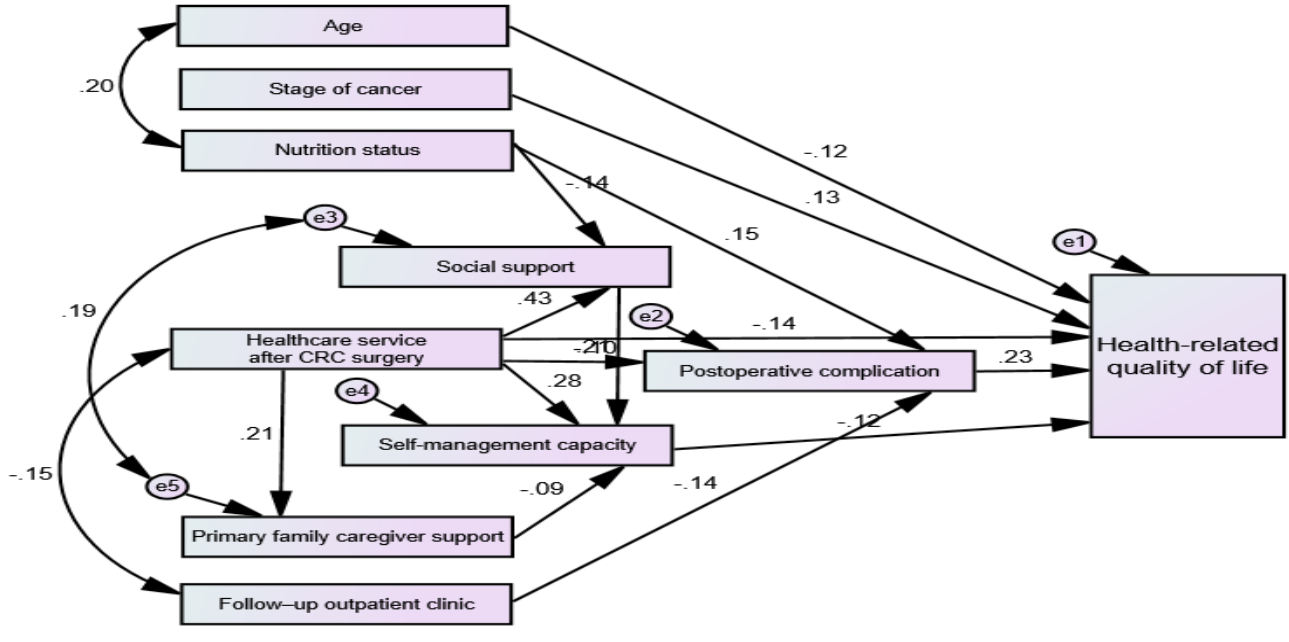

Fig 2. Final modified model: relationships between model of follow-up care, healthcare service after CRC surgery, postoperative complication, primary family caregiver support, social support, self–management capacity, patients' dimensional factors and HRQoL in final modified model.

TABLE 4. Direct effect, indirect effect, and total effect of study variables in the final modified model.

Endogenous (dependent) variable	Exogenous (independent) variable	Direct effect	Indirect effect	Total effect
HRQoL	Age	-0.12*	-	-0.12*
	Stage of cancer	0.13**	-	0.13**
	Postoperative complication	0.23**	-	0.23**
	Healthcare service after CRC surgery	-0.14**	-0.07**	-0.21**
	Self-management capacity	-0.12*	-	-0.12*
	Follow-up outpatient clinic	-	-0.03**	-0.03**
	Primary family caregiver support	-	0.01*	0.01*
	Social support	-	-0.02*	-0.02*
	Nutrition status	-	0.04**	0.04**
Postoperative complication	Follow-up outpatient clinic	-0.14**	-	-0.14**
	Nutrition status	0.15*	-	0.15*
	Healthcare service after CRC surgery	-0.10*	-	-0.10*
Self-management capacity	Social support	0.21**	-	0.21**
	Healthcare service after CRC surgery	0.28**	0.07**	0.35**
	Primary family caregiver support -0.09*	-	-0.09*	
Social support	Healthcare service after CRC surgery	0.43**	-	0.43**
	Nutrition status -0.14**	-	-0.14**	
Primary family caregiver support	Healthcare service after CRC surgery	0.21**	-	0.21**

*p<0.05, **p<0.01, ***p<0.001

through the postoperative complications. Moreover, social support (ß = -0.02, P<0.05), primary family caregiver support (ß =0.01, P<0.05) and healthcare service after CRC surgery (ß = -0.07, P<0.01) had indirect effects on HRQoL through self–management capacity.

DISCUSSION

This study provides a comprehensive model for postoperative CRC survivors that illustrates the relationships among the model of follow-up care, healthcare service following CRC surgery, severity of complication, primary

family caregiver support, social support, self–management capacity, patients' dimensional factors and HRQoL in patients undergoing CRC surgery. Postoperative complications were shown to have a significant direct effect on HRQoL, while nutritional status, healthcare service following CRC surgery and the follow–up outpatient clinic were shown to have a significant indirect effect through postoperative complications. This result may indicate that 123 (31.1%) participants developed one or more postoperative complications. The most frequently encountered complications were wound infections (16.9%). A previous study found that patients with postoperative complications have poorer HRQoL and suffer from pain, insomnia and problems eating than patients without complications.[35] The results of this study show that nutritional status (ß=0.15, P<0.05) had significant positive direct effects on postoperative complications, possibly because the prevalence of participants at malnutrition was 269 (66.9%). Malnutrition was an independent risk factor for anastomotic leakage, wound dehiscence and wound infection following CRC surgery.[36] The finding revealed that comorbidities did not have significant direct or indirect effects on HRQoL. A possible reason for this finding is that the participants (54.5%) had no comorbidities. In addition, 36.7 percent of the participants had mild comorbid severity. As a result, comorbidity had no significant direct effect on postoperative complications.

Not surprisingly, this study showed that the type of follow–up outpatient clinic has a direct effect on postoperative complications. This result might be because postoperative complications were highest in the first week following hospital discharge (55.5%). Visits from participants (40.4%) at the clinic tended to occur from 8 to 14 days after discharge. Of the patients who made follow-up visits at the clinic, most (48.6%) received follow-up care from a general surgeon, a medical oncologist and a registered nurse. According to a previous study, shorter waiting times from symptom onset following discharge to first contact with health-care professionals increased quality of life.[14] As a result of the healthcare service they received following their CRC surgeries, the majority of the participants reported good service in the areas of treatment accessibility, continuity of information, continuity of management, continuity of relationship and effectiveness of services provided. As previously reported, continuity of care was significantly associated with an improvement in physical functioning, role functioning, general health and emotional functioning.[37] Accordingly, the results show that the healthcare service received after CRC surgery had a significant direct effect on HRQoL.

Although several studies revealed that the follow-up outpatient clinics and telephone visits, as well as follow-up home visits, have a direct effect on HRQoL[38,39], these actions were not shown to have a statistically significant direct effect on HRQoL in this study, but merely mediated the ensuing post-operative complications. As regards telephone follow-ups, a possible reason for this finding is that the median time to the first discharge call was 22.5 days (IQR, 22.5 to 30.7). During each phone call, a nurse would assist the patient in coordinating his/her appointments, as well as chemotherapy treatments, and in dealing with possible side–effects. Acher et al. (2017) suggested that a telephone follow-up within 48 to 72 hours after discharge with continued calls every three to four days can identify early health problems and social difficulties before patients enter a critical stage, thereby reducing postoperative complications.[40] As regards home visits, the median time to the first home visit was seven days. However, the participants reported the lowest median score on the subject of management continuity, thereby indicating very poor continuity of management in surgical-wounds care. This result may have been influenced by the average distance of 47.95 kilometers from a village to a hospital providing treatment. Thus, the participants would need to use public transportation in order to access medical care.[41]

Self-management capacity was shown to have a significant relationship with HRQoL. The participants who reported higher self-management capacity perceived a higher HRQOL. One possible reason for these findings was that the majority of the participants (66.6%) reported level ≥3 self-management capacity during their postoperative periods, a level indicating that the majority of the participants felt confidence in managing their health and were ready to make behavioral changes as they adopted new behaviors to support their health. These findings were similar to those of previous studies, which found that the patients with higher self-management capacity were at an advantage, since their self-management abilities were significantly and directly related to a greater quality of life and better overall health status.[42]

Social support is an important factor in Thai society.[43] In this study, the participants with higher social support had higher self-management capacity, possibly because the participants had the highest degree of support from their families (25.73±3.41). The social environment is an important determinant for the ability of patients with CRC in their efforts to cope with stressful situations during times of illness. Previous literature has indicated

that patients with high levels of social support had 2.23 times higher levels of self-management capacity than individuals reporting low levels of social support.[44] Another important factor that had significant, positive, direct effects on self-management capacity in this study was primary family caregiver support. This result may have come about because most caregivers (52.9%) were in a spousal or partnered relationship with the patients. In Thai culture, the primary family caregivers normally played significant roles in looking after their older relatives, especially when they were sick.[45] Accordingly, the participants in this study were more advanced in age, resulting in a higher HRQoL. When considering the primary family caregiver support, most family caregivers often arranged for the patients to receive sufficient food. As regards psychosocial support, the family caregivers often provided support to the patients and thus bolstered their efforts to manage their own health problems. In this way, the caregivers gave their patients the perception that they were their own health supporters and helped them to meet with their peers and neighbors. Furthermore, caregivers often provided health resource accessibility. Therefore, higher family caregiver support is significantly associated with a higher level of patient self-management.[42] Therefore, the caregivers played significant roles in looking after their older relatives, especially when they were sick (Subgranon & Lund 2000, Jullamate et al. 2007 the participants in this study had a higher age level leading to higher HRQoL.

CONCLUSION

From the results of this study, it was found that CRC patients suffer mostly from postoperative complications during the early phase. For that reason, the health service system, which is intended to promote the HRQoL of CRC survivors, should address this situation by selecting the most effective models of follow-up care. Especially in cases of malnutrition, there needs to be early efforts underway to prevent complications, together with clinical-practice guidelines and adequate healthcare service following CRC surgery. Only in this way will it be possible to provide the specific follow-up care that needs to be developed in order to support improved HRQoL of CRC survivors.

Conflict of interest: There are no conflicts of interest.

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Visual Inspection of Non-Prescription Monthly Colored Contact Lenses: Safety Issues for Contact Lens Wearers

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ABSTRACT

Objective: To survey the prevalence of non-prescription monthly colored contact lenses (CL) defects in an electronic marketplace (e-marketplace) in Thailand using visual inspection (VI).

Materials and Methods: This cross-sectional study included the 252 items listed from 23 online shops in an e-marketplace in Thailand during April 2021. Online customer reviews for each shop were examined and complaints regarding colored CL product defects, delivery, services and abnormal symptoms after use were collected. Product packing and visible internal and external product characteristics were visually inspected under sufficient light for the prevalence of defects by three examiners.

Results: Sixteen out of twenty-three online shops (69.57%) had customer complaints. Wrong delivery was the most common complaint (60.87%). Five characteristics of product defects were described by customers, of which abnormal scratches/marks on CL (8.70%) was the most common. Abnormal symptoms after use were found in 43.84% of the shops. Two hundred and thirty-seven pairs of colored CL (94.05%), 470 vials and four blisters from 19 shops were examined. Defective products were found to be 8.02%. The most common visible external and internal product defects were dirty products (3.80%) and foreign bodies in the original sealed manufacturer's containers (1.90%), respectively. Other defects, e.g. scratched or peeling label, incompletely closed aluminum cap, surface wear of CL, abnormal scratches or marks on CL and immobility of CL in solution were also found.

Conclusion: Non-prescription monthly colored CL in the e-marketplace have many visible defective characteristics that CL wearers should be concerned about. This study suggests that VI of CL products before use may be an important potential safety factor for CL wearers.

Keywords: colored contact lens, e-marketplace, defective product, dirty product, foreign body (Siriraj Med J 2021; 73: 587-593)

INTRODUCTION

Nowadays, the Centers for Disease Control and Prevention (CDC) warns about the risks to sight and eye health from using non-prescription colored contact lenses (CL).[1] In Thailand, these colored CL which are approved for permission by Thai Food and Drug Administration (FDA), are still found freely sold in the flea markets, on streets and at beauty shops.[1-4] It is noticeable that many colored CL are also sold in electronic marketplaces (e-marketplaces). The self-care process and awareness of Thai CL wearers are important in this situation due to there being no laws to regulate the sellers and no monitoring system for CL dispensation.[2,5]

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Visual inspection (VI) is a manual activity that involves careful and critical assessment of an object with reference to a predefined standard.[6] VI has been proposed for the detection and minimization of the introduction of unintended particles in various situations, e.g. industry, parenteral product vials and pharmaceutical products.[6-8] Compromised or defective products should be rejected due to the risk to sterility. Although there is a continuous process of improvement by manufacturers to meet the goal of zero defects, the defects still occur. In addition, the probabilistic nature of the human inspection process has limitations, especially concerning particles or foreign bodies less than 200 μm in diameter.[9]

Complications from CL use regarding CL-related microbial keratitis were found among CL wearers.[10-16] Recent studies have demonstrated many product defects and contaminations in the original sealed manufacturer's containers, e.g. expired products, dirty products, turbidity of fluid surrounding the CL, foreign bodies and bacterial contamination.[17-19] Purchasing colored CL from an e-marketplace is questionable with regard to the quality and sterility of these products. To investigate the presence of visible monthly colored CL defects in the e-marketplace, we conducted the current study to survey the prevalence and defective characteristics of non-prescription monthly colored CL in Thailand's e-marketplace. The results of this study can provide information to CL wearers that will help them avoid using CL with these visible defects that might result in the risk to eye health and sight.

MATERIALS AND METHODS

This study was a cross-sectional study and conducted in accordance with the Declaration of Helsinki, approved by the Committee for the Protection of Human Participants in Research, Ubon Ratchathani University, Thailand [UBU-REC-46/2564]. The primary objective of this study was surveying the prevalence of defects of non-prescription monthly colored contact lenses in an e-marketplace by using the VI technique.

The subjects recruited in this study were the monthly colored contact lens items that are sold on an e-marketplace website in Thailand during April 2021. To find the total amount of monthly colored CL items, we used the keywords of "contact lenses" combined with the settings in the related categories bar, which were colored contact lenses, zero power and monthly contact lens usage. The sample size in this study was calculated with Yamane's formula, and sampling was done by the systematic random sampling method. All online shops underwent shop characteristic assessment, including the period of time that they had been opened, types of monthly colored CL and customers' complaints about the colored CL, e.g. defective CL products, delivery, services and abnormal symptoms after use, via the online customer reviews.

All the samples were ordered from the website and sent by postal delivery. In the parcel boxes, the CL products from each shop were assessed for the packing methods. Each of the CL products were examined in a sufficient light room using VI by three examiners, an ophthalmologist, a pharmacist and a scientist. All of the examiners had normal color vision according to the Ishihara's test, as well as near and distant visual acuity with correction to 20/20 in both eyes. A result of 2 out of 3 opinions were considered a consensus regarding each variable. All CL products in their original sealed manufacturer containers were assessed for three parts. The first part was general product details, e.g. prices, brands, countries of manufacture and CL materials, which were assessed by observing the information on the CL boxes, labels and medical device documentation (MDD) and 2) the external product characteristics, e.g. packaging, FDA number, expired products, scratched or peeling of the labels, unclear/unreadable labels, unclear/unreadable MDD, application of other labels that obscure text, broken packages, dirty products and integrity of aluminum capping for the vial, were observed. In the third part, the internal product characteristics, e.g. clarity of the solution, sediment, amount of CL, scratches or marks on CL surface, surface wear of CL, CL movement in solution, visible foreign bodies and evidence of used CL in the CL case, were also observed. For the internal product characteristic examinations, we looked through the containers from the bottom up with diffused light across the inspection zone. The time used for inspection was at least 20 seconds per sample. Slow careful swirling of the CL solution and avoidance of making the air bubbles within the container were done for observation of the motion of any foreign body and its characteristics. If the position of a foreign body was uncertain, removal of the label was done to distinguish between the outside and inside foreign body. To confirm the findings for "immobility of CL in solution", we used the technique of turning the container upside down and slightly shaking it three times. If there was no free movement of the CL in the solution, it was classified as "immobility of CL". The images in this study were recorded with a smart phone (Samsung® Galaxy Note 20, Vietnam).

Statistical analysis: A descriptive analysis of categorical variables was presented as absolute frequency and percentages. Means ± standard deviations were used to summarize the continuous variables in this study.

RESULTS

There were 678 items listed that were found from searching with the keywords in the e-marketplace in Thailand. The results of the sample, 252 items listed from 23 online shops, were included in this study. Most of the shops (47.83%) had been open less than one year and about 3 out of 5 shops sold colored CL only for decorative purposes. Sixteen out of twenty-three online shops (69.57%) had complaint messages in their online customer reviews from customers who purchased monthly colored CL. The most common complaint was wrong delivery (60.87%). There were five characteristics of product defects, which were abnormal scratches/marks on CL (8.70%), surface wear of CL (4.35%), missing CL (4.35%), used CL found in CL case (4.35%) and unspecified external defect (4.35%) (Table 1). CL wearers from 10 online shops (43.84%) had posted reviews about their abnormal symptoms after use of colored CL, which were foreign body sensation, burning sensation, ocular pain, ocular discomfort, dryness, tearing, red eye, dizziness and loose CL fitting (Table 2).

Two hundred and thirty-seven pairs of monthly colored CL (94.05%) from 19 shops (82.61%) were sent via postal delivery. There were 15 items from four shops that were cancelled by the sellers. Air bubble wrapping was the most common method that the shops used for shock-proofing the CL product(s) (89.47%). Plastic bags and plastic trays were used for product packing via postal delivery at about 47.37% and 10.53%, respectively. Only three out of 19 shops (15.79%) sent CL boxes to the customers, and some of the CL (13.14%) were paired with a rubber band around the vial neck. Contact lens packing in the parcel boxes is shown in Fig 1A - C.

Twelve brands, 470 vials and four blister packs of CL made from 2-hydroxy-ethyl methacrylate (HEMA) hydrogel were examined (Table 3). All of the CL products were imported from Korea and Taiwan with import approval by the Thai FDA. The average cost of a pair of CL was 99.36 ± 58.47 baht. Defective products were found in 38 out of 474 samples (8.02%). Dirty products were found to be the most common problem of the external product defects, 0.84% of the samples had scratched or peeling labels, and 0.21% of the vial containers had incompletely closed aluminum caps (Fig 1D - F).

The most common problem of the internal product defects was a foreign body in the original sealed containers (1.90%). Immobility of CL in solution when upside down and shaken, surface wear of the CL, and abnormal scratches/marks on CL were also found, as shown in Fig 2A - C. Regarding foreign bodies in the original sealed containers, dot-like foreign bodies were the most common type of foreign body, which were found in 7 out of 9 samples (77.78%). Thread-like foreign bodies were found having both white and black color (Fig 3).

DISCUSSION

This study demonstrated that non-prescription monthly colored CL in an e-marketplace in Thailand have seven characteristics of both visible external and internal product defects. Visible foreign bodies in their original sealed CL containers were the most common internal product defect with a prevalence of 1.90%. Dirty products were the most common external product defect (3.80%) similar to the previous research from beauty shops and flea market conducted in Thailand.[2] Introduction of a foreign body into the eyes may result in mechanical effects on the ocular surface, eye infection or specific reactions depending on the type of foreign bodies.[15,20] Surface wear of the CL can be found at 0.21%, which may lead to its edge scratching the cornea and causing corneal abrasion.[15] This study found that the sticking of CL to the bottom of the container causes the immobility of CL in solution. The CL may lose its shape and cause eye irritation when applied to the eyes.[2,15] Abnormal scratches or marks on CL and incomplete closure of aluminum caps for vials were also be found. All of these visibly defective products should be rejected by the CL wearers due to the lack of sterility and the risk of eye irritation, eye injury and even eye infection that could possibly occur.[2,9,15-16] Comprehensive VI of the external and internal of CL products to detect these visible defects before use may be the potential safety factor for the CL wearers.

Five defective characteristics of CL products were described in online customer reviews, which were abnormal scratches/marks on CL (8.70%), surface wear of CL (4.35%), missing CL (4.35%), finding used CL in CL case (4.35%) and unspecified external defects (4.35%). A foreign body in the original sealed container was found to be the most common internal product defect in this study, while there was no report of this defect by the customers. From this point, we speculate that most CL wearers were not aware of this existing small defect and thus, did not detect it. Human VI for detection of product defects involves tacit knowledge that is influenced by many factors.[6] Although VI is tedious, time-consuming and highly dependent on the inspectors' experiences, conditions or moods[8], it still crucial for CL wearers in this situation. To develop the VI tacit knowledge of CL wearers, the improvement of providing information, e.g. transferring the comprehensive knowledge about CL products, well written VI standards regarding pictures

TABLE 1. Complaints about CL product, delivery and services in online customer reviews [23 shops]

Variables	Frequency	Percent (%)
External CL products		
No medical device documentation	0	0.00
No FDA number	0	0.00
Expired product	0	0.00
Scratched or peeling label	0	0.00
Unclear/unreadable label	0	0.00
Unclear/unreadable medical device documentation	0	0.00
Application of other labels that obscure text	0	0.00
Broken package	0	0.00
Dirty product	0	0.00
Incomplete closed aluminum cap for vial	0	0.00
External defect, unspecified	1	4.35
Internal CL products		
Non-clear solution	0	0.00
Sediment	0	0.00
Missing CL in container	1	4.35
Abnormal scratch/ mark on CL	2	8.70
Surface wear of CL	1	4.35
Immobility of CL in solution	0	0.00
Foreign body in container	0	0.00
Used CL found in CL case	1	4.35
Delivery and services		
Delayed delivery	9	39.13
Wrong delivery	14	60.87
Poor product packing	1	4.35
Damaged parcel	1	4.35
Missing item	6	26.09
Missing CL case	1	4.35
Seller services	2	8.70
unsatisfied, unspecified	9	39.13

Abbreviations: FDA; Food and Drug Administration, CL; contact lens

TABLE 2. Abnormal symptoms after use colored CL in online customer reviews [23 shops]

Variables	Frequency	Percent (%)
Ocular discomfort	2	8.70
Dryness	2	8.70
Itching	0	0.00
Burning	5	21.74
Fluctuation of vision	0	0.00
Sensitive to light	0	0.00
Foreign body sensation	6	26.09
Tearing	1	4.35
Red eye	1	4.35
Ocular pain	4	17.39
Dizziness	1	4.35
Loose CL fitting	1	4.35

Abbreviation: CL; contact lens

TABLE 3. Product characteristics

Variables	Frequency	Percent (%)
Brands	12	100.00
Countries of manufacture		
Korea	11	91.67
Taiwan	1	8.33
CL materials		
HEMA hydrogel	470	100.00
External product characteristics		
Vial	470	99.16
Blister	4	0.84
No FDA number	0	0.00
Expired product	0	0.00
Scratched or peeling label	4	0.84
Unclear/unreadable label	0	0.00
Unclear/unreadable medical device documentation	0	0.00
Application of other labels that obscure text	0	0.00
Broken package	0	0.00
Dirty product	18	3.80
Incomplete closed aluminum cap for vial	1	0.21
Internal product characteristics		
Non-clear solution	0	0.00
Sediment	0	0.00
Missing CL or more than 1 CL in container	0	0.00
Abnormal scratch/ mark on CL	2	0.42
Surface wear of CL	1	0.21
Immobility of CL in solution	3	0.63
Foreign body in container	9	1.90
Used CL found in CL case	0	0.00

Abbreviations: CL; contact lens, HEMA; 2-Hydroxy-ethyl methacrylate, FDA; Food and Drug Administration

Fig 1. Contact lens packing in the parcel boxes and external product defects
A: air bubble wrap (top), plastic bag (middle), contact lens vials and cases (bottom); B: plastic trays; C: contact lens boxes; D: peeling labels; E: clean product (left) and dirty product (right); F: completely closed (left) and incompletely closed (right) aluminum caps for vials

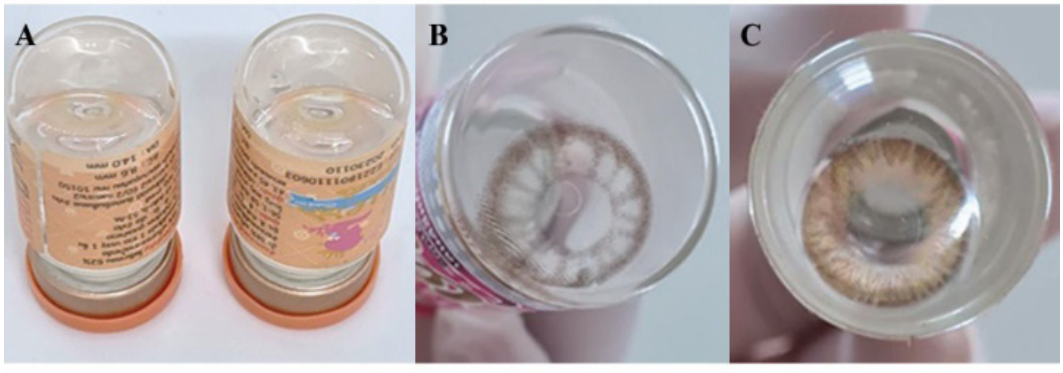

Fig 2. Internal product defects
A: contact lenses sticking to the bottom of vials, B: surface wear of the contact lens (circular shape), C: abnormal circular mark at the center of contact lens

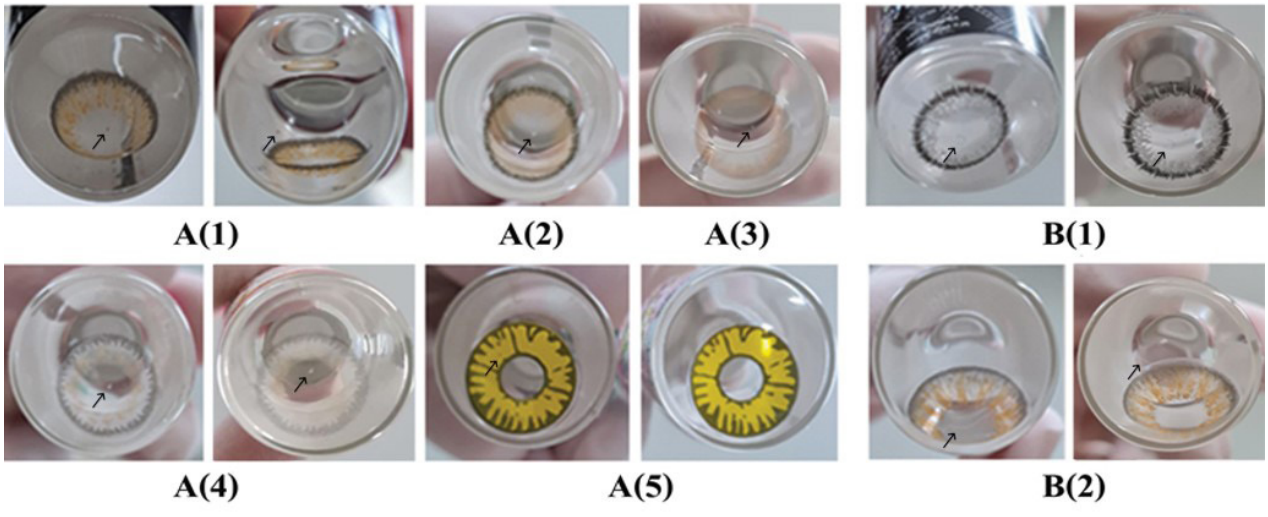

Fig 3. Foreign bodies in original sealed containers
A: Dot-like foreign bodies: A (1) movement of blackish dot-like foreign body when changing vial's position; A (2-4) whitish dot-like foreign bodies, A (5) brownish dot-like foreign body at 10 o'clock (left) compared to normal CL (right); B: Thread-like foreign bodies: B (1) black thread-like foreign body, B (2) white thread-like foreign body

or photographs, defect classification systems, e.g. defect type, defect location and characteristics, are needed.[6]

This study had the advantage of focusing on the visible product defects by VI, which is simulated as the CL wearers' situation with no special equipment required. However, there are some limitations of this study. First, the opinions expressed by customers in online customer reviews may not reflect the exact total of CL wearer problems in the e-marketplace. Some customers may have ignored these defects and did not provide feedback to the sellers via this channel, and some sellers may have edited the negative reviews of customers. Second, blister type CL was found at only 0.84%, which is too small a sample to perform a subgroup analysis between vials and bister containers. Third, microscopic examination and microbial culture were not done in this study, which therefore cannot lead to a conclusion of microbial contamination in these defects. More blister container sampling, microscopic examination and microbial culture should be planned and investigated in further study.

In conclusion, non-prescription monthly colored CL in the e-marketplace have many characteristics of both visible external and internal product defects. Raising CL wearers' awareness in order to make them concerned about these visible defects before use may be a potential safety factor. Most importantly, improvement of VI skills for CL wearers should be done in the correct way.

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Differentiation Between the Aalignant Mesothelioma of Pleura and Pleural Metastasis with Contrast Enhanced CT, Is It Possible?

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ABSTRACT

Objective: To compare CT findings between malignant pleural mesothelioma (MPM) and metastatic pleural disease (MPD).

Materials and Methods: CT chest images of 157 cases of pathologically-proven malignant pleural disease (21 MPM, 136 MPD) were retrospectively reviewed by two radiologists who were blinded to the diagnosis. Findings of interest included pleural effusion, pleural thickening, organ invasion, lymphadenopathy, dominant lung nodule, pulmonary or extra-thoracic organ metastasis, and asbestos-related disease.

Results: Findings commonly found in MPM compared with MPD are circumferential pleural thickening (52.4% vs 14.0%, p<0.001), pleural mass (33.3% vs 7.4%, p<0.001), organs invasion (57.1% vs 9.6%, p<0.001), and asbestos related disease (19% vs 0%, p<0.001).

Conclusions: Circumferential pleural thickening, pleural mass, presence of organ invasion, and CT finding of asbestos-related pleural disease were the CT findings that raise the possibility of MPM.

Keywords: Malignant pleural mesothelioma, pleural metastasis (Siriraj Med J 2021; 73: 594-602)

INTRODUCTION

Malignant pleural mesothelioma (MPM), which is a tumor that arises from the mesothelial lining, is the most common primary malignancy of the pleura.[1] MPM is associated with history of asbestos exposure with a latency period of at least 20-30 years.[2,3] Metastatic pleural disease (MPD) is a secondary malignant process of the pleura that is most commonly due to lung and breast cancers, and it has a higher prevalence compared to that of MPM.[4,5] The clinical presentations of MPD, including dyspnea, chest pain, and weight loss, can also be observed in patients with MPM; however, the treatment and prognosis differ between these two conditions. Treatment for MPM is resection in patients with T1 and T2 (early-stage) disease, and the two-year survival rate is 38-46%.[6] In contrast, the treatment for MPD, which is considered an advanced disease with a median survival ranging from 3 to 12 months, is palliative care.[7,8] It is, therefore, essential that these two diseases be accurately distinguished from each other, and the gold standard method for diagnosis is histopathologic examination.[9,10] However, histopathologic diagnosis requires an adequate tissue specimen[9], and not all patients are sufficiently fit to undergo pleural biopsy. An alternative non-invasive method for differentiating

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between MPM and MPD, such as computed tomography (CT), is therefore needed. Guidelines published in 2018 by the British Thoracic Society (BTS), and in 2020 by the European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS)/European Association for Cardio-Thoracic Surgery (EACTS)/European Society for Radiotherapy and Oncology (ESTRO) (ESR/ESTS/EACTS/ESTRO) task force suggested the usefulness of CT for evaluating MPD, as well as for staging and guidance for tissue diagnosis of MPM.[9,11]

Several CT features have been reported as being helpful for MPM evaluation. Mediastinal pleural thickening, thickening of interlobar fissure, and chest wall or diaphragm involvement were CT features with specificity over 90%; however, the latter two had sensitivity less than 30% for MPM diagnosis.[12-16] Prior studies[17,18] evaluated the use of CT features for differentiating between MPM and MPD. Yoon, et al.[17] reported circumferential pleural thickening and pleural mass to be common features in MPM. In contrast, Mehrdad, et al.[18] reported nodular pleural thickening and contraction of involved hemithorax to be more frequently found in MPM.

The use of CT to differentiate between MPM and MPD would be beneficial due to its non-invasive nature; however, the heterogeneity of the findings and results of previous studies that investigated CT for its ability to distinguish MPM from MPD indicate that more study is needed. Accordingly, we set forth to investigate for features of contrast-enhanced CT that can distinguish MPM from MPD.

MATERIALS AND METHODS

Patients

The protocol for this study was approved by the Institutional Review Board (IRB) and the requirement to obtain written informed consent was waived due to our study's retrospective design. This retrospective chart and imaging review included patients who were diagnosed at our center with pathologically confirmed MPM or MPD during January 2015 to December 2017. The MPD group was subclassified into the two following groups: 1) primary lung cancer with pleural metastasis (PL-PM); and, 2) extrapulmonary cancer with lung metastasis (EP-PM).

Reference standard

Confirmation of all MPM (21 patients) diagnoses was made by histopathologic examination of pleural biopsy. Confirmation of MPD was made by either histopathologic examination of pleural biopsy (63 patients) or pleural cytology obtained from thoracocentesis (73 patients).

CT acquisition and imaging review

Chest CT studies were performed using either a Siemens Dual-Source CT (Siemens Healthineers AG, Erlangen, Germany) or a GE Medical Systems LightSpeed VCT 64 (GE Medical Systems, Chicago, IL, USA). All patients had two axial scan sequences, including pre-contrast and 45-second postcontrast phases with 1.25 mm slice thickness. Coronal and sagittal reformation were also obtained.

The chest CT studies must have been performed within three months before or after the pathology report. Suboptimal imaging quality, such as no contrast medium administration or severe motion artifact, were excluded.

All CT studies were retrospectively reviewed by two thoracic radiologists with 20 and 19 years of experience, respectively. Image reviews were conducted independently, and both reviewers were blinded to the pathological results. The reviewers recorded CT features of interest, including side of lesion, site of lesion in hemithorax, pleural effusion, pleural thickening, adjacent organ invasion, coexisting pulmonary abnormality, lymphadenopathy, extra-thoracic organ metastasis, and mediastinal shift. Any disagreement in image reads that occurred between reviewers was resolved via discussion and subsequent consensus.

The amount of pleural effusion was divided into three groups by visual assessment: small, moderate, and large. Small effusion was defined as effusion occupying less than 1/3 of the hemithorax; moderate effusion was defined as effusion occupying more than 1/3, but less than 2/3 of the hemithorax; and, large effusion was defined as effusion occupying more than 2/3 of the hemithorax. The presence loculated pleural effusion was also recorded.

Pleural thickening was categorized into 4 patterns, as follows: 1) thin, 2) thick/nodular, 3) circumferential, or 4) pleural mass. Thin pleural thickening was defined as smooth pleural thickening with a maximal thickness on axial scan of less than 1 cm, and not involving more than 3/4 of the hemithorax on axial scan. Thick/nodular pleural thickening was defined as pleural thickening with a maximal thickness of greater than 1 cm, but less than 3 cm, and not involving more than 3/4 of the hemithorax on axial scan or discrete pleural nodules. Circumferential pleural thickening was defined as continuous pleural thickening that involved more than 3/4 of the hemithorax on axial scan. Pleural mass was defined as a pleural lesion with a short axis larger than 3 cm on axial CT scan (Fig 1). Site of pleural thickening included peripheral, mediastinal, diaphragmatic aspect of pleura, or interlobar fissure involvement.

Presence of adjacent organ invasion was recorded

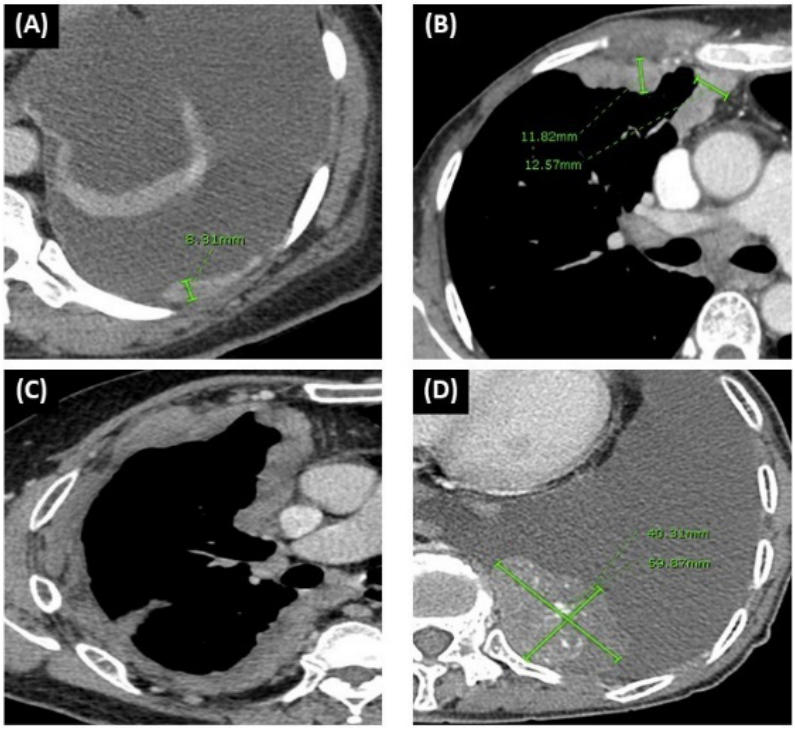

Fig 1. CT scan images show four patterns of pleural thickening. **(A)** *Thin pleural thickening*: smooth pleural thickening with a maximal thickness on axial scan of less than 1 cm, and involving not more than 3/4 of the hemithorax on axial scan. **(B)** *Thick/nodular pleural thickening*: pleural thickening with a maximal thickness of greater than 1 cm, but less than 3 cm, and involving not more than 3/4 of the hemithorax on axial scan or discrete pleural nodules. **(C)** *Circumferential pleural thickening*; continuous pleural thickening involving more than 3/4 of hemithorax on axial scan. **(D)** *Pleural mass:* pleural lesion with a short axis larger than 3 cm on axial CT scan.

as 1) chest wall, 2) pericardium, 3) diaphragm, or 4) other mediastinal organs.

For coexisting pulmonary abnormality, we recorded 1) dominant pulmonary nodule/mass, 2) pulmonary metastasis, 3) lymphangitic carcinomatosis, and 4) asbestos-related lung and pleural disease. Dominant pulmonary nodule was defined as the presence of a solitary pulmonary nodule or a mass with feature suspicious for primary lung cancer. Pulmonary metastasis was defined as bilateral non-calcified pulmonary nodules sized greater than 0.3 cm with a count of at least 10 nodules overall.[19,20] Asbestos-related lung and pleural disease was defined as subpleural dot-like opacities, subpleural curvilinear lines, parenchymal bands, intralobular and interlobular septal thickening, honeycomb appearance, and calcified or non-calcified pleural plaque.

Lymphadenopathy was considered for hilar, mediastinal, supraclavicular, axillary, cervical, and intra-abdominal lymph nodes larger than 1 cm, for cardiophrenic lymph nodes larger than 0.8 cm[21], and for internal mammary lymph nodes larger than 0.5 cm (all images in short axis).[22]

Presence of extra-thoracic organ metastasis was recorded, and presence of mediastinal shift was recorded and divided into ipsilateral or contralateral.

Statistical analysis

SPSS Statistics version 23 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Demographic data and the CT findings in the MPM, MPD, PL-PM, and EP-PM groups were compared using chi-square test or Fisher's exact test. Continuous data are shown as mean plus/minus standard deviation, and categorical data are shown as number and percentage. The significance of CT findings was analyzed using p-value, odds ratio (OR), and 95% confidence interval (CI). A p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 157 patients that were included, 21 patients were diagnosed with MPM, and 136 patients had MPD. Of the 136 patients with MPD, 66 patients had PL-PM, and 70 had EP-PM. There was no significant difference in age or gender between the MPM and MPD groups. Tumor-Node-Metastasis (TNM) staging in the MPM group is shown in Table 1. Demographic and clinical characteristics compared between the MPM and MPD groups are summarized in Table 2.

Table 3 presents the findings of CT imaging compared between the MPM and MPD groups. The odds ratios (OR) [and their respective 95% confidence intervals (CI)] of CT findings are shown in Table 4. We found no significant difference between groups for side of lesion, site of lesion in hemithorax, and amount or appearance of pleural effusion.

All patterns of pleural thickening were found significantly more often in MPM than in MPD (p<0.001-0.004). Circumferential pleural thickening and pleural mass were more common patterns in the MPM group than in the MPD group. (52.4% vs. 14.0%, and 33.3% vs.

TABLE 1. TNM staging of 21 patients with malignant pleural mesothelioma (8th edition AJCC/UICC for malignant mesothelioma).

T	N	M	Stage
T1: 3	N0: 6	M0: 19	IA: 0
T2: 2	N1: 12	M1: 2	IB: 1
T3: 7	N2: 3		II: 4
T4: 9			IIIA: 4
			IIIB: 10
			IV: 2

TABLE 2. Characteristic of patient in malignant pleural mesothelioma (MPM) and metastatic pleural disease (MPD) groups.

Characteristic	MPM (n = 21)	MPD (n = 136)	P-value
Age, years (Mean ± SD)	58.1 (±11.6)	60.5 (±14.2)	0.47
Sex (M/F)	10/11	38/98	0.069
Histologic subtype of MPM			
- Epithelioid	10 (47.6%)		
- Desmoplastic	4 (19.0%)		
- Sarcomatoid	1 (4.8%)		
- Unspecified	6 (28.6%)		
Primary cancer of MPD			
- Non small cell lung cancer		64 (47.1%)	
- Small cell lung cancer		2 (1.5%)	
- Breast cancer		42 (30.9%)	
- Gastrointestinal cancer		7 (5.1%)	
- Genitourinary cancer		6 (4.4 %)	
- Head and neck cancer		4 (2.9%)	
- Malignant thymoma		5 (3.7%)	
- Soft tissue sarcoma		4 (2.9%)	
- Hematologic malignancy		2 (1.5%)	

Abbreviations: SD: Standard deviation, M: Male, F: Female
Except where otherwise indicated, data were reported in frequency with percentage in parentheses.

TABLE 3. Comparison of CT findings of malignant pleural mesothelioma (MPM) and metastatic pleural disease (MPD) divided into primary lung cancer with pleural metastasis (PL-PM) and extrapulmonary cancer (EP-PM) with pleural metastasis subgroups.

CT characteristic	MPM (n = 21)	MPD (n = 136)	MPD PL-PM (n = 66)	MPD EP-PM (n = 70)	p^*	p^+	p^∞
Side					0.105	0.847	
Right	9 (42.9%)	59 (43.4%)	33 (50.0%)	26 (37.1%)			
Left	11 (52.4%)	51 (37.5%)	30 (45.5%)	21 (30.0%)			
Bilateral	1 (4.8%)	26 (19.1%)	3 (4.5%)	23 (32.9%)			*0.010*
Pleural thickening							
Thin	2 (9.5%)	58 (42.6%)	31 (47.0%)	27 (38.6%)	*0.004*	*0.002*	*0.012*
Thick/Nodular	1 (4.8%)	49 (36.0%)	19 (28.8%)	30 (42.9%)	*0.004*	*0.023*	*0.001*
Circumferential	11 (52.4%)	19 (14.0%)	13 (19.7%)	6 (8.6%)	*<0.001*	*0.004*	*<0.001*
Mass	7 (33.3%)	10 (7.4%)	3 (4.5%)	7 (10.0%)	*<0.001*	*<0.001*	*<0.001*
Location							
Periphery	19 (90.5%)	127 (93.4%)	58 (87.9%)	69 (98.6%)	0.627	0.745	0.068
Mediastinal	15 (71.4%)	91 (66.9%)	40 (60.6%)	51 (72.9%)	0.681	0.370	0.898
Diaphragm	17 (81.0%)	113 (83.1%)	54 (81.8%)	59 (84.3%)	0.809	0.929	0.718
Fissure	11 (52.4%)	68 (50.0%)	28 (42.4%)	40 (57.1%)	0.839	0.424	0.700
Pleural effusion							
Appearance							
Free	4 (19%)	47 (34.6%)	18 (23.7%)	29 (41.4%)	0.158	1.000	0.061
Loculated	13 (61.9%)	84 (61.8%)	48 (72.7%)	36 (51.4%)			
Amount							
Small	7 (33.3%)	46 (33.8%)	25 (37.9%)	21 (30.0%)	0.068	0.194	0.151
Moderate	4 (19%)	54 (39.7%)	29 (43.9%)	25 (35.7%)			
Large	6 (28.6%)	32 (23.5%)	12 (18.2%)	20 (28.6%)			
Organ invasion	12 (57.1%)	13 (9.6%)	7 (10.6%)	6 (8.6%)	*<0.001*	*<0.001*	*<0.001*
Chest wall	8 (38.1%)	8 (5.9%)	3 (4.5%)	5 (7.1%)	*<0.001*	*<0.001*	*<0.001*
Pericardium	4 (19.0%)	4 (2.9%)	4 (6.1%)	0	*0.002*	*0.073*	*<0.001*
Diaphragm	5 (23.8%)	2 (1.5%)	2 (3.0%)	0	*<0.001*	*0.002*	*<0.001*
Other mediastinal organs	6 (28.6%)	4 (2.9%)	1 (1.5%)	3 (4.3%)	*<0.001*	*<0.001*	*0.001*
Pulmonary Abnormality							
Dominant nodule/mass	2 (9.5%)	79 (58.1%)	64 (97.0%)	15 (21.4%)	*<0.001*	*<0.001*	*0.220*
Pulmonary metastasis	0	82 (60.3%)	37 (56.1%)	45 (64.3%)	*<0.001*	*<0.001*	*<0.001*
Lymphangitic carcinomatosis	2 (9.5%)	58 (42.6%)	29 (43.9%)	29 (41.4%)	*0.004*	*0.004*	*0.007*
Asbestos related disease	4 (19.0%)	0	0	0	*<0.001*	*<0.001*	*<0.001*
Lymphadenopathy							
Hilar	4 (19.0%)	60 (44.1%)	34 (51.5%)	26 (37.1%)	*0.033*	*0.011*	0.185
Mediastinum	8 (38.1%)	83 (61.0%)	40 (60.6%)	43 (61.4%)	*0.048*	0.071	0.059
Supraclavicular	1 (4.8%)	25 (18.4%)	11 (16.7%)	14 (20.0%)	0.118	0.168	0.099
Internal mammary	6 (28.6%)	45 (33.1%)	25 (37.9%)	20 (28.6%)	0.681	0.438	1.000
Cardiophrenic	4 (19.0%)	48 (35.3%)	21 (31.8%)	27 (38.6%)	0.212	0.406	0.120
Others#	0	23 (16.9%)	8 (12.1%)	15 (21.4%)	*0.041*	0.094	*0.020*
Extra-thoracic organ metastasis	0	37 (27.2%)	7 (10.6%)	30 (42.9%)	*0.006*	0.120	*<0.001*
Mediastinal shift					0.353	0.492	0.106
Ipsilateral	3 (14.3%)	15 (11.0%)	10 (15.2%)	5 (7.1%)			
Contralateral	6 (28.6%)	23 (16.9%)	14 (21.2%)	9 (12.9%)			

p^*: p value, Chi-square test-comparison MPM versus overall MPD, p^+: p value, Chi-square test-comparison MPM versus PL-PM, p^∞: p value, Chi-square test-comparison MPM versus EP-PM, #Extra-thoracic stations included axillary, cervical and intra-abdominal lymphadenopathy.
Abbreviations: CT, Computed tomography
Data were reported in frequency with percentage in parentheses.

TABLE 4. Odd ratio (OR) of CT findings in malignant pleural mesothelioma.

CT Characteristics	OR (95% CI)
Pleural thickening	
Thin	0.14 (0.03-0.63)
Thick/Nodular	0.09 (0.01-0.68)
Circumferential	6.77 (2.53-18.12)
Mass	6.30 (2.07-19.17)
Organ invasion	12.62 (4.48-35.56)
Chest wall	9.85 (3.17-30.60)
Pericardium	7.77 (1.78-33.94)
Diaphragm	20.94 (3.75-116.91)
Mediastinal organs	13.20 (3.34-52.12)
Pulmonary Abnormality	
Dominant nodule/mass	0.08 (0.02-0.34)
Pulmonary metastasis	NA
Lymphangitic carcinomatosis	0.14 (0.03-0.63)
Asbestos related disease	NA
Lymphadenopathy	
Hilar	0.29 [0.09-0.93]
Mediastinum	0.39 [0.15-1.01]
Others[#]	NA

[#]Extra-thoracic stations included axillary, cervical and intra-abdominal lymphadenopathy
Abbreviations: CT, Computed tomography; CI, Confidence interval; NA, Not applicable

7.4%, respectively). In contrast, thin and thick/nodular pleural thickening were less frequently observed in MPM group patients compared to MPD group patients (9.5% vs. 42.6%, and 4.8% vs. 36.0%, respectively).

Overall adjacent organ invasion was significantly more commonly seen in MPM patients than in MPD patients (57.1% vs. 9.6%, p<0.001). Invasion to the chest wall, diaphragm, and pericardium was found in 38.1%, 23.8%, and 19.0% of patients, respectively.

Presence of asbestos-related disease was also significantly higher in the MPM group than in the MPD group (19% vs. 0%, p<0.001). In contrast, other pulmonary abnormalities, including dominant lung nodule/mass, pulmonary metastasis, and lymphangitic carcinomatosis, were significantly less often observed in the MPM group (9.5 vs. 58.1%, p<0.001; 0% vs. 60.3%, p<0.001; and, 9.5% vs. 42.6%, p=0.004, respectively).

Presence of lymphadenopathy at the hilar, mediastinal, and extra-thoracic (i.e., axillary, cervical, or intra-abdominal) locations was significantly less frequently found in the MPM group compared to the MPD group (19.0 vs. 44.1, p=0.033; 38.1 vs. 61%, p=0.048; and, 0% vs. 16.9, p=0.041, respectively).

Presence of extra-thoracic organ metastasis was also significantly lower in the MPM group than in the MPD group (0% vs. 27.2%, p=0.006). Mediastinal shift showed no significant difference between the MPM and MPD groups.

Subgroup analysis between the MPM and PL-PM groups, and between the MPM and EP-PM groups, showed results consistent those from comparison between MPM and MPD, except for bilateral disease involvement, which was significantly more commonly found in the EP-PM subgroup (p=0.01) (Table 3).

DISCUSSION

In the present study, we found several CT features that were statistically significantly suggestive of MPM compared to MPD. Although MPM is a rare pleural tumor with poor prognostic outcome, patients with early-stage

disease can be treated by resection[6], which is in contrast to the palliative care treatment strategy that is used to manage patients with MPD. Precise diagnosis between these two entities must be confirmed by histopathologic study; however, CT can be used as a first-line imaging tool for differential diagnosis, staging, and tissue sampling guidance.[9,11]

Presence of circumferential pleural thickening was found to be a common CT feature that had a strong correlation with MPM (OR: 6.77). This pattern was found in 52.4% of patients with MPM, which is in agreement with prior studies that reported prevalence rates ranging within 31-72%.[13-17,23] In smaller percentage, we also observed circumferential pleural thickening in MPD cases that was caused by primary lung cancer or breast cancer (Fig 2). Pleural mass was another common pattern that was observed in 33.3% patients with MPM. This prevalence rate is similar to those from prior studies (range: 8-38%).[16,17,23] In our study, thin and thick/nodular pleural thickening patterns were uncommon in MPM patients, but were common in MPD patients. This result is similar to that reported by Yoon, et al.[17], but different from other studies that reported a prevalence in MPM patients ranging from 21% to 86%.[12,14,16]

Organ invasion was another significant CT characteristic found to be associated with MPM (57.1%, OR: 12.62), and the two most commonly involved organs were chest wall and diaphragm. This demonstrated the locally aggressive behavior of MPM, which was also observed in prior studies.[14,17,18] Concerning location, some prior studies[16-18] suggested that interlobar fissure involvement was more related with MPM. However, we did not find this in the present study. This difference between studies may be due to the use thin-slice CT with multiplanar reconstruction images that increase the detection of MPD lesions at interlobar fissures.

In the present study, all of the MPM cases that were suspicious for asbestos-related disease had pleural plaque (19%), while there was no pleural plaque found in the MPD group. Pleural plaque is the most common radiographic finding for asbestos exposure[2,3,24], and the reported prevalence of pleural plaque in MPM patients ranged from 21% to 66%.[12,14,16,17] Based on this finding, we propose that the presence of pleural plaque should increase suspicion for MPM (Fig 3).

Regarding the types of MPD, primary lung cancer is one of the most common causes of pleural metastasis accounting for 40%.[25,26] Other malignancies that have

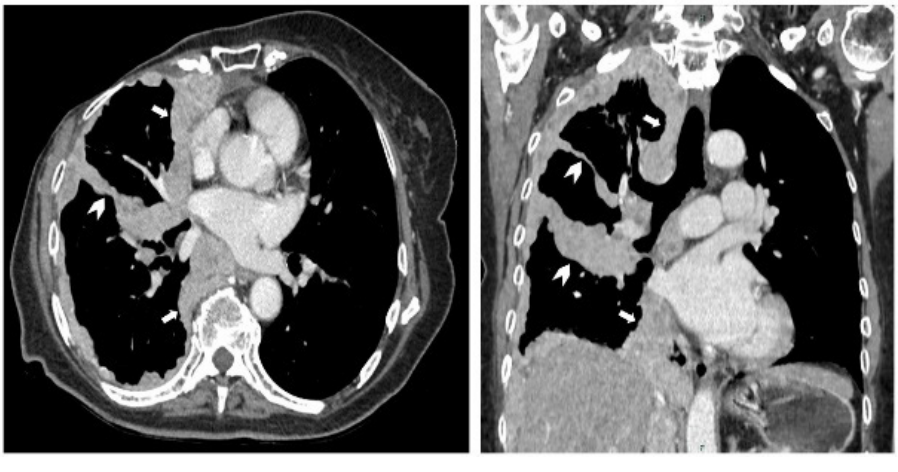

Fig 2. CT scan of a patient diagnosed with right breast cancer and post-right mastectomy. Axial and coronal CT scan shows circumferential pleural thickening at right hemithorax. Involvement of mediastinal pleura (arrow) and interlobar fissure (arrow head) are also demonstrated.

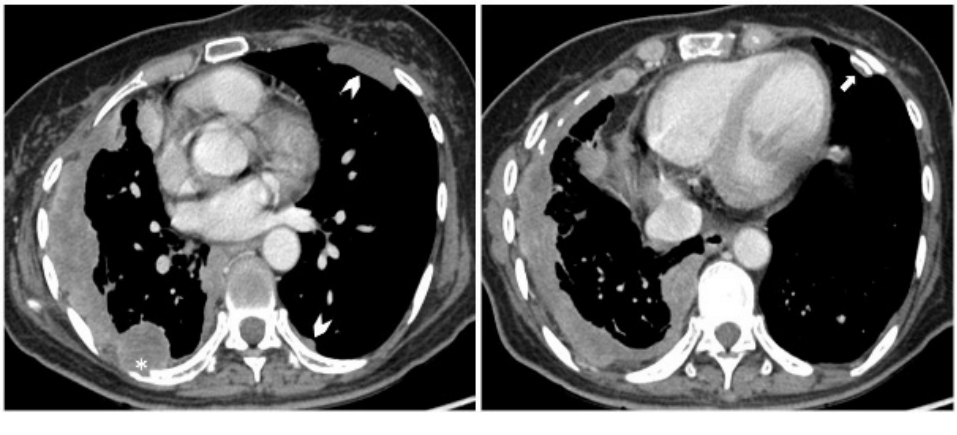

Fig 3. CT scan of a patient diagnosed with MPM. Axial CT scan shows circumferential pleural thickening at right hemithorax with rib destruction (*). A few calcified (arrow) and non-calcified (arrow head) pleural plaques at left hemithorax are also demonstrated.

a propensity for pleural metastasis are breast, gastrointestinal, genitourinary, and hematologic malignancies.[25,26] In subgroup analysis comparing MPM and EP-PM, we found bilateral pleural involvement, pulmonary metastasis, lymphangitic carcinomatosis, extra-thoracic lymphadenopathy, and extra-thoracic organ metastasis to be more common in the EP-PM group, which confirms the concept of extensive dissemination of tumor via hematogenous and lymphatic routes in advanced-stage cancers.[27,28]

The lymphatic drainage of pleura is a complex system. The visceral pleura and the lung parenchyma drain via lymphatic vessels in the interlobular septa toward pulmonary hilar and mediastinum. In contrast, the parietal pleura drains toward different lymph node stations, such as the internal mammary and cardiophrenic lymph nodes.[29,30] We found hilar and mediastinal lymphadenopathy to be less commonly found in MPM compared to MPD. Prior study[31] suggested that the mechanism of the spread of MPM to hilar lymph nodes may be via lung invasion rather than direct spreading of the pleura. The presence of these nodes may be due to primary lung cancer and coexisting pulmonary metastasis in the MPD group.

Limitations

This study has some mentionable limitations. First, the retrospective nature of this study renders it vulnerable to both incomplete data and selection bias. Second, this study was conducted at a large tertiary care center where complicated cases were routinely referred. Thus, our findings may not be generalizable to other patient care settings. Third, we had a small number of patients in the MPM group, which could have limited the statistical power of our study to identify all significant differences and associations between groups. A multi-center study with long-term follow-up is needed to confirm the results of this study.

CONCLUSION

Several CT features were found to be significantly different between the MPM and MPD groups. Circumferential pleural thickening, pleural mass, adjacent organ invasion, and presence of asbestos-related disease were significantly more commonly observed in MPM compared to MPD.

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Outcomes of Proximal Femoral Locking-plate Fixation for Pathological Fractures of the Proximal Femur

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ABSTRACT

Objective: To study the treatment outcomes of proximal femoral locking-plate fixation of pathological fractures of the proximal femur relative to clinical results, implant failure, and surgical complications.

Materials and Methods: From 2007 to 2018, 17 patients (18 femurs) with a diagnosis of impending or existing pathological fracture of the proximal femur were treated with proximal femoral locking-plate fixation. Data collected included operative duration, estimated blood loss, ambulatory status, hardware failure events, and postoperative complications.

Results: Of the 18 femurs that were included, 13 were existing pathological fractures and 5 were impending fractures. The mean age of patients was 53.7 years (range: 28-89), and 12 of them were female. The mean follow-up time was 11.3 months (range: 1-67). Ten of 17 patients (62.5%) had progressive lung disease from pulmonary metastasis or from lung primary. No patient developed oxygen desaturation or cardiac arrest during the intraoperative or postoperative period. Thirteen of 17 patients (76.5%) could walk with or without an assistive device at the time of final follow-up. Two patients required close postoperative monitoring in the intensive care unit due to poor preoperative status, and both of those patients died within one month after surgery from other medical problems. No hardware failure occurred.

Conclusion: For pathological fracture of the proximal femur, proximal femoral locking-plate fixation is a treatment option that results in fewer perioperative and postoperative cardiopulmonary events and surgical complications. Most patients can ambulate with or without an assistive device at the final follow-up.

Keywords: Outcomes; proximal femur; locking-plate fixation; pathological fracture; LCP® Proximal Femur Plate (Siriraj Med J 2021; 73: 603-608)

INTRODUCTION

Pathological fracture of the proximal femur is not uncommon and management is challenging. Bone metastasis at the proximal femur is the third most common site after spine and pelvis.[1,2] Immediate fixation or prosthetic replacement provides pain control, return to previous ambulatory status, improved psychological well-being, and improved quality of life.[1-6] Intramedullary nailing of long bones is an accepted technique for management of existing or impending pathological fracture, especially of the proximal femur. Cephalomedullary nail fixation has been shown to be biomechanically superior to the locking-plate system.[7-9] However, serious complications, including pulmonary embolism, have been reported in

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patients treated with intramedullary nailing with or without reaming.[10-11] Proximal femoral locking plate fixation is an alternative implant for impending or pathological fracture in benign or metastatic bone tumors that can reduce the incidence of pulmonary embolism in pathological fractures of the proximal femur.[12-14] Wide excision of tumor with prosthetic reconstruction is a treatment option for patients with hypervascularized metastatic bone disease; however, increased blood loss is often observed during intralesional curettage. This procedure is also considered for patients with a single metastatic bone lesion who have a good prognosis following wide excision of the metastatic tumor, but this reconstruction is complicated and relatively expensive.[6,15,16]

In this study, we evaluated the treatment outcomes of patients who underwent proximal femoral locking-plate fixation for impending or existing pathological fracture of the proximal femur. The outcome parameters that were evaluated were clinical results, implant failure, and surgical complications.

MATERIALS AND METHODS

This was a retrospective observational clinical study. Patient medical charts from 2007 to 2018 were reviewed after the study was approved by our centre's Institutional Review Board (approval number 563/2555). The inclusion criteria were impending or existing pathological fracture and surgical fixation with a proximal femoral locking plate (Synthes LCP® Proximal Femoral Plate, DePuy Synthes Trauma, West Chester, PA, USA). The patients with impending fracture in metastatic bone disease had been scored more than 9 according to Mirels scoring system.[17] Other patients with impending fracture were considered when lesion involved more than 2/3 of bone circumferential with pain on weight bearing.

Operative technique

All surgeries were performed on a fracture table under image intensification. After placing patients under relative-hypotension anaesthesia, a longitudinal incision was made at the lateral aspect of the hip. The lesion was biopsied and the sample sent for pathological examination. After frozen-section results confirmed the diagnosis, meticulous intralesional curettage of the tumor, followed by open reduction of the pathological fracture was performed. After acceptable alignment was confirmed under image intensification, the locking plate was centred over the greater trochanter and the lateral aspect of the femoral shaft. Under image intensification, the fracture was reduced and provisionally held in position with Kirschner wires and reduction forceps. For pertrochanteric fractures, a partially threaded cancellous screw was inserted into a proximal 7.3-millimeter mL hole to achieve better fracture compression. This screw was subsequently replaced with a locking screw after the rest of the locking screws had been secured. Depending on the fracture configuration, the distal end of the plate was secured with a combination of locking and cortical screws.

Patients with metastatic bone disease received a cement-augmented implant. In those with benign lesions, allograft bone chips were packed into the defect. Intravenous antibiotic coverage with cephalosporin was given once preoperatively and continued for 72-hours postoperatively or until drains were removed. Suction drains were removed routinely once the drainage diminished to less than 50 milliliter (mL) in a 24-hour period. No patients received prophylactic anticoagulation. Active range of motion of the hip and knee was begun on postoperative day 1. Ambulation generally began on postoperative day 3 with progressive partial weight bearing with a walker or axillary crutches. Patients were allowed full weight bearing 3 months postoperatively. Patients were reviewed every 3 months for the first 2 years after surgery, then every 6 months for 3 years, and then annually thereafter. Data collected included operative duration, estimated blood loss, duration of hospital stay, number of days to regain previous ambulatory status, and incidence of implant failure or loss of fixation. Pulmonary status was monitored via oxygen saturation, which was recorded intra- and perioperatively. Plain radiographs of the affected extremity and lungs were reviewed from the time of surgery to the final follow-up for each patient.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 18, (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to test for normality. Data are reported as mean and range or median and interquartile range (IQR). Postoperative ability to walk was tested using a binomial test with test proportion of 0.5 and calculated for a 95% confidence interval (CI).

RESULTS

A summary of patient clinical characteristics, perioperative data, and outcomes is presented in Table 1. Eighteen proximal femurs (13 existing pathological and five impending fractures) were treated in 17 patients (12 females, five males; mean age 53.7 years [range: 28-89]) were enrolled in this study. One patient underwent fixation on both femurs with a staged procedure performed with a 2-week interval between operations. Mean follow-up

TABLE 1. Summary of patient data

Fracture number	Age (years)	Gender	Diagnosis	Operative duration (min)	EBL (mL)	Hospital stay (days)	Time to ambulation (days)	Ambulatory status at final F/U	ICU stay	Lung pathology	O_2 saturation (%)
1*	39	Female	Carcinoma of lung	125	1,200	8	5	Walker	No	Yes (Primary tumor)	100
2#	36	Female	Carcinoma of breast	175	800	11	5	Walker	No	No	99–100
3*#	36	Female	Carcinoma of breast	100	200	8	5	Walker	No	No	100
4	62	Female	Carcinoma of lung	130	600	20	4	Walker	No	Yes (Primary tumor)	100
5	28	Female	Simple bone cyst	175	1,200	13	9	No AD	No	No	100
6	39	Female	Carcinoma of breast	180	1,200	31	10	Wheel chair	No	Yes (Pleural effusion)	100
7	70	Female	Carcinoma of breast	55	200	28	-	Bedridden	Yes	No	100
8	89	Female	Carcinoma of sigmoid colon	105	2,000	68	-	Bedridden	No	No	99–100
9	54	Female	Carcinoma of lung	180	500	18	30	Walker	No	Yes (Primary tumor)	100
10	53	Male	Ewing sarcoma	120	250	22	4	Walker	No	Yes (Metastases)	99
11*	53	Male	MPNST	190	1,000	21	5	No AD	No	Yes (Metastases)	100
12	82	Female	Carcinoma of lung	150	800	37	5	Walker	No	Yes (Primary tumor)	100
13	62	Female	Carcinoma of breast	135	400	16	7	Walker	No	No	99–100
14*	41	Male	Fibrous dysplasia	260	1,000	18	5	No AD	No	No	100
15	56	Male	Carcinoma of lung	80	200	41	6	Walker	No	Yes (Primary tumor)	100
16	57	Male	Hepatocellular carcinoma	115	700	56	-	Bedridden	Yes	Yes (Metastases)	100
17	36	Female	Carcinoma of lung	120	50	7	5	Walker	No	Yes (Primary tumor)	100
18*	71	Female	Carcinoma of lung	140	800	34	2	Walker	No	Yes (Primary tumor)	100

*Patient with impending fracture, # same patient

Abbreviations: MPNST = malignant peripheral nerve sheath tumor; AD = assistive device; EBL = estimated blood loss; ICU = intensive care unit; F/U = follow-up

duration was 11.3 months (range: 1-67). Mean operative duration was 140.8 minutes (range: 55-260). Mean intraoperative estimated blood loss was 688.9 mL (range: 50-2,000). Mean blood transfusion volume after operation was 1.6 units (range: 0-3 units). Average hospital stay was 25.4 days (range: 7-68). Mean number of days to achieve previous ambulatory status was 7.1 (range: 4-30).

Ten of 17 patients (62.5%) had progressive lung disease from pulmonary metastasis or lung primary. No patient developed oxygen desaturation intra- or postoperatively. Binomial test of postoperative ambulatory status revealed that a significantly greater number of patients (13 patients; three [17.6%] without an assistive device, and ten [58.8%] with a walker) achieved their previous ambulatory status postoperatively than did not (p=0.049; 95% CI: 0.54-0.99). No hardware failure occurred in this study. Two patients (11.8%) required close monitoring in the intensive care unit (ICU) postoperatively due to poor preoperative status. Both of those patients subsequently died from other medical problems, one 2-weeks postoperatively and the other one-month postoperatively.

The patient with pathological fracture from a simple bone cyst was followed for 67 months (Figs 1 A-C). This patient underwent a second operation for tumor recurrence with intralesional curettage and bone grafting 11 months after the first operation. She could walk normally and was pain-free at the final follow-up. One patient (fracture number 2) with pathological fracture from metastatic breast cancer underwent fixation with cement augmentation and was followed for 20 months. This patient had multiple bone metastases, but was alive and able to walk with a walker at the final follow-up (Figs 2 A-C).

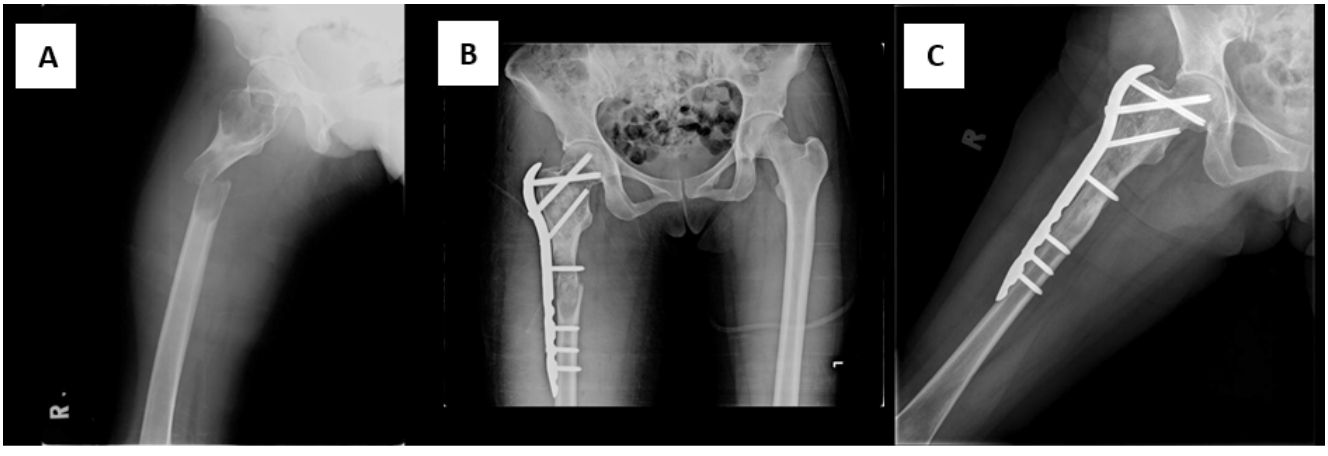

Fig 1. Preoperative radiograph of patient number 5 showing simple bone cyst with subtrochanteric pathological fracture (a). Postoperative radiograph following proximal femoral locking-plate fixation (b). Postoperative radiograph showing complete bone healing at the 67-month follow-up (c).

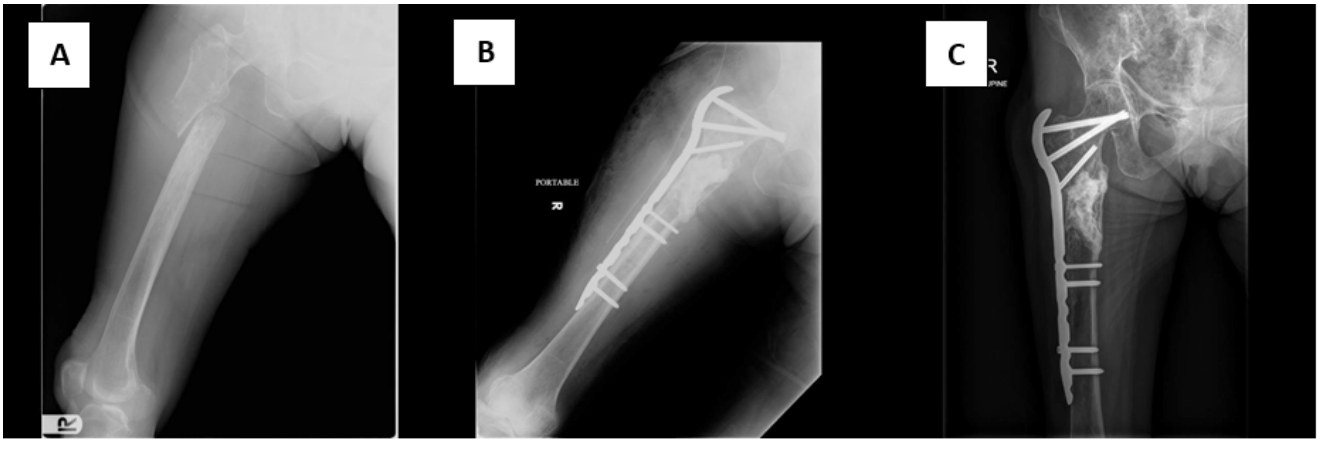

Fig 2. Preoperative radiograph of patient number 2 showing breast cancer metastasis with subtrochanteric pathological fracture (a). Postoperative radiograph following proximal femoral locking-plate fixation with cement augmentation (b). Postoperative radiograph at the 20-month follow-up (c).

DISCUSSION

Surgical fixation for pathological fracture of the proximal femur can relieve pain and re-establish patient mobility.[1,4] Cephalomedullary nail fixation is an accepted method for pathological fracture of the proximal femur. The biomechanical advantage of intramedullary nail systems has been reported.[7-9] A recent study demonstrated that cephalomedullary nailing was biomechanically superior to either a locking-plate or a 95-degree blade-plate construct.[7] However, techniques for nail insertion may cause problems, such as heterotopic ossification, superior gluteal nerve injury, hip abductor muscle weakness, and limping gait.[18-20]

A serious complication of intramedullary nail fixation is fat or tumor embolism that is probably generated by increased pressure during reaming within the closed intramedullary canal. These emboli can travel along the blood stream to the lung parenchyma and cause devastating pulmonary complications, and this has also been reported in fixation with an unreamed intramedullary nail.[10,21] Using transesophageal echocardiography, Coles, *et al.* quantified the embolic load to the lungs created by reamed and unreamed femoral nailing, and they found that emboli were generated with both methods.[22] Those authors concluded that unreamed nailing did not protect the patient from pulmonary embolization of marrow contents. Kerr, *et al.* reported cardiac arrest in six patients during intramedullary nailing procedures for femoral bone metastases.[23] Three of the six patients in that study had simultaneous fixation of both femurs, and four of the six died from embolus. Similarly, in a report by Charnley, *et al.*, one of 52 patients developed hypotension during insertion of the second femoral nail in a single-stage operation, and subsequently developed cardiac arrest and died in the recovery room. A postmortem study revealed massive pulmonary embolus. Those authors recommended that a second surgery be separated by a 2-week interval from the first surgery to avoid this complication.[24]

Another option for management of a metastatic lesion in the proximal femur is wide resection of the tumor and endoprosthetic reconstruction. However, although this method has a low mechanical failure rate, the complication rate varies widely, and the cost is comparatively high. Wide excision of a metastatic lesion has been recommended in patients with isolated hypervascularized tumors, such as in thyroid or renal cell carcinoma. Many studies suggested wide excision and endoprosthetic reconstruction of a metastatic lesion of the proximal femur in patients who might survive for a longer time. They recommended this reconstruction because the endoprosthesis has a lower rate of mechanical failure and a higher rate of implant survival than intramedullary nails.[6-15] Endoprosthetic reconstruction was reported to have the lowest rate of mechanical failure (less than 3.7%), with complication rates of 6-35%.[15,16,25] However the cost of this reconstruction, which is higher than that of other devices, must be considered when treating patients in developing countries.

Reports on the use of the LCP® Proximal Femoral Plate (Synthes, Inc.) in musculoskeletal oncology reconstruction are limited.[12-14,26] Virkus, *et al.* reported bone union in 23 of 25 pathological fractures, nonunions, or oncologic reconstructions, with the advantage of a lower rate of implant failure in locking plates at a mean follow-up of 18.2 months.[14] In this study, we included the patients with bone lesion of the proximal femur with lateral cortical bone destruction. These particular bone metastasis of the proximal femur might affect the stability fixation of lag screw of cephalomedullary nail fixation. All these patients in this study were treated by locking-plate fixation technique. In the present study, we demonstrated a locking-plate fixation technique for pathological fracture of the proximal femur with lateral cortical bone destruction that did not result in hardware failure, oxygen desaturation, and it yielded satisfactory outcomes. There have been reports of LCP® Proximal Femoral Plate (Synthes, Inc.) implant failure.[27,28] However, these failures occurred in patients with mechanical collapse due to varus deformity with inadequate posteromedial support of severely comminuted fractures. In the present study, all patients with metastatic lesions had cement-augmented implants, and bone defects in patients with benign bone tumors were packed with allograft bone chips. Secure fixation augmented with cement or bone grafting can, thus, lessen the chance of fixation failure, as our series suggests. Most of the patients in this study could ambulate independently with or without an assistive device postoperatively.

The limitations of our study were its retrospective nature and the small number of included patients. However, our results suggest that using LCP® Proximal Femoral Plate (Synthes, Inc.) fixation for pathological fracture may reduce the incidence of pulmonary embolism and promote pain-free postoperative ambulatory status in these patients. None of the patients in our study experienced hardware failure. Further studies, particularly with more patients and longer follow-up periods, are needed to confirm the benefits of this implant in the treatment of existing or impending pathological fracture of the proximal femur.

In conclusion, proximal femoral locking-plate fixation is a treatment option for patients with pathological fracture of the proximal femur that results in fewer perioperative and postoperative cardiopulmonary events and surgical complications. Most patients can ambulate with or without an assistive device at final follow-up.

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Conflicts of interest

No conflicts of interest

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Study of Congenital Malformation in a Tertiary Care Teaching Hospital

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ABSTRACT

Background: Congenital anomaly is one of the most important causes & being the 5th most common cause of neonatal mortality & morbidity. It may present as a structural or functional abnormality. These defects occur due to defective embryogenesis. Associated factors may be maternal age, maternal TORCH infection, drugs, genetic factors. Antenatal USG reduces the incidence.

Materials and Methods: A cross-sectional study was done in the Pediatric department over 1 year. Diagnosis of all congenital anomalies was done by the concerned pediatrician& pediatric surgeon. Data was collected in the specified format.

Results: A total of 10205 cases of age group 1 month to 5 years presented to the paediatric OPD, out of which 193 children were diagnosed as congenital anomalies in 1 year. Males were found to be affected the most. The most common system involved was found to be the genitourinary system (36.78%). The second most common system involved was the gastrointestinal system (33.67%). The least common system involved was the musculoskeletal system.

Conclusion: Congenital anomalies are a major cause of neonatal & infantile mortality & morbidity. Routine screening with a level II targeted scan for all the pregnant mothers should be mandatory. Adequate nutrition, parental education & Rubella vaccination of the mother can decrease the prevalence of congenital anomalies to some extend.

Keywords: Congenital anomalies, Genitourinary system, Gastrointestinal system, Hypospadiasis (Siriraj Med J 2021; 73: 609-613)

INTRODUCTION

The period of organogenesis or early fetal age (5-8 weeks of gestation) is the most vital period for the normal development of the fetus. Better maternal care & improved life standards of living, impact the outcome of congenital birth anomalies.[1] Congenital anomalies are caused due to structural or functional abnormalities that occurred in intrauterine life. A congenital anomaly is the most important cause of neonatal morbidity & mortality in developing and developed countries. It accounts for 8-15 % of perinatal deaths & 13-16% of neonatal deaths.[2,3] About 94% of congenital anomalies are seen in low to middle-income countries.[4] Maternal nutrition, infectious diseases & social stress are the most important factors for congenital anomalies in developing country like India. Several factors affect the incidence, e.g. maternal age, consanguinity, nutrition, TORCH infection, genetic factors and certain medicinal & recreational drugs, including alcohol, tobacco & radiation.[4] Vaccinations, adequate folic acid intake, iron, iodine fortification & proper antenatal care are the few preventable measures.

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Congenital defects are the emerging causes of morbidity & mortality.[5] Most congenital anomalies have serious medical, surgical & cosmetic consequences contributing long term defect impacting family life.

MATERIALS AND METHODS

Our study is a cross-sectional study done over 1 year from January 2019 to December 2019 in the pediatric department at IMS & SUM Hospital, Bhubaneswar. Children presented to the paediatric outpatient department of age group 1 month to 5 years were taken as a subject. The study aimed to find out the incidence and different proportion of congenital anomaly presenting to our hospital using a structured form containing the age of presentation, sex, type of congenital anomalies & its association with various maternal risk factors, e.g. maternal anemia, parity, education of mother, antenatal check-up & antenatal iron & folic acid intake.

The diagnosis was made by the concerned pediatricians & pediatric surgeon. Informed consent was taken from the parents. Detailed general physical & systemic examination was done. Ultrasonogram, neurosonogram, X-Ray & 2D ECHO were done to rule out the internal anomalies. CT, MRI brain & karyotyping were done in selected cases.

Out of all congenital cases collected, all are divided into genitourinary, gastrointestinal, vascular, musculoskeletal, cardiovascular system (CVS), central nervous system (CNS). The variables were analysed by frequencies & chi-square test using SPSS Version 20.

RESULTS

A total of 10205 children presented to the pediatric OPD, out of which 193 children were diagnosed with congenital anomalies and referred to the peadiatric surgery department of IMS & SUM Hospital during the study period with different congenital anomalies. It has been seen that the most common age group of presentation is 1-3 years (38%) (Table 1) with a male predominance (93.3%). It is found that the genitourinary system is the most common type of system involved (36.78%) & musculoskeletal system anomalies being the least involved one (1%) (Table 2).

Inguinal hernia is the most common gastrointestinal anomaly in this study, consisting of 81.5%. Tongue-tie is the second most common anomaly, which is 9.2%. Neuroblastoma & umbilical granuloma are the least common types of gastrointestinal anomalies in this study. Hypospadiasis is the most common presentation (36.61%). Hydrocele is the 2nd most common congenital genitourinary anomaly in this study. Vaginal synachiae & Posterior urethral valve are the least common types. The most common cardiovascular presentation is patent ductus arteriosus (PDA), which accounts for 42.8%. The second most common CVS anomaly is a ventricular septal defect (28.6%) (Table 3).

Out Of 193 children, 6 children presented with CNS anomalies and all of them presented as a case of hydrocephalus. Only 2 children presented with musculoskeletal anomalies, one with dermoid cyst & another with supernumerary little finger 10 children presented with respiratory anomalies in the form of laryngomalacia. Only 4 children presented with vascular anomalies, e.g. Hemangioma. 5 children presented with a thyroglossal cyst, whereas 2 children with thyroglossal fistula.

Low maternal education significantly increases the risk of congenital anomalies (P-value- <0.00001). The association of maternal anemia & congenital anomalies is statistically significant in our study (P-value < 0.00001). Improper dosing intake of iron & folic acid statistically increases the risk of congenital anomalies P-value-0.003). There was no association found between parity & antental check-up with risk of congenital anomalies in our study. (P-value- 0.2 & 0.14 respectively) (Table 4)

DISCUSSION

Congenital anomalies are an important cause of childhood morbidity. The pattern of presentation & prevalence of congenital anomalies may vary according to geographical distribution.[1] Nutritional deficiency & maternal infection are the most common causes of congenital anomalies in developing countries like India. Approximately 1 in 33 infants & 3.2 million congenital defects are reported worldwide annually.[2] Every year around 2.7 lakhs neonates die during the neonatal period due to congenital anomalies worldwide. Praneshwari et al. 2019 did a study where they found congenital anomalies in male babies are more (61.5%).[6] Another study was done by Devi et al. 2018 which showed congenital anomalies are more in males (57.1%).[7] Vinodh et al. 2017 in their study done in 2017, found male predominance in congenital anomalies (54.4%).[8] Our study, it is found that congenital anomalies are more prevalent in males, which comprises 93.3%.

Our study's most common presenting age group in our study is between 1-3 years that is 38%. Other studies done by pabbati et al & Vinodh et al where they included newborns as their study population.[8,10] The most common system involved in a study done by Shatanik sarkar et al. in 2013 was the musculoskeletal system (33.2%).[9] Jayalakshmi pabbati et al in 2016 did a study where they found the most common system

TABLE 1. Age distribution of congenital anomalies.

Age Group	Percentage (%)
1 Month-1 Year	28
1-3 Year	38
3-5 Year	34

TABLE 2. System wise distribution of congenital anomalies.

System	Number (Percentage)
Cardiovascular System	28 (14.5%)
Gastrointestinal System	65 (33.67%)
Genitourinary System	71 (36.78%)
Masculoskeletal System	2 (1%)
Respiratory System	10 (5.1%)
Vascular System	4 (2%)
Central nervous system	6 (3.1%)
Miscellaneous	7 (3.8%)

TABLE 3. System wise distribution of congenital anomalies.

System	Number (Percentage)
Gastrointestinal System	
Inguinal Hernia	53 (81.5%)
Tongue tie	6 (9.2%)
Umbilical Hernia	3 (4.6%)
Neuroblastoma	2 (3%)
Umbilical granuloma	1 (1.5%)
Genitourinary System	
Hypospadiasis	26 (36.61%)
Undescended Testes	11 (15.49%)
Hydrocele	14 (19.7%)
Posterior urethral valve	3 (4.22%)
Phimosis	13 (18.3%)
Vaginal synache	1 (1.3%)
Cardiovascular system	
Dextrocardia	3 (10.7%)
PDA	11 (39.2%)
VSD	8 (28.6%)
ASD	5 (17.9%)
TAPVC	1 (3.6%)

TABLE 4. Association of various parameters with Congenital anomalies.

	Congenital Anomalies		
	Present	**Absent**	**P-value**
Maternal education			<0.00001*
Less than High school	109	4123	
High school & above	84	5889	
Maternal anemia			<0.00001*
Present	74	119	
Absent	2107	7905	
Parity			0.2
High Parity (>3)	91	102	
Low Parity (<3)	5113	4899	
Antenatal Check up			0.14
>4 Check up	60	3621	
<4 Check up	133	6391	
Iron- Folic Acid Intake			0.003*
Not/Partially Taken	149	6738	
Taken	44	3274	

*p <0.05 is considered significant

involved in congenital anomalies was the musculosketetal system (37.6%).[10] Another study was done by S Swain et al where they found CNS (39.5%) was the most common system involved.[11] Kokate P et al, in 2016 conducted a study & found that craniospinal involvement is the most common presentation.[12] Devi KR et al in 2018 did a study where they found the musculoskeletal system as the most common system involved in congenital anomalies (50.5%).[7] The most common system in our study is found to be a genitourinary system which comprises 36.78% of children presented with various congenital anomalies. In our study, hypospadiasis is the most common congenital genitourinary anomaly consist of 36.61%. A similar prevalence was found by Dr S. Lakshmi Vinodh et al & Rameswarapu et al in 2017 & 2013, respectively.[8] Inguinal hernia is the most common congenital gastrointestinal anomaly found in our study (81.5%). On the contrary omphalocele & diaphragmatic hernia are the most common presentations found in studies done by Devi KR et al in 2018 & Dr S. Lakshmi Vinodh et al in 2017 respectively.[7,8]

In this study the most common congenital CNS anomaly is hydrocephalus similar to the study done by Dr S. Lakshmi Vinodh et al. They found hydrocephalus was the most common CNS presentations.[8] Dr S. Lakshmi Vinodh et al in their study found VSD as the most common cardiovascular anomaly, whereas in our study PDA is the most common presentation which comprises of 42.8% of the cardiovascular cases.[8] In our study association of maternal anemia & antenatal intake of iron & calcium tablet with congenital anomalies is statistically significant (P-value <0.00001), whereas the association of high parity with congenital anomalies is statistically not significant. A similar result was found in a study done by Thaddanee R et al in 2016.[13] The Association of antenatal check-up with congenital anomalies is statistically not significant in our study.

On the contrary, the association was significant in the study done by Thaddanee R et al in 2016.[13] In our study it is found that the association of maternal education with congenital anomalies is statistically significant (P value- 0.00001). Similar result was found in a study done by Dingemann C et al in 2019.[14]

CONCLUSION

Congenital anomalies are one of the major causes of stillbirth & infant mortality. All pregnant mothers should be counseled regarding the level II targeted scan

at 18-22 weeks to rule out the congenital anomalies. Various management modalities should be discussed with the concerned neonatologist, pediatric surgeon & neurosurgeon if any anomaly is detected. If an anomaly is compatible with life & parents are willing to continue the pregnancy, then proper precautions with utmost care should be taken. If the anomaly is incompatible with life, parents should be advised for termination. Parental education, maternal vaccination for Rubella & maternal adequate nutrition with iron & folic acid supplements can reduce congenital anomalies. This study was done to see the prevalence of various congenital anomalies presented to a tertiary care hospital so that we should maintain a record & with emphasis on routine screening of every pregnant mother to decrease morbidity & mortality.

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Conceptualization of Bioactive Materials in Dental Caries Prevention

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ABSTRACT

Clinicians always face a challenge in selecting the appropriate material for clinical use. Presently, the term bioactive is being used judiciously and unquestionably in the field of dental materials. The introduction of nanotechnology brought about a revolution in material science leading to the development of bioactive materials for caries prevention and management. This review comprehensively evaluates the use of bioactive materials for modification of the oral biome, prevention of dental caries, and the management of dental caries as restorative materials. Six online database (PubMed, Scopus, Science Direct, Embase, Web of Science, and Cochrane library) were systematically searched using broad keywords. Published articles were scrutinized, analyzed and the full-text articles were selected. Data reveals relatively limited application of tissue engineering and regeneration for enamel and dentin due to their limited ability to remodel. However, many steps are being taken in biomimetic approach for the modification of dentin. The path to overcoming any challenges will require active collaboration among clinicians, a material scientist and pulp biologist.

Keywords: Bioactive material, dental caries, demineralization, nanoparticles, remineralization, restorations. (Siriraj Med J 2021; 73: 614-632)

INTRODUCTION

Larry Hench first suggested the concept of a bioactive material in the late 1960s, when he discovered the ability of special glasses to bond to the bone substrate.[1] Subsequently, a bioactive material was defined as one that elicits a specific biological response at the interface of the material resulting in a bond formation between the tissues and material.[2] The resulting bioactivities include the stimulation of cell differentiation and proliferation, stimulation of gene and tissue regeneration, and release of bioactive molecules to respond actively and effectively restore and repair the impaired functions of the organs.[3]

Bioactive materials (second generation) efficiently control interactions with the surrounding biological environment and contribute to tissue regeneration. Biomimetic bioactive materials (third-generation) that mimic the natural bioactive behaviour have been designed to modulate a particular gene, activating the process of tissue regeneration (in tissues like bone cartilage, vascular tissue, and nerves) via cell adhesion, proliferation, and

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differentiation.[4] Tissue regeneration has replaced the concept of tissue replacement through either *in situ* regeneration or tissue engineering strategies.[4]

Bioactivity is the property of a biomaterial to form apatite-like materials on its surface when immersed in simulated body fluid for some time.[5] A wide range of bioactive substances is used for caries management, a global infectious disease, where each individual of different age groups has experienced/undergone preventive measures. Hence, for a better understanding of dental caries management, bioactive materials can be categorized as a) bioactive agents/materials used for altering the oral microbiota in caries-prone individuals, b) bioactive agents/materials for dental caries prevention, c) bioactive agents/materials as a restorative material for dental caries management.

MATERIALS AND METHODS

Literature search

The Extensive data was compiled using search engines of Pubmed, Scopus, Science Direct, Embase, Web of Science, and Cochrane library. The search included the review articles, In vitro studies, and clinical studies. The Key terms were bioactive materials, biomimetic materials, bioactivity, and biomineralization in prevention and managing dental caries. The present review has discussed the applications, concepts, and advance potential uses of bioactive components in the management of dental caries.

Papers selection and data extraction

Following the preliminary search, terms more specific to each category were included to reduce the number of articles retrieved. Selected titles and abstracts were examined (SG, AJ). Specific keyword searched was "effect of bioactive materials on the carious tooth structure". Any potential conflicts were resolved by mutual discussion and consensus between the authors. An independent reviewer (NM) was consulted to resolve the complex studies.

Inclusion criteria

Systematic reviews and literature reviews on bioactive agents.

Chapters on bioactive agents.

Laboratory studies.

Studies on bioactive agents having antimicrobial action on caries micro-organisms.

Studies on bioactive agents helps in prevention of dental caries.

Studies on bioactive agents used as a restorative material.

Exclusion criteria

Studies on Bioactive agents used in endodontic therapy.

Studies on periodontal diseases.

RESULTS & DISCUSSION

Categorization of the Bioactive materials.

A total of 2859 in posse articles up to March 2020 were identified through the database and considered (Fig 1) After removal of duplicates the selected articles were categorized based on (a) bioactive material that can alter the oral microbiome in caries risk individual, (b) prevention of dental caries and, (c) as a restorative material in carious tooth. Full text reading was carried for 146 articles and 72 articles met the eligibility criteria. Out of 72 publications, 23 articles for category (a), 42 articles for (b), and 8 articles for (c) were included for the final review.

The types of bioactive compounds currently used, and their general applications are shown in Tables 1 and 2.[6] The two basic concepts of creating bioactive elements are the top-down and bottom-up approaches. The top-down approach is based on existing well-accepted biomaterials, either bio-inert or bioactive, and the addition of bioactive elements to meet the clinical requirements, (Fig 2). The bottom-up approach involves the designing of a bioactive material at the molecular level to produce new bioactive materials (Fig 3). As shown in Table 2, bioactive materials have vast applications in medicine and dentistry.[7]

Pathogenesis of dental caries

The pellicle, comprising of glycoproteins, is formed immediately on the tooth after brushing. Acid-induced demineralization of the hard tissue occurs due to the decrease in salivary pH and microbial metabolism of carbohydrates. The aetiology of dental caries involves three microbial hypotheses: a. specific plaque hypothesis, which proposes that a few species of the total microflora, such as *Streptococcus mutans (S. mutans), Streptococcus sobrinus (S. sobrinus)*, and lactobacilli, are actively involved in the disease; b. nonspecific plaque hypothesis, which suggests that caries is the consequence of the overall interaction of all groups of bacteria within the plaque; and c. ecological plaque hypothesis, which indicates that caries is the result of an imbalance in the microflora due to ecological stress, resulting in an enrichment of certain disease-related microorganisms.[8,9] The common supragingival microbes in the oral cavity are listed in Table 3.[10]

In the presence of carbohydrate substrates, *S. mutans* generate three forms of glucosyltransferase (GtfB, GtfC,

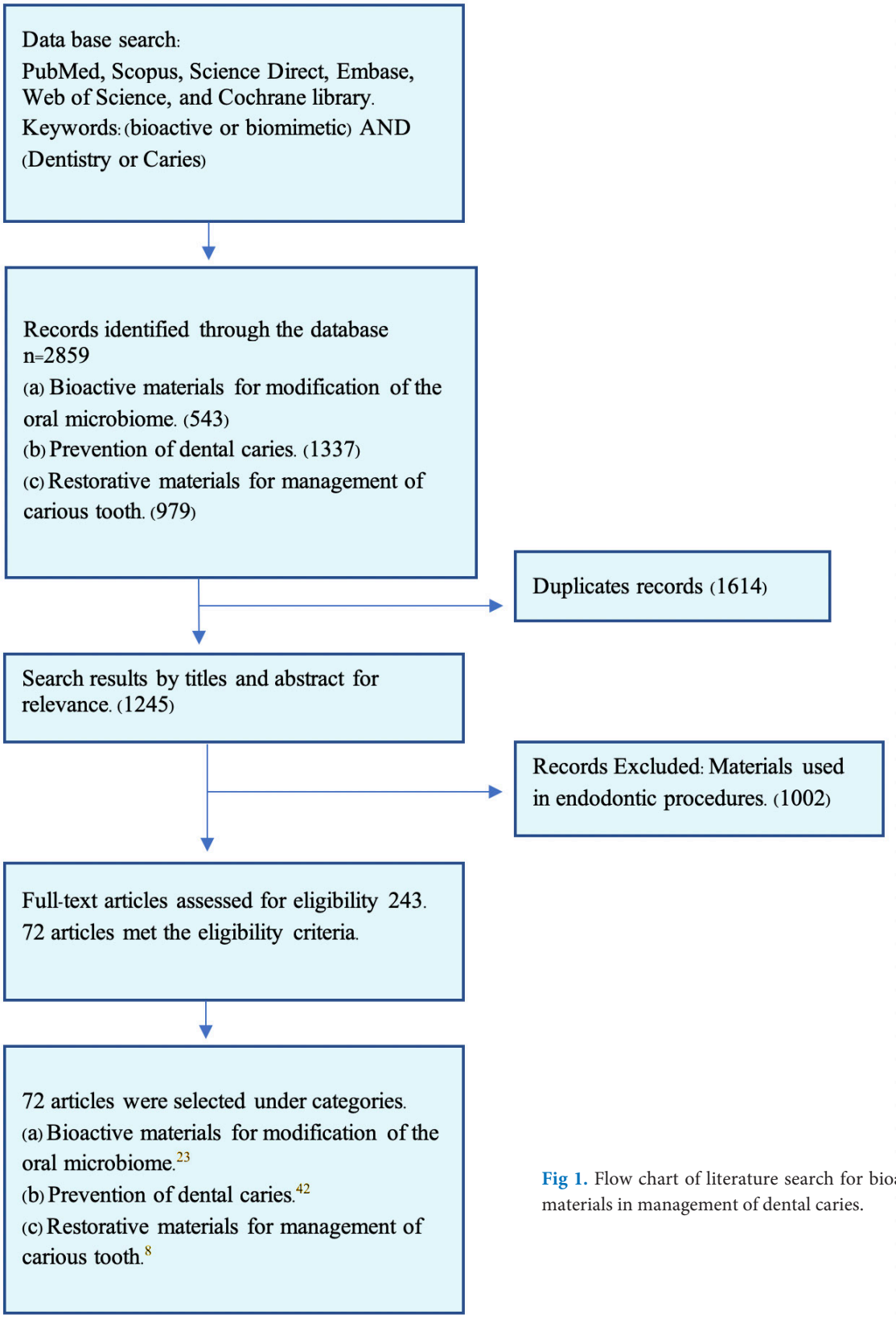

Fig 1. Flow chart of literature search for bioactive materials in management of dental caries.

and GtfD), which polymerize into α-1,3-and α-1,6-linked glucans. Attracting glucans via glucan-binding proteins (lectin-like molecules GbpA, GbpB, GbpC, and GbpD) and Gtfs promotes bacterial adherence, interbacterial adhesion, and biofilm formation on the tooth surface. GtfB, GtfC, and GtfD, and GbpA, GbpB, GbpC, and GbpD combined with their adhesive extracellular glucans, constitute the sucrose-dependent pathway by which the *S. mutans* is established on the tooth surface, leading to acid production and localized enamel decalcification.[11]

TABLE 1. Types of bioactive compounds (*Zhao X et.al., 2011*)

Class	Application
Enzymes	Electrochemical Biosensors, active packaging, formation of extracellular matrix bioreactors, Immunoassays, microanalytical devices.
Peptide	Self-assembling peptide including regeneration, encapsulation of chondrocytes, osteoblast differentiation. Tissues engineering, regulation of matrix metalloproteinase(MMP), antimicrobial surfaces, focal adhesion kinase (FAK) phosphorylation, bioactive gene delivery systems, Gel-based drug delivery system.
Polysaccharide	Skin regeneration, angiogenesis, Tissue engineering, hemocompatible materials, antimicrobial surfaces.
Phospholipid analogue	Tissue remineralization, phospholipid-mediated nucleation of apatite crystals, Biocompatible/hemocompatible materials, copolymer formulations in methacrylate-based composites materials, Nano/microparticulates, and drug conjugates
Antibody	Immunologic activity, antibody-secreting hybridomas, biosensors
Polyethylene glycol	Cell adhesion motifs, hemofiltration membranes, drug conjugates, development of zirconia-based composite material, dental implants
Antimicrobial agent	Prevention of bacterial colonization
Oligonucleotide	Biosensors Scaffolds for growth factors Biocompatibility Active packing, antimicrobial textiles Microarrays, biosensors.
Collagen	Recombinant human collagen, graft material

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
1. Hap (hydroxyapatite) 2. Bioglass (BAG) contains silicon, sodium, calcium, and phosphorus oxides 3. TCP (tricalcium phosphate) 4. Hap/TCP 5. Calium hydroxide 6. Mineral trioxide aggregate 7. Nanoparticles of Calcium phosphate compounds	Hard tissue repair	Hard tissue repair; Bone defect repair/bone grafts; Joint replacements; Restorative materials; Remineralization of teeth; Anticarcinogenic agent; Dentin hypersensitivity; Dental implant; Pulp capping materials and scaffolds in pulp tissue engineering.	Polymers	Poly(methyl methacrylate; PMMA) bone cement/twist or PrePack® Artelon implant – biodegradable polyurethane urea for tissue repair Artificial disc – Freedom® lumbar disc using a viscoelastic polymer Polyurethane foam, co-foam for vascular occlusion device DASCOR® device – artificial disc Cemex®, antibiotic-impregnated bone cement; OpteMx® Porous Tissue Matrix™ (PTM) technology based on polylactides, polylactide-co-glycolides, polycaprolactones, polycarbonates (e.g., TMC), polyurethanes. Elastomer: polycarbonate polyurethane (PCU) Precision polyurethane manufacture (PPM). Bioscorp – cervical bioresorbable corpectomy implant (polyester tube coated with PLLA). Dental composite: 3M, Ivoclar Vivadent. Dentures, Glass ionomer cements, Impression materials.
8. Metal/polymers containing bioactive molecules such as antimicrobial substances Biodegradable polymers + bioglass 9. Casein phosphopeptide and amorphous calcium phosphate (CCP-ACP)		Dental applications Bone tissue repair; Dentin hypersensitivity; and remineralization of dentin.	Biopolymer	Collagen-guided tissue repair membranes Collagen/ceramic bone graft substitutes New generation of collagen matrix for repairing cartilage, degenerative disc disease Vitoss®; Vitagel® – control bleeding and facilitate healing HEMA based copolymer used in bonding systems and restorative materials for remineralization and desentization.

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*) (Continue)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
10 Collagen n-Hap/collagen Hap/collagen/chitosan Biodegradable polymer + Hap + cells	Soft tissue	Soft tissue augmentation as cosmetic surgery Vascular grafts, tendons, and ligaments Skin substitutes	Bioceramics	Demineralized bone matrix putties/gels 40% β-TCP + 60% Hap CELLPLEX® TCP graft CopiOs™ bone void filler NuCore® injectable nucleus chronOS is a fully synthetic cancellous bone graft substitute comprising pure β-tricalcium phosphate Medicrea® OSMOSYS® sticks (60% Hap + 40% β-TCP) DuoFix™ Hap (hydroxyapatite coatings) CERAMENT™ injectable bone substitute materials CERAMENT™ (bone void filler) CERAMENT™ (spine support) (calcium sulfate + hydroxyapatite) Ostim® – 100% synthetic, nanoparticular, phase hydroxylapatite bone matrix in paste form. Novamin, Toothmin, GC tooth Mouse, Remin pro for remineralization and anticarcinogenic
11 Zinc polyalkenoate cements 12. Glass polyalkenoate cements		Pulp protection Sandwich techniques, restorative materials		
13. Chitosan		Wound tissue repair	Composites	BILOK TCP/PLLA screw (absorbable); PLLA (2–3 years) GraftLock screws. High-density, long carbon fiber-reinforced polymer (LCFRP) for spinal defect repair . Mozaik™ osteoconductive scaffold (80% highly purified beta-TCP granules + 20% highly purified type-1 collagen); Polyactive (1000PEGT-70PBT30); OsSatura BCP (biphasic calcium phosphate) and OsSatura TCP (synthetic bone void fillers). Origen DBM with bioactive glass. OsteoMax synthetic bone graft for enhanced bone regeneration.

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*) (Continue)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
14. Graphene oxide		Dental prostheses Graphene composite (few-layer graphene); Drug delivery carriers; Imaging agents; Bimolecular analysis; Tissue engineering scaffolds.		Provides optimal osteoconduction. Reduces the time for the bone to regain its full structural function. Osteotech's Plexur™ – bone void filler. Neudisc™ – tubular, fabric-reinforced hydrogel designed to mimic the behavior of a normal disc nucleus. Dental composite as a restorative material.
15. Gelatin		Implant for urinary incontinence. Hemostasis, as scaffolds for soft tissue healing	Biomatrix	OsteoSponge® demineralized bone matrix (DBM) OsteoSponge® Block and Filler, 100% cancellous form of DBM derived from donor bone DiscCell/to restore the function of a degenerated; intervertebral disc; NuBone® DBM putty; NuBone® DBM gel (gelatine) Novocart 3D (biophasic matrix) – autologous chondrocyte transplantation (collagen-based matrix)
16. Demineralized bone matrix (DBM) containing bone growth factors	Tissue engineering	Tissue engineering bone and cartilage repair		

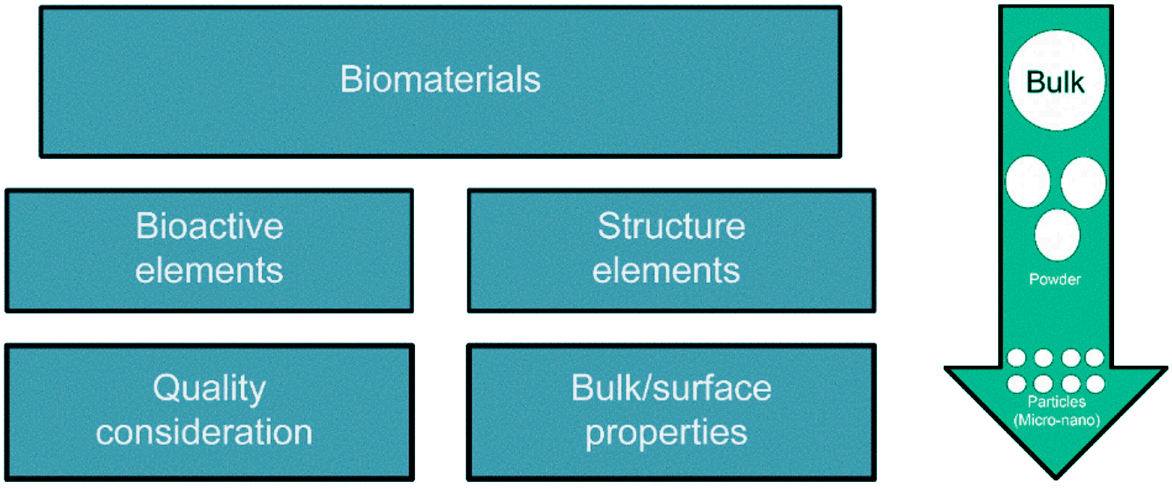

Fig 2. Illustrate the basic concept of bottom-up approach of bioactive material.

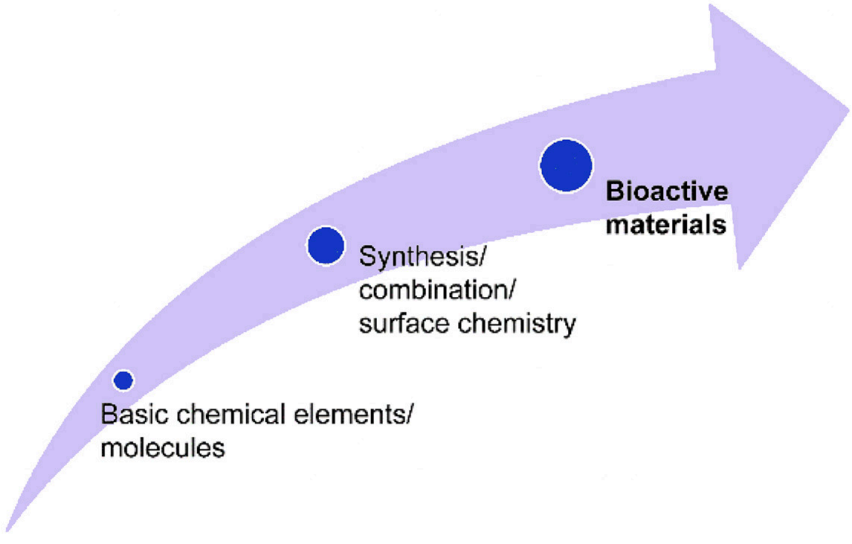

Fig 3. Illustrate the basic concept of bottom-up approach of bioactive material.

TABLE 3. Common microorganism that cause dental caries.

Common oral microbes	Disease
Actinomyces israelii	Gingivitis, periodontitis, and pericoronitis
Actinomyces naeslundii	Bacterial infections and one of the pathogenic bacteria in root caries
Actinomyces viscosus	Carcinogenic bacteria found in root caries and related to periapical infections, dacryosolenitis, and abdominal and faciocervical actinomycos
Bifidobacterium dentium	Biochemically active; can ferment d-ribose, l-arabinose, lactose, sucrose, cellobiose, trehalose, raffinose, melibiose, mannitol, salicin, starch, galactose, maltose, fructose, xylose, mannose, and glucose to produce acid; cannot ferment sorbitol and inulin; Isolated from adult dental caries
Lactobacillus acidophilus, Lactobacillus casei	Found in material from deep caries
Lactobacillus fermentum	Oral infectious diseases such as dental caries and root canal infections
Streptococcus mutans	Glucan and fructan from sucrose colonization; key virulence factors in of dental caries formation
Streptococcus sobrinus	Second highest rate of carcinogenicity after *S. mutans*

(a). Bioactive agents/materials used for altering the oral microbiota in caries-prone individuals, and categorized into natural and synthetic biomaterials.

Natural biomaterials

The bioactive plant compounds derived from secondary metabolism (phytochemicals) have antioxidant activity with low potency as a bioactive compound; however, regular consumption may have distinct unceasing physiological effects. Based on extraction type[12,13], materials are classified as hydrophilic or polar compounds (e.g., phenolic acids, flavonoids, organic acids, and sugars) and lipophilic or nonpolar compounds (e.g., carotenoids, alkaloids, terpenoids, and fatty acids).[14] The most commonly available natural materials are as follows:

Flavonoids. Geismann and Hinreiner 1952 (correlated the group of natural substances with variable phenolic structures to the 2-phenylchroman heterocyclic system (flavan).[15]

- *Propolis* is a nontoxic resinous natural substance that inhibits the adherence of *S. mutans* and *S. sobrinus* and is mainly associated with the control of *Candida albicans*; besides, *propolis* is known to have immunomodulatory effects.[15,16]
- *Nidus Vespae* (honeycomb) is a conventional Chinese medicine used for caries treatment. The chloroform/methanol (CHL/MeOH) chemical extract from this medicine has anti-F-ATPase and anti-lactate dehydrogenase activity against *S. mutans*, along with anti-acidogenic properties. The isolated quercetin and kaempferol flavonoids present in the CHL/MeOH extract exhibit potential preventive and therapeutic actions against dental caries.[17]
- *Polyphenols* are an exclusive class of bioactive natural products with antioxidant, anti-cariogenic, anticancer, and anti-inflammatory effects. An analysis of the literature[18,19] suggests that *polyphenols* can directly act against *S. mutans*; they can inhibit the adherence of bacterial cells and functions of glucosyltransferase and amylase as well as interact with the microbial membrane proteins. Some examples of these compounds include xanthorrhizol, macelignan, magnolol, artocarpin, artocarpesin, quercetin, tannins, myricetin, proanthocyanidin,[11] naringin, and hesperidin.[20]

Prebiotic and probiotic bacteria. Prebiotic and probiotic bacteria are beneficial bacteria that can improve the microecological balance of the host. Generally, the microbiota of subjects with mature oral microbiota plays an insignificant role in the process of permanent colonization in the oral cavity. The probiotic bacteria include the genus *Lactobacillus, Bifidobacterium,* and *Streptococcus. In vitro* studies have shown favourable inhibition of the growth of cariogenic bacteria and *Candida albicans*.[21,22] The common strains of bacteria used are *Lactobacillus rhamnosus* GG, *Lactobacillus casei, Lactobacillus reuteri, Lactobacillus plantarum, Lactobacillus brevis* CD2, *Bifidobacterium* spp., *Streptococcus thermophilus*, and *Streptococcus salivarius* (K12, M18, and JH).[23,24]

Xylitol. Xylose (wood sugar) is a naturally occurring five-carbon sugar alcohol derived from hardwood.[25] Xylitol disrupts the energy-producing process in *S. mutans*, leading to a futile energy consumption cycle and cell death. Furthermore, it inhibits enamel demineralization (i.e., reduces acid production), reduces plaque formation and bacterial adherence, and has a direct inhibitory effect on *S. mutans*. It is readily available in the form of gums, gummy bear snacks, syrups, mouth rinses, and dentifrices. Xylitol acts by forming xylitol-5-phosphate through the phosphoenolpyruvate phosphotransferase system in the cell of *S. mutans* and inhibits its growth and ability to produce acids. It increases the concentration of ammonia and amino acids in plaque, thereby neutralizing the plaque acids; thus, microorganisms in the plaque cannot ferment the xylitol.[26]

Green tea extract. This is a natural bioactive component containing fluoride, catechin, and polyphenols. The indirect antibacterial effect of green tea is exerted by the stimulation of protective components such as immunoglobulins, lysosome, lactoferrin, histatin, and mucin. Green tea can control the pH by inhibiting the action of lactate dehydrogenase, leading to a decrease in acid production after sugar consumption.[27] This extract is effective against the growth of *S. mutans* and *Lactobacillus*.[11,28]

Synthetic biomaterials (biochemicals)

Cetylpyridinium chloride. Cetylpyridinium chloride (CPC) is a cationic quaternary ammonium compound, which exhibits antibiofilm activity during early biofilm formation. It acts as an antiplaque agent at a concentration of 0.025% - 0.1%. Long-term use of this compound causes tooth stains. Furthermore, CPC exhibits strong anti-*S. mutans* biofilm activity.[29,30] A reduction in fluoride ion (F^-) uptake by the action of chloride ions (Cl^-) will lead to an increased incidence of caries. NaCl solution (0.5 mol/L) does not cause any damage to the carious root surface, whereas cerium chloride alone or in combination with F^- can significantly reduce mineral loss from the carious lesion and inhibit its progression.[31]

Chlorhexidine gluconate. This is a cationic bisbiguanide and an antimicrobial agent that inhibits the growth of *S. mutans*. Chlorhexidine varnishes have been reported to cause the most persistent reduction in *S. mutans*, followed by gels and mouth rinses. However, the results of chlorhexidine-fluoride therapy for the prevention of caries are inconclusive.[32-34]

Quaternary ammonium methacrylates (QAM). These are widely used as antibacterial agents. The antimicrobial activity is because the negatively-charged bacterial cells come in contact with the positively-charged quaternary amine (N^+), there is a change in osmotic pressure, resulting in a disturbance of the electric balance and the bacterium explodes.

Long cationic polymers disrupt bacterial cell membranes, akin to a needle bursting balloons, thus proving effective against dental biofilms. In 1994, Imazato et al. first incorporated a QAM into dental composite resin materials.[35] QAMs such as 12-methacryloyloxydo-decyl pyridinium bromide (MDPB), methacryloxyethyl-cetyl ammonium chloride, quaternary ammonium dimethacrylate[36], and quaternary ammonium polyethylenimine have been integrated into dental materials, such as etching-adhesive system, glass ionomer cement (GIC), and composites.[37,38]

Others therapies

Replacement therapy. Replacement therapy involves the implantation of relatively innocuous "effector" bacteria that can competitively exclude or outgrow potential disease-causing bacteria without significantly disrupting the balance of the existing microbial system. Many studies have reported the challenge of successfully introducing effector strains into the human mouth.[39,40]

Gene therapy. In the early 1980s, the "genetic replacement therapy" was introduced to protocols involving an element of gene transfer. Gene therapy is a method of insertion of therapeutic genes into an individual's cells and tissues to treat a disease, such as a hereditary disease in which deleterious mutant allele is replaced with a functional one. *Ex vivo* and *in vivo* are the two approaches for delivering genes into the cells of the body. In *ex vivo* gene transfer, the tissue is removed and cells are genetically modified extracorporeally; then, the modified cells are reimplanted. For *in vivo* gene delivery, the vectors are administered directly to the recipient and gene transfer occurs *in situ*.[6,41,42]

Gene transfer strategy requires three essential elements: a vector (gene delivery system), a gene to be delivered (therapeutic gene), and a relevant target cell to which the DNA or RNA is delivered. Generally, the vectors proposed for gene delivery fall into two categories: viral, which is assembled in a cell, and nonviral, which is constructed in a test tube. Viral vectors are difficult to produce and expensive, which include retrovirus, adenovirus, lentivirus, adenovirus, and herpes simplex virus, whereas nonviral vectors are considered to be less toxic, less pathogenic, and immunogenic and can be produced on a large scale. Natural and synthetic nonviral gene vectors include lipid-based vectors, polymeric vectors (polyethyleneimine, poly-L-lysine, polymethacrylate, carbohydrate-based polymers, linear poly (amidoamine), chitosan, dextran, β-cyclodextrin, polyphosphoester, poly (amino ester)), dendrimer-based vectors (PAMAM dendrimer and polyporpyleneimine), polypeptide vectors, and nanoparticles. *In vivo* gene therapy helps in enhancing the healing of the dento-pulp complex.[43-45]

(b). Bioactive agents/materials for dental caries prevention

The bioactivity approaches used to prevent caries are as follows:

a. Reduction/modulation of biofilm formation [discussed in section (a)].

b. Control/prevention of tooth-mineral loss.

Bioactive substances to Control/prevention of tooth-mineral loss: Dynamic of demineralization and remineralization

Initial mineral loss can be assessed only by an electron microscope. Demineralization is the process of removing mineral ions from hydroxyapatite (HAp) crystals in the hard tissues. The process of restoring this mineral loss by adding HAp crystals is called remineralization. Chemical demineralization on the enamel surface occurs in two phases: at the atomic level, when the bacteria metabolize fermentable carbohydrates and produce organic acids, which diffuse through water among the crystals in the tooth, and when the acid in the susceptible crystal site dissolves the calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions into the surrounding aqueous phase between the crystals. If the critical pH continues to remain at 5.5, it eventually leads to cavitation. A sufficient concentration of fluoride ions on the crystal surface before or during demineralization can increase the adsorption of the surface of the crystals and remarkably inhibit acid demineralization. During remineralization (natural repair of the initial carious lesion) process, Ca^{2+} and PO_4^{3-} ions from the saliva (enhanced by Statherian salivary protein) and topical sources diffuse into the tooth along with F^- to form a fluorapatite (FAP) acid-resistant remineralized layer.[46-49]

Nanoparticles based

Nanoparticles of Amorphous calcium phosphate (ACP).

ACP ($Ca_3(PO_4)_2$), a precursor of the final crystalline HAp is a suitable remineralizing agent and has an average diameter of 0.95 nm with a spherical cluster of ions (Ibrahim et al., 2018). It has a thermodynamically stable calcium phosphate (CaP) phase, i.e., HAp and octacalcium phosphate in a dry or wet state by reacting with atmospheric water. Enamel remineralization occurs according to two principles: (a) gradual release of Ca^{2+} and PO_4^{3-} ions resulting in a local supersaturation that triggers the remineralization of hard tissues and (b) attachment to the hard tissue surface, from where it is transformed to Hap[50,51] to stabilize the crystalline phase of ACP. Several additives and ions, such as adenosine triphosphate, casein phosphopeptides (CPP), polyethene glycol (PEG), carboxymethyl chitosan, polyaspartic acid, magnesium ions, and poly (ethylene glycol)-block-polylactide have been studied. A systematic review suggests that for remarkable enamel remineralization to occur CPP-stabilized ACP (CPP-ACP) should be directly applied on the tooth surface (i.e., marketed as GC tooth mousse).[51] Inpatient with lactose intolerance, CPP is contraindicated as it is a milk-derived protein. The trade names of this compound are "GC tooth mousse, MI Paste, and MI Paste plus," and "Topical C-5".[52,53]

Calcium glycerophosphate. It is a fine white, slightly hygroscopic powder of Ca salt of gylcerophophate and commercially available as a mixture of Ca beta-, D-, and L- alpha-glycerophosphate. On direct interaction with hydroxyapatite, a combination of calcium glycerophosphate and sodium monofluorophosphate has been found to decrease the acid formation and enhance remineralization of the enamel due to increased uptake of fluoride in the non-alkaline-soluble form at the expense of a fraction remaining in the alkaline-soluble form (CaF); moreover, calcium glycerophosphate buffers the pH of the plaque and increases plaque Ca^{2+} and PO_4^{3-} levels, thus providing cariostatic effect.[54]

Dicalcium phosphate dihydrate. Dicalcium phosphate dihydrate (DCPD) has a stable CaP phase under acidic conditions and helps in the remineralization of carious lesions by forming FAP. DCPD has high solubility and is resorbable compared to HAp in the oral environment.[4]

Hydroxyapatite-tricalcium phosphate. This is a biphasic material, and its resorption ability and biological behaviour depend on the hydroxyapatite-tricalcium phosphate (HAp/TCP) ratio.[55] A constitutive proportion of 2:8 has the most significant effect on mesenchymal stem-cell-induced bone formation. Furthermore, beta-tricalcium phosphates[56] can induce hard tissue formation, although HAp alone has no dentinogenetic impact on pulp tissue as a pulp capping agent. Dentinal tubule-like structures observed in most of the hard tissue and columnar cells showed positive immunoreactions for dentin sialoprotein and heat shock protein 25 and were aligned beneath the hard tissues.[57] Some examples of TCP include Clinpro™ 5000 with 5000 ppm fluoride (USA), Clinpro Tooth Crème with 850-950 ppm fluoride (Asia/Australia), and Clinpro™ White Varnish with 26,000 ppm fluoride (USA/Asia/Australia).

Relatively, the specific area of ACP nanoparticles (17.76 m^2/g) is high compared to that of CaP particles (about 0.5 m^2/g) in dental resins.[58] Owing to the increased release of Ca^{2+} and PO_4^{3-} ions by the nanostructured compound, it has led to new possibilities for combating enamel demineralization. It has exemplary osteoconductivity, bioactivity, high cell adhesion, and modified biodegradation. Other applications of this compound include the production of hybrid composites when mixed with polymers, coatings on metallic prostheses, and chemical-setting injectable cement.

Mussel-inspired polydopamine and polydopamine-assisted hydroxyapatite. Mussels are fouling organism that can adhere to assorted aqueous conditions ranging from natural organic and inorganic materials to synthetic materials; they are rich in 3,4-dihydroxy-l-phenylalanine (DOPA) and lysine amino acids.[59] Mussels have a unique robust adhesive property under wet conditions because the oxidative polymerization of dopamine in aqueous solutions spontaneously forms polydopamine (PDA), mimicking DOPA. Zhou et al. (2012)[60] investigated the formation of polydopamine-assisted hydroxyapatite, an influential novel approach in creating HAp-based organic-inorganic hybrid biomaterials, regardless of the type, size, and shape of the hybridized correspondent materials (noble metals, ceramics, semiconductors, and synthetic polymers). They concluded that it remarkably promoted the remineralization of demineralized dentin and dentin tubule occlusion with densely packed HAp crystals. Thus, the coating on the dentin surface with polydopamine may induce enamel and dentin remineralization in the presence of a metastable Ca^{2+} and PO_4^{3-} solution.

Fluoride. Fluoride is an essential mineral for hard tissues (bone and teeth) and appropriate exposure and method of usage are beneficial for both bone and tooth integrity. Fluorohydroxyapatite (FAP) are generally present along with HAp in the outermost layer of the healthy human enamel, and the OH groups (<5%) in HAp are replaced by fluoride (depth, 50 μm).[61] Fluoride helps in reducing the demineralization of the enamel, increasing remineralization in early enamel caries, and inhibiting

bacterial activity. Overwhelming proven literature is available on various modes and forms of application, and the adverse effects of fluorides.[62,63] The tolerable upper intake limit is 0.10 mg/kg/d daily over an extended period in infants, toddlers, and children up to 8 years of age. Studies have shown that CaF^2 and NaF have a similar effect on caries-like enamel lesions.[64] Under an acidic pH, the F- ions are released from CaF^2 deposits due to the reduced hydrogen phosphate ($HPO4_{2-}$) ions, which help stabilize the CaF^2 and make a solubility-inhibiting protective film on the tooth surface. Hence, CaF^2 functions as a pH-driven F– ion reservoir, which releases F– at low pH conditions during an acid attack and remains stable for a longer period on the enamel surface at a neutral pH.

Arginine technology. Arginine amino acid (1.5%) was recently incorporated into toothpaste containing 1450 ppm fluoride in the form of sodium monoflurophosphate and insoluble calcium carbonate. The toothpaste was customized for the prevention of development of new lesion and remineralization of early caries lesions. The amino acids are deaminated by the arginine deaminase (enzyme) system in saliva producing ammonia, which is highly alkaline, and induce a pH increase within the oral environment. Thus, an ideal condition for the reduction in the pathogenicity of the cariogenic plaque as well as for remineralization is created.[65] Some of the examples of toothpaste with this addition include Colgate Sensitive Pro-Relief™ Toothpaste with Pro-Argin and Tom's of Maine Rapid Relief Sensitive Natural Toothpaste.

Silver diamine fluoride (SDF) (fluoride compound) functions to arrest the inner dental caries and prevent secondary caries formation after treatment. The American Academy of Pediatric Dentistry recommends the use of SDF (38%) to arrest the active cavitated caries lesion in primary dentition as part of a comprehensive caries management program. Although SDF is not advised for use for primary (active) caries prevention, Studies have demonstrated signs of initial prevention when applied to other sites in the oral cavity. This product should be handled by specifically trained professionals during the application, as there is persistent black staining of the carious tooth, soft tissues (lips, buccal, and lingual mucosa, and tongue) and operator's fingers and clothing.[66] Amine fluorides have a slightly acidic pH and are biannually applied intra-orally Studies have suggested that acidified fluoride-containing dentifrices may have a specific effect on enamel remineralization.[67]

Silver nitrate. Ammoniacal silver nitrate or Howe's solution is used to reduce pain due to aphthous stomatitis, disinfect the root canals, and treat deep carious lesions; moreover, it can be used for indirect pulp capping because silver particles can diffuse into the affected dentin and demineralize dentin. Silver nitrate hinders cell division; positive silver ions bind to the negatively-charged peptidoglycans on the bacterial cell wall. Additionally, the bacterial cell wall system facilitates binding between proteins and DNA, wherein the silver ions bind to sulfhydryl groups on enzymes and inactive them, eventually stabilizing the DNA and its replication. Enhanced antibacterial effects of monodispersed Ag-doped silica (Si) particles are obtained by the incorporation of silver nitrate.[68]

Silver, gold nanoparticles, platinum, and diamond nanoparticles. Nano-Ag particles adhere specifically to the bacterial cell wall and evoke and bind to the released substance from the microorganisms.[69] Nano-Pt disintegrates the bacterial cell walls and causes the release of substance leaking from the cells. Nano-Au particles act in "noncontact" manner by stimulating biofilm production and aggregating within the biofilm. Nano-D binds closely to the microbial cell wall surface without causing visible damage to the cells, indicating good self-assembling ability. Taken together, these findings suggest that nanoparticles can be used as antimicrobial agents against caries activity.[70]

Zinc compounds (zinc chloride, zinc oxide). Generally, low concentrations of zinc can reduce enamel demineralization and modify remineralization. The addition of zinc to fluoride toothpaste has not affected their ability to reduce caries. Zinc is readily desorbed from HAp by Ca^{2+}, which is abundant in plaque and saliva. In instances where the crystal-growth sites remain occluded by zinc, they may simply be "overgrown" by remineralization initiated at unoccupied sites. Zinc chloride (2.0%) is effective in reducing calculus accumulation, whereas zinc oxide is effective in preventing root caries.[71]

Vitamin K. Vitamin K2 has been tested as a possible anticaries agent by virtue of its enzyme-inhibiting activity in the carbohydrate degradation cycle. A healthy tooth is nourished by centrifugal fluid (dentinal fluid) in the dentin, which is moderated by the hypothalamus/parotid axis, signalling the endocrine portion of the parotid glands. High sugar intake induces increase reactive oxygen species and oxidative stress in the hypothalamus. When this signalling mechanism stops or reverses the dentinal fluid flow, it renders the tooth vulnerable to the oral bacteria, leading to enamel surface dissolution and dentin disintegration. Vitamin K2 has antioxidant potential in the brain and can preserve the endocrine-controlled centrifugal dentinal fluid flow.[72,73]

Platelet-rich fibrin (PRF) and concentrated growth factors (CGF). PRF belong to second-generation platelet concentrate and are easily prepared with no added biological agents with increased osteogenic ability. CGF is obtained from autologous blood using a centrifuge device. Various centrifugation speeds permit the isolation of a fibrin matrix that is remarkably larger, denser, and richer in growth factors as compared to previous-generation platelet concentrate products. The effect of PRF and CGF on exposed dental pulp tissue is to act as scaffolding material and also as a reservoir to deliver certain growth factors and proinflammatory cytokines at the implantation sites. As PRF and CGF are collected from autologous blood, no hypersensitivity reactions are expected.[74]

Polymer-based bioactive materials

P***olyamidoamine polymethylmethacrylate***. Amino-terminated polyamidoamine (PAMAM) dendrimers are highly branched polymers with internal cavities and numerous reactive terminal groups and are used as nucleation templating analogues for biomineralization. PAMAM polymethylmethacrylate has been referred to as an "artificial protein" due to its biomimetic property.[36] They have three generations: the first and second generations are linear molecules, while the third generation comprises spherical molecules with a large number of functional groups. The terminal groups comprise amine-terminated PAMAM (PAMAM-NH_2), carboxyl-terminated PAMAM (PAMAN-COOH), hydroxy-terminated PAMAM (PAMAM-OH), and phosphorylated PAMAM (PAMAM-PO_3H_2). A study by Liang et al. shown that PAMAM-COOH acts as an organic nucleation template and absorbs Ca^{2+} and PO_4^{3-} ions within collagen fibrils to induce intrafibrillar remineralization. PAMAM-PO_3H_2 produces enamel prism-like structures and binds to dentin collagen to stimulate the regeneration of a demineralized dentine surface. PAMAM-OH helps in occluding the dentinal tubules, whereas PAMAM-NH_2 macromolecules adhere to dentin collagen fibrils by electrostatic interactions.[75] Overall, PAMAM has dual effects of mineralization and antibacterial properties.

Synthetic polymers. Synthetic polymers such as polylactic acid (PLA), ploy glycol acid (PGA), and PEG hydrogels offer the advantages of non-toxicity, low immunogenicity, biocompatibility, and ability to undergo *in vivo* degradation. PLA and PGA scaffolds help in the seeding of stem cells like SHED, DPSCs, and dental pulp fibroblasts. PEGs are hydrophilic oligomers synthesized from ethylene oxide and consist of a repeating unit of -(O-CH_2-CH_2)-. PGE is used in tissue regeneration, cell culture, cancer diagnostics and for drug delivery, surface modifications, wound healing, and tissue scaffolds. Synthesized hydrogel are included in peptidic substrates to induce the secretion of the matrix metalloproteinase (MMP) enzyme form tissue cells during migration.[76-79]

Polytetrafluoroethylene(PTFE). PTFE is a linear polymer of tetrafluoroethylene that resembles polyethene (PE) chemically, except that fluorine atoms are completely replaced by the hydrogen atoms. The characteristics of PTFE are as follows: chemically inert nature, very low coefficient of friction (resulting in high surface smoothness), resistance to high temperatures without degradation between 260°C to 400°C, insoluble in water and any organic solvents, non-stick, low dielectric constant (excellent electric insulator), and malleability. The disadvantages are low creep resistance, poor weldability, high microviod content, and low radiation resistance. The application of this agent in dentistry includes the following: Teflon tape, surgical sutures, dental floss, a membrane for guided bone regeneration, and the coating of accessories and dental instruments.[80]

Biopolymer composites. Composite restorations play a vital role in restorative dentistry, changes in composition are done by adding spherical silicon dioxide nanofiller (average size of 540 nm or 0.00050.04 μm), amorphous $CaPO_4$ nanostructures (obtained from calcium chloride (30 mM) and sodium acid phosphate (20 mM) in the presence of buffer, anticaries CaF^2 nanoparticles, recombinant amelogenins to develop biomimetic composites, and variety of CaPs (HAp ACP, tetracalcium phosphate, and dicalcium phosphate anhydrous) to produce mineral-releasing dental composite.[81] In case of smart composite, ACP is converted into HAp and precipitated into gel form within seconds when the pH level in the oral cavity drops to below 5.8, which then forms into amorphous crystals in less than 2 min, resulting in Ca^{2+} and PO_4^{3-} production.[82]

Recently, the inclusion of zirconia-hybridized pyrophosphate-stabilized ACP (Zr-ACP), and tetraethoxysilane or $ZrOCl_2$ to ACP was considered to improve the mechanical properties (biaxial flexural strength and marginal adaptability). Zr-ACP is more soluble than HAp and allows controlled release of Ca^{2+} and PO_4^{3-}.[83] Bioactive composites have enhanced adhesion to the tooth surface and antibacterial activities, thereby reducing biofilm formation and increasing the reliability and longevity of the adhesive restoration compared to conventional composite.

It constitutes resin-filled epoxy microcapsules. The self-repairing mechanism is based on microcapsules, a crack in the epoxy composite material will destroy the microcapsules located nearby the crack and release the

resin, which will subsequently fill the crack and react with a Grubbs catalyst (dispersed in epoxy composite) resulting in resin polymerization and crack repair. Clinical performance of such material is better as compared to the conventional macroscopic repair approach.[82]

These materials can be categorized based on the composition: polyethyl or butyl methacrylate, polymethyl methacrylate, micro filled bisphenol A-glycidyl dimethacrylate, polymethyl methacrylate, and urethane dimethacrylate (light-polymerizing resins). Clinical performance of methyl methacrylates and bis-acryl resins are superior as compared to ethyl methacrylate which has poor aesthetics and wears resistance.[84]

3.3.1.c. Other bioactive components

Peptide derivatives. The DGEA (aspartic acid-glycine-glutamine-alanine) peptide, derived from the αβ1 integrin-binding domain of collagen I, is a potential target ligand for the stimulation of osteogenesis. In one study, DGEA peptide-mediated cell adhesion utilized peptides adsorbed on the HAp crystals in the presence of fetal bovine serum. Leucine-rich amelogenin peptide is a product of alternative splicing of the *amelogenin* gene, regulates HAp crystal formation depending on its phosphorylation status, and is potentially used for the treatment of enamel lesions or defects.[85,86]

Chitosan. It is a natural carbohydrate biopolymer; its grafted hydrophobic chains make chitosan molecule amphiphilic and enhance the antimicrobial activity by increasing its electrostatic interactions with the bacterial cell wall. Studies have suggested that chitosan-based chewing gum and mouthwash have antibacterial effects and can reduce the mucoadhesion of cariogenic bacteria. The addition of nano-chitosan to GIC could develop anti-cariogenic properties and improve mechanical properties. The addition of chitosan to adhesives reduced collagen destruction starting with the endogenous MMP and prevented water permeation in hybrid layers, thus suggesting its role in eliminating bacteria from the dentin surfaces.[87,88] Amelogenin-chitosan (CS-AMEL) hydrogel and chitosan+collagen have been reported as promising materials for *in situ* enamel growth. During enamel remineralization with CS-AMEL hydrogel, microstructure formation with an organization similar to that of enamel is promoted, thus resulting in a successful reconstruction.[87,89,90] Addition of chitosan in the nano-diamond-based form to of methyl methacrylates and bis-acryl resins is suitable for functional temporary restorative applications.[91] Chitosan in combination with nanohydroxyapatite is used as a chemo-chemical solution in removal of caries.

Collagen. A popular biomaterial found as an abundant collagen protein in ECM; it is used as a coating material. Due to its natural origin, collagen has a wide range of applications, such as being a suitable binding site for cellular attachment and an appropriate bone substitute material in combination with bioactive inorganic phases. Moreover, bone morphogenetic proteins and collagen I and IV have been commercialized as dermal substitutes.[93] Collagens are refined and produced in sponges, sheets, films, or injectable scaffolds. Collagen films are in practice for corneal replacement and infection treatment along with anti-inflammatory drug delivery system.

Fibrin glue. Fibrin is a biocompatible, biodegradable, natural scaffold that provides initial stability to the grafted stem cells, which is commonly used for tissue engineering. The growth factor in fibrin glue stimulates and promotes proliferation, cell migration, tissue repair, matrix production by accelerating angiogenesis, and enhances the healing of the exposed pulp tissue (pulp capping agents). The advantages of autologous fibrin scaffolds are easily manufactured in large quantities, cost-effective, easy handling, and reduced probability of viral or prion transmission. Therefore, they are excellent for tissue engineering and appear to be a promising scaffold in regenerative endodontics and maxillofacial surgery.[94]

Hyaluronic acid hydrogel. Hyaluronic acid (HA) is a natural, biocompatible, biodegradable glycosaminoglycans and is found as a tissue component in ECM. It is widely distributed in the mammalian body, especially in the synovial fluid of the joints, umbilical cord, and vitreous body of the eyes. It is a linear polysaccharide with a repeating unit of disaccharide of glucuronic acid and N-acetyl-D-glucosamine and a molecular weight ranging from 10^4 to 10^7 g/mol. It has anti-inflammatory, antibacterial, and tissue-healing properties.[6,83]

(c). Bioactive agents/materials as a restorative material for dental caries management:

This section discusses replacement dentistry and cavitated lesion management with no chance of initial remineralization; the tooth defect has to be restored with restorative materials. The cost of restorative/replacement dentistry can vary worldwide; for example, in the USA, the annual cost is $5 billion.[95] Currently, the concept of minimally invasive dentistry (MID) has emerged due to the increased understanding of the caries process and advancement of the adhesive system. According to Ericson, "MID is the application of systemic respect for the original tissue"; the concept of remineralization and restoring (small filling) incipient lesions.[81]

Briefly, restorative dental elements comprise synthetic

constituents such as primers, bonding agents, liners, cement bases, amalgam, resin-based composites, hybrid ionomers, compomers, cast metals, metal ceramics, ceramics, and denture polymers, which can be used to mend or replace the missing structure of the teeth. Certain materials are created to be controlled-delivery devices for the release of agents for treatment or diagnosis. The use of restorative material is temporary, short-term (temporary cement, crowns, and resin bridges), or long-term (dentin bonding, indirect inlays, crowns, onlays, overlays, removable dentures, fixed multiple unit, and orthodontic appliances). Materialistic advantages have been executed with aid of nanotechnology; it is possible to facilitate interaction with cell components, control cell proliferation and differentiation, and produce an organized ECM. Nanobiomaterials include nanoparticles, nanocrystals, nanoclusters, nono-wires, nanofilms, and nanofibers.[81]

Bioactive Glass based material

Bioactive glass. In 1969, the first bioactive glass (BAG) was introduced as Na, Ca, and PO_4 silicate glass. The two classes of BAG are silicate-based and phosphate-based glasses. The increase in pH promotes the precipitation of HAp from the tooth surface. The Ca^{2+} and PO_4^{3-} ions from BAG and mineralizing agents in saliva may promote the remineralization process. A commonly available noncrystalline amorphous BAG (Bioglass 45S5; NovaMin; GlaxoSmithKline, UK) is used in toothpaste for dentin hypersensitivity (96). Various combinations of bioglass are discussed below:

Silicate-based glasses: The particles or granules of Bioglass 45S5 (Si-based) comprise 45 wt% of SiO_2, 24.5 wt% of CaO, 24.5 wt% of Na_2O, and 6.0 wt% of P_2O_5.[4] Based on the amount of free oxygen available for the branching and interconnection of the glass, four types of silicate-based glasses structures are available: Q0, with no free oxygen; Q1 or end unit, with one free oxygen; Q2 or middle unit, with two free oxygens; and Q3 or branching units, with three free oxygens. The common network modifiers can be oxides of Na, K, Ca, Mg, Ti, and Ca. In general, as the Ca/PO_4 ratio decreases, the ability to bond also decreases. The addition of specific atom substitutions (like fluoride) induces some changes in glass properties, which reduces the dissolution rate. The increase in pH promotes network dissolution by breaking the Si–O–Si bonds and is followed by the formation of silanol groups (SiOH). The polymerization of the SiO_2-rich layer occurs through the condensation of the SiOH groups. The migration of the Ca^{2+} and PO^{4+} groups to the surface of the Si-rich layer results in the formation of CaO-P_2O_5-rich film.[81]

Phosphate-based glasses. They have wide biomedical applications, as they rapidly dissolve when exposed to an aqueous environment, wherein the Na^+ ions are exchanged with hydrogen ions (H^+). Meanwhile, Ca^{2+} and PO_4^{3-} ions are released from the biomaterial, which increases the localized pH and induces the precipitate to form CaP-rich layer on the lesion surface. The Si network from BAG can react with hydroxyl ions from the aqueous solution and form soluble silanol compounds. The increase in Ca^{2+} and PO_4^{3} contents is inversely proportional to Si content. Ultimately, the newly formed layer that is structurally similar to the enamel and dentin has excellent abrasion resistance and transforms into HAp layer.[97,98]

Hydroxyapatite and bioglass. The combination of HAp and bioglass (BG) favours bone formation but has potential as a restorative material for cavitated carious lesions. The intrinsic osteoinductivity property of BG induces degradation process whereby growth factors remain captured within the gel phase formed during material degradation and are consequently released into the cells upon complete material dissolution. Furthermore, fibronectin (ECM) structural proteins form strong bonds with particles of the degrading material. The silicon ions of BG stimulate osteoblast (progenitor cell) differentiation and subsequently form a new bone.[93]

Mesoporous bioactive glasses. Mesoporous bioactive glasses are synthesized into particles, spheres, fibres, three-dimensional (3D) scaffolds, and composites with organized mesoporous channel structures, have excellent bioactivity and used for drug delivery and bone regeneration.[6]

Ag-doped bioactive glass nanoparticles (Ag-BGNs). The addition of silver oxide (0.2–0.5 mol%) to SiO_2-CaO-P_2O_5-Na_2O glass composition at the expense of Si did not allow the glasses to crystallize by melt-quench firing method.[99] Studies have investigated the antimicrobial property of silver and its effect on remineralization. The drawback of this agent is the staining due to the silver content.

Tri-Calcium Silicate Based Materials

Mineral trioxide aggregate. During the last decade of the 20th century, a bioactive material MTA was developed as a root-end filling material at Loma Linda University.[99] It consists of Portland cement (75%), gypsum (5%), bismuth oxide (20%), and traces of Sio_2, CaO, MgO, K_2SO_4, and Na_2SO_4. Portland cement comprises tricalcium aluminate, dicalcium silicate, tricalcium silicate, and tetracalcium aluminoferrite. The removal of tetracalcium aluminoferrite removes the grey colour resulting in the production of the white MTA. It is used for pulp capping, root perforation, retrograde root-end filling, and the obturation.[74]

Biodentine. comprises tricalcium silicate, dicalcium silicate, calcium carbonate, calcium oxide, and zirconium oxide (radiopaque). The liquid consists of calcium chloride and hydro-soluble polymer based on polycarboxylates (responsible for low water content and consistency of the mixture). Biodentine was used as a bioactive build-up material in large areas where the tooth structure is missing and for treating pulp exposures and root perforations. It sets in 10–12 minutes.[81]

Smart materials

Bioceramic-based and smart ceramics. The physical, chemical and biological properties of bioceramic (third-generation orthopaedic biomaterials) are similar to the natural bone.[100] Some of the most commonly investigated bioactive ceramics are β-tricalcium phosphate (β-TCP), HAp (HA), and BAG 4 5S5. These materials are osteoconductive and biocompatible but differ considerably in the rate of resorption. Resorption rate of HA is very slow compared to β-TCP and BAG. Bioceramic-based materials are used as a permanent restorative material.

Smart ceramics are polycrystalline ceramic containing zirconia instead of glass. High-tech ceramic zirconia is used in space shuttles, the brake disks of sports cars, and spherical heads of artificial hip joints. Zirconia is monoclinic at room temperature and tetragonal at firing temperature, with a monoclinic unit cell occupying about 4.4% more volume than when tetragonal. This transformation resulted in crumbling of material on cooling; therefore, in the late 1980s, ceramic engineers suggested to add small amounts of Ca and later, yttrium or cerium (approximately 3–8 mass%) to stabilize the tetragonal form at room temperature. But this form is only "metastable," as trapped energy still exists within the material to convert back to the monoclinic state. CAD-CAM (computer-aided system) technology is implemented using 3D data set of either the prepared tooth or a wax model of the desired substructure. The ceramic powder (Procera, Nobel Biocare, Gothenburg, Sweden) is packed and fired on the enlarged die and in some cases, it is used to machine an oversized part for firing (ZirCAD, Ivoclar Vivadent; Cercon Zirconia, Dentsply Prosthetics, York, Pa.; Lava Zirconia, 3M ESPE, St. Paul, Minn.; Vita In-Ceram YZ, Vita Zahnfabrik). In both procedures, the firing shrinkage can be managed or predicted accurately if well-characterized ceramic powder (i.e., tight control over particle size and packing density) are packed. The highly localized stress ahead of a propagating crack can trigger grains of ceramic to transform around the crack tip. In this case, 4.4% more volume becomes beneficial by altering the material conditions around the crack tip and protecting it.[82]

Graphene-based restorative material. In restorative dentistry, graphene family of nanomaterials (GFNs) includes reduced GO, ultrathin graphite, graphene sheets, few-layer graphene, graphene oxide (GO; from a monolayer to a few layers). Studies have suggested that GFNs have the potential to improve the mechanical properties of antimicrobial and antibiofilm fillers when reinforced with resin polymer matrices and glass ionomer (polyacrylic acid). Additionally, a combination of graphene gold nanoparticles filler and GFNs showed remarkable improvement in the degree of conversation and surface properties, thus providing a stable solution in improving physicochemical properties of dental nanocomposites.[81,101,102]

CONCLUSION

Currently, materials with excellent biocompatibility and regenerative properties have been utilized by clinicians to save teeth that were under various therapeutic modalities and condemned to extraction. However, the compiled data presented will help the clinicians to have complete knowledge and periodic updates regarding these materials and their clinical applications. As to conclude for prevention of dental caries still fluoride therapy is followed; nanohydroxyapatite, bioactive glass, and natural bioactive based materials are used for restorative materials. Researchers are emphasising in tissue engineering and regeneration for enamel and dentin. The path to overcoming any challenges regarding will require active collaboration among clinicians, a material scientist and pulp biologist.

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Concerted Actions toward Healthy Ageing in ASEAN Countries

To the editor:

Since the World Health Organization (WHO) formally launched the United Nation's Decade of Healthy Ageing (2021–2030) on the last International Day of Older Persons, October 1, 2020, the momentum for concerted global action seems to have been overshadowed by the ongoing coronavirus pandemic. However, given the fact that the number of older people in the Asia–Pacific region is rising at an unprecedented rate, placing the region at the forefront of the global phenomenon of population ageing, it is vital for the regional governments to respond to this global initiative. While the proportion of people aged 60 or above in Southeast Asia was 9.8% in 2017, it is forecast to increase to 13.7% and 20.3% by 2030 and 2050, respectively.[1] Indeed, by 2035, all ASEAN (the Association of Southeast Asian Nations) countries will be considered as ageing societies, while Thailand and Singapore will become super-aged societies (i.e., more than 20% of the population is 65 years old or more).

The health issues older people face are diverse, such as non-communicable diseases, mental health issues, including dementia, and injuries and disabilities due to their declining functional ability. To achieve healthy ageing for all across the whole ASEAN region is, therefore, very challenging since there are wide inequalities in the infrastructure and systems necessary for delivering the health and social policies and practices needed to fulfill this goal. According to the World Bank classification, five countries in ASEAN can be considered to be in the category of low-middle income countries, three countries are in the upper-middle income group, and only Brunei and Singapore are high-income countries. In 2010–2015, life expectancy at birth within ASEAN ranged from 65.4 years old to 82.3 years old. When looking at the employment and educational status of older people, the Philippines ranked highest, while Indonesia excels in the domain of having an enabling environment for change.[2]

Regarding the strategic actions of healthy ageing within ASEAN, there is a mix of scenarios possible with each strategy. Combating ageism is considered one of the lowest priority problems in the region, with one indicator showing that the majority of older people – ranging from 60% to 80% of older adults – live with their children in line with the ingrained culture of filial piety in Asian societies. The other two strategies, i.e., long-term care arrangement and ensuring an age-friendly environment, are more recent strategies but still face issues, and ASEAN is lagging behind other regions in their take-up. The most significant provision of care within ASEAN countries is still provided by close relatives, typically without financial support; while a much smaller amount of long-term care is provided by limited national budget support, or by local government support or charity organizations; albeit this latter support is typically inadequate and not well organized yet in the region. In Thailand, a long-term care welfare program was formally set up in 2016. The main care providers are health volunteers in the local community, who receive a small monthly stipend. However, this system has gradually been undermined by many skilled caregivers moving to the private sector.

While there has been an increasing trend toward the encouragement of age-friendly communities and cities in high-income countries, an international study conducted among four ASEAN countries using WHO standards for measuring the perceived age-friendliness of an environment revealed a number of inadequacies in the current environments in terms of age-friendliness, with the five main ones being: "(1) participating in an emergency-response training session; (2) enrolling in any form of education or training; (3) having opportunities for paid employment; (4) involvement in decision-making about important political, economic, and social issues in the community; and (5) having personal care or assistance needs met in the older adult's home setting by government/private care services".[3]

Lastly, aligning a health system to serve the needs of older people remains challenging. With the unique clinical features of older patients, namely, reduced body reserves, atypical presentation, multiple pathology, polypharmacy, and social adversity, the current organ-based healthcare systems that are widely implemented in ASEAN countries are considered unsuited to older patients. Also, there is a severe shortage of geriatric clinics where comprehensive geriatric assessment is mandatory.[4]

Given all the above challenges, the Thai government proposed, at the 30th ASEAN Summit in Manila in April 2017, the establishment of a knowledge center to support

evidence-informed policies, strategies, and guidelines on active ageing, with a view to implementing capacity development programs and so on within ASEAN. Consequently, the ASEAN Center for Active Ageing and Innovation (ACAI) was launched by the ASEAN leaders at the 35th ASEAN Summit on November 3, 2019, in Bangkok, Thailand. With the setting up of ACAI, the Thai government already allocated a ceiling budget of US$ 5 million per year for 5 years to drive momentum in the region. In line with the United Nations proclamation of 2021–2030 as the Decade of Healthy Ageing, concerted action within ASEAN under the platform of ACAI is highly needed and should now progress.

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