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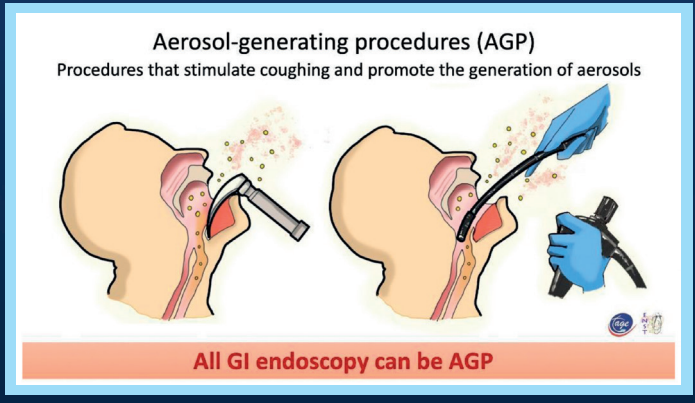

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Coronavirus Disease 2019 (COVID-19) and Its Gastrointestinal and Hepatic Manifestations

Paul Wasuwanich, M.D.*,, Supharerk Thawillarp, M.D.***, Thammasin Ingviya, M.D.****,*****, Wikrom Karnsakul, M.D.***

Division of Pediatric Gastroenterology, Nutrition, and Hepatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA; ***Department of Disease Control, Ministry of Public Health, Thailand; ****Medical Data Center for Research and Innovation, Prince of Songkla University, Songkhla, Thailand; *****Department of Family and Preventive Medicine, Prince of Songkla University, Songkhla, Thailand.*

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a severe respiratory disease caused by the virus SARS-CoV-2 that became classified as a pandemic on March 11, 2020. COVID-19 is known to produce similar clinical manifestations to SARS of the last decade. Fever, dry cough, fatigue, myalgia, dyspnea, and sore throat are some of the most common symptoms and the median incubation period is around 4 days. While the respiratory symptoms often bring the patients to medical attention, clinical manifestations on the gastrointestinal tract and hepatobiliary system have also been cautiously observed. It has been reported that approximately 1-5% of cases developed diarrhea and nausea or vomiting, sometimes preceding the respiratory symptoms. As hemorrhagic colitis was reported in one case with SARS-CoV-2, detected in stool, there is a possibility of fecal-oral transmission of the virus is possible in humans. Thus, it is widely recommended that non-urgent and low prior endoscopic procedures be postponed. For patients requiring urgent endoscopic procedures, SARS-CoV-2 nucleic acid testing from the throat swabs is used as a screening test within 48 hours prior. Minimal personnel, infection control training, and usage of negative pressure rooms are recommended. Abnormal liver function tests have been commonly reported. Patients infected with SARS-CoV-2 can have a true liver injury, which is however mild. The abnormal liver function test values may be caused, at least partially, by muscle injury or hemolysis. Nevertheless drugs with hepatotoxicity should be used with increased caution.

Keywords: Epidemiology; Hepatology; SARS-CoV-2; Transplantation; Endoscopy (Siriraj Med J 2020; 72: 272-282)

Virology and Epidemiology

The coronavirus disease 2019 (COVID-19) is caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which originated from Wuhan, China in 2019.[1] SARS-CoV-2 is a positive-sense, RNA virus in the genus Betacoronavirus, genetically distinct from other severe coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) with only 50% and 79% similarity, respectively.[2]

The SARS-CoV-2 outbreak was officially declared a pandemic by the World Health Organization on March 11, 2020.[3] As of April 1, 2020, there have been more than 850,000 cases of COVID-19 globally affecting almost every country in the world (180 of the 195 countries) including the United States.[4,5] The reported COVID-19

Corresponding author: Wikrom Karnsakul
E-mail: wkarnsa1@jhmi.edu
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ORCID ID: http://orcid.org/0000-0001-7288-5459
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cases from the United States have surpassed 200,000 cases putting the United States' patient count as the highest globally with an epicenter in the state of New York. A similar trend was observed in deaths with reports of approximately 5,000 deaths and rising. The scale of the pandemic has overwhelmed New York's healthcare capacity and stressing several medical supply chains including ventilators, drug supplies, and personal protective equipment causing hospital administrators all over the United States and abroad to prepare for the worst-case scenarios.[6]

Clinical Manifestations

COVID-19 clinical presentation was similar to SARS from the last decade. Fever, dry cough, fatigue, myalgia, dyspnea, and sore throat are some of the most common symptoms.[7-9] The median incubation period was 4 days in an interquartile range (IQR) of 2 to 7 days.[10] The incubation period range of 2 to 14 days is commonly used in public health such as the United States Centers for Disease Control and Prevention (CDC) though that information has been based on the known incubation period of MERS-CoV viruses. However, Lauer et al. recently modeled that with a 14-day quarantine less than 1% of infected cases could develop symptoms after 14 days.[11] According to current evidence, SARS-CoV-2 can be transmitted through close contact or droplets, similar to influenza, via coughing or sneezing with a transmission radius of pathogen-bearing droplets of all sizes of 23 to 27 feet (~7-8 meters). Social distancing for a radius of 6 feet (~2 meters) is typically recommended by public health institutions though this should be seen as a minimum.[12–17] Currently, there have been no reports of airborne transmission of SARS-CoV-2, and the basic reproduction number (R_0) of SARS-CoV-2 is known to be approximately 2.2, lower than airborne diseases such as measles and rubella.[12,18] A study by van Doremalen et al. found that SARS-CoV-2 is viable and has a half-life of 1.1 hours in aerosol, similar to SARS-CoV.[19] This suggests that airborne transmission is possible, but it should be noted that SARS-CoV, which has similar survivability to SARS-CoV-2 in aerosol, is not known to be transmitted via aerosol. SARS-CoV-2 was found to be most stable on stainless steel and plastic surfaces with half-lives of 6-7 hours, and least stable on copper and cardboard surfaces with half-lives of 1-3 hours.[19] Transmission of SARS-CoV-2 by asymptomatic cases have been reported.[20] Although asymptomatic spread can occur during the prodromal phase particularly during the first week after infection, respiratory viral shedding is greatest when symptoms appear.[21]

Older patients and patients with significant chronic medical conditions including cardiopulmonary diseases, diabetes, chronic kidney disease, decompensated cirrhosis, HIV with low CD4 cell count, immunosuppression, and solid organ transplant recipients are at higher risk of acquiring and developing more serious presentation and outcomes such as acute respiratory distress syndrome and multi-organ failure.[10,22–27] Pregnant women with COVID-19 do not appear to have additional complications compared to the non-pregnant population with COVID-19 and vertical transmission of SARS-CoV-2 does not appear to occur.[28] The case-fatality rate is around 5%.[5] The pediatric population appear to have milder symptoms and may harbor the virus while appearing asymptomatic.[29] No data are currently available in children with immunocompromised conditions or chronic lung diseases. In addition to respiratory clinical manifestation, during the early report of COVID-19 in China in December 2019, several gastrointestinal symptoms were reported along with elevated liver enzyme values.[30] Hepatic manifestations have been suspected in multiple studies, but the evidence is not completely clear.

In this study, we reviewed the currently available published data on SARS-CoV-2 or COVID-19 and given gastrointestinal and hepatic manifestations, clinical outcomes, and management. Herein, we discuss recommendations and guidelines to ensure safety to healthcare providers and patients.

Review Methodology

We conducted a systematic search on PubMed and Google Scholars for research articles with the main keywords "COVID-19," "coronavirus disease 2019," "2019 novel coronavirus," or "2019-nCoV." These keywords were supplemented with "liver," "hepatic," "characteristics," "gastrointestinal," and "endoscopy." Non-English research articles, if translatable, were also reviewed. All relevant research articles found in the search were reviewed. Unpublished articles that have not been peer-reviewed were generally avoided. We reviewed research articles published between June 1, 2019 to March 30, 2020.

Gastrointestinal Manifestations and Considerations

In numerous studies of COVID-19, diarrhea was reported as a complication of the disease, ranging from 1-5% of cases.[1,10,22,23,31,32] Nausea or vomiting was reported in 1-5% of cases.[10,22,23,31] The frequency of gastrointestinal symptoms including nausea and/or diarrhea have typically been reported to be below 5% but a small study by Zhang et al. of 28 patients reported diarrhea in 50% of cases.[33] We believe the report by Zhang et al. would likely be an outlier and the cohort of patients studied may have been

exposed to co-infections or local environmental factors independent of SARS-CoV-2 that result in diarrhea. There have been some reports of just diarrhea as a first presentation preceding cough and fever which are the most common presentations with cough at 67.8%, fever at 43.8%, fatigue at 38.1%, sputum production at 33.7%, and shortness of breath at 18.7% of cases.[10] In a case report by Carvalho et al., a woman who was diagnosed with COVID-19 presented initially with bloody diarrhea, approximately 9 days before developing respiratory symptoms. The woman was also found to have hemorrhagic colitis which the authors have ruled out all other etiologies except for SARS-CoV-2.[34]

Reports from China have confirmed that SARS-CoV-2 can be detected in the feces of COVID-19 patients.[35] A study by Zhang et al. on 14 patients with COVID-19 reported that fecal specimens had similar accuracy to pharyngeal swab specimens in the diagnosis of COVID-19.[36] Due to this evidence, the possibility of fecal-oral transmission of SARS-CoV-2 is of great concern. A study on the viral structure of SARS-CoV-2 predicted that the virus would have intermediate levels of fecal-oral transmission and the authors also found that SARS-CoV-2 had the hardest outer shell of the coronavirus family, harder than those of SAR-CoV and MERS-CoV, suggesting that SARS-CoV-2 would be more resilient in body fluids and the environment.[37] However, there are currently no reports of human to human transmission via the fecal-oral route.

Recent evidence suggests the potential for SARS-CoV-2 transmission via fecal shedding.[38,39] Since the virus may be present in gastrointestinal secretions and viral RNA is detectable in stool, potential fecal-oral transmission from gastrointestinal contamination must be considered. As the outbreak of COVID-19 has quickly spread from China to other countries, governments and the medical institutions are taking action to prevent transmission, from common-sense recommendations to more extreme quarantine measures.[40] This is quite an unprecedented phenomenon.

Transplant Donor Considerations

Due to the potential of SARS-CoV-2 transmission through the transplantation of human cells, tissues, or cellular/tissue-based products, several public health institutions have added recommendations on increased precautions and screening of donors. On February 14, 2020, the United States Food and Drug Administration has suggested considering the donor for the following within the past 28 days of tissue recovery: travel to areas with COVID-19 outbreaks, cohabitation with infected individuals, or diagnosis/suspicion of COVID-19.[41] Similar guidelines were published by the European Society for Blood and Marrow Transplantation.[42] In Italy, an epicenter of COVID-19 pandemic in Europe, stronger measures were taken by the Italian National Transplant Center which has recommended testing for COVID-19 in all potential tissue and stem-cell living donors, as well as deceased donors.[43]

One of the transplantations of concern is fecal microbiota transplantation, a novel treatment that has been used in the management of recurrent *Clostridium difficile* infection which is becoming increasingly more widespread and standardized.[44] We believe that more cautious measures are needed in addition to existing guidelines for fecal microbiota transplantation such as those by Cammarota et al. as the risk of transmitting SARS-CoV-2 by fecal microbiota transplantation might be higher than that in other tissue transplants as evidence has shown that the SARS-CoV-2 can be found in feces and stool samples can remain positive for SARS-CoV-2 even after it is undetectable in respiratory tract.[39,45]

To prevent potential SARS-CoV-2 transmission, Ianiro et al. have recommended the following additions to current guidelines for fecal microbiota transplantation. Physicians should screen donors for the following within the previous 30 days: common COVID-19 symptoms such as fever, fatigue, dry cough, myalgia, dyspnea, and headache within the previous, donor's history of travel to regions known to be affected by COVID-19, or close contact with individuals known or suspected of having COVID-19. If any of the above is positive, the potential donor should either be tested for SARS-CoV-2 or simply be rejected. In countries where COVID-19 is widespread such as the United States and Italy, the SARS-CoV-2 testing should be considered in all donors, even those who appear asymptomatic or lack a history of high-risk travel or contact. An alternative method if SARS-CoV-2 testing is limited is that donor stools could be stored and quarantined for 30 days before use and released only if the donor does not develop symptoms. For stool already stored in stool banks, physicians should retrospectively check the health status of the donor before using frozen feces if the donation was made after community spread of COVID-19 had occurred in the country to avoid further potential spreading of SARS-CoV-2.[40]

Fecal-Oral Transmission Route Poses a Threat to Inflammatory Bowel Disease Patients

Due to the potential risk of fecal-oral transmission of SARS-CoV-2 and its presence in the gastrointestinal tract, patients with inflammatory bowel disease (IBD) are suspected of being a vulnerable group. Because

reports on the characteristics of COVID-19 on patients with IBD were lacking, SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion – Inflammatory Bowel Disease) was created. SECURE-IBD is an international collaboration to create a global pediatric and adult registry to monitor and report on outcomes of COVID-19 occurring in IBD patients. The database contains only de-identified data and the summary data is displayed on the website at https://covidibd.org/. As of April 1, 2020, 239 cases have been reports on the SECURE-IBD database globally with preliminary data showing greater morbidity and mortality in patients with ulcerative colitis compared to those with Crohn's disease or unspecified IBD.[46]

Considerations in Patients Requiring Endoscopic Procedures

Gastrointestinal contamination with SARS-CoV-2 poses potential risks during endoscopy and colonoscopy to other patients, endoscopy personnel, as well as populations without clean drinking water. Recommendations for gastrointestinal endoscopy include rescheduling elective non-urgent endoscopic procedures. Some non-urgent procedures are high priority and may need to be performed such as cancer evaluations, prosthetic removals, or evaluation of significant symptoms. Classification of procedures into non-urgent/postpone and non-urgent/perform may be useful.[47] Of note, the United States Surgeon General on March 14, 2020 advised hospitals to postpone all elective surgeries.[48]

Pre-screening of all patients is mandatory for those with a high risk of exposure or symptoms of fever or respiratory symptoms, family members or close contacts with symptoms of COVID-19, any contact with a confirmed case of COVID-19, and recent travel to high-risk regions or countries.[49] Before undergoing endoscopy, the patient should also be checked for body temperature and symptoms upon arrival at endoscopy unit.[50] An alternative strategy that has been used in Thailand is to quarantine non-urgert patients in a hotel for 7-14 days or use mobile apps to ensure that the patient has been quarantined at home before arriving for the procedure.

In countries experiencing shortages of personal protective equipment (PPE), conservation of PPE is critical. Only essential medical personnel should be present for the endoscopy procedures. As for the endoscopy team, appropriate PPE should be reviewed and prepared for the availability on the day of procedures including gloves, masks, eyeshield/goggles, face shields, and gown per the guideline from the United States CDC.[51] All members of the endoscopy team should be trained in proper usage of PPE and any additional requirements given by public health institutions due to COVID-19.[50]

For patients confirmed to have COVID-19 or patients under investigations awaiting test results, isolation precautions should be taken with procedures performed in negative pressure rooms. Aerosolizing procedures should also be done in negative pressure rooms.[50,52] After the procedure, we recommend a follow-up by phone call within 7-14 days to inquire about a potential COVID-19 diagnosis or development of COVID-19 symptoms. Telemedicine should be utilized whenever possible for pre-procedure and post-procedure care.[53,54] Recently published recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) provide similar guidelines for pediatric patients.[55]

The use of an "aerosol box," basically a transparent box designed to cover the head or upper body of a patient, has been suggested as a method to reduce droplet contamination during endoscopic procedures. Canelli et al. found that the use of an "aerosol box" during endotracheal intubation can effectively contain droplet contamination within the box.[56] Ljubicic et al. demonstrated the successful use of an "aerosol box" during lower endoscopy, specifically endoscopic retrograde cholangiopancreatography (ERCP).[57] While the use of an "aerosol box" during upper endoscopy has not been reported in the published literature, commercial "aerosol boxes" designed to be used during upper endoscopy such as EndoSim's AerosolBarrier (TM). Although the "aerosol box" can reduce droplet spread, it is not recommended as a replacement of standard PPE, but rather a tool to be used with standard PPE. Since the box is not designed to be disposable, safe and effective methods for handling and sterilizing the box after procedures have to be in place.

Hepatic Manifestations and Considerations

During the past outbreaks of SARS and MERS, cases of liver injury have been reported in multiple studies with prevalence, based on elevated ALT, ranging from 53-87% in SARS and 11-56% in MERS.[58–64] This suggested that SARS-CoV-2 may have similar hepatic complications.

Abnormal liver enzymes have been observed in approximately 20-30% of patients with COVID-19. Multiple studies have reported liver injury in patients with COVID-19 indirectly with serum biomarkers such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT); however, there have been no direct confirmations via liver biopsies.[1,10,65] ALT was found to be elevated in 21-31% of cases and AST was

found to be elevated in 16-53% of cases.[1,10,22,23,31,66,67] Additionally, elevated total bilirubin was reported in 11-18% of cases, elevated lactate dehydrogenase was reported in 41-76% of cases, and low albumin was reported in 38-98% of cases.[1,10,22,23,66] In a large study of 1,099 patients with COVID-19 in China, Guan et al. found that 2.1% had a preexisting hepatitis B infection.[10] Acute liver injury has also been reported in an infant whose liver enzymes returned to normal after the virus was cleared.[68] Patients admitted to the ICU were reported to have higher frequencies of acute liver injury, 66.7% versus 26.2% according to a study of 102 patients with COVID-19 in China.[69] Additionally, patients admitted to the ICU were found to have significantly higher ALT, higher AST, higher lactate dehydrogenase, higher total bilirubin, and lower albumin levels compared to those not admitted to the ICU.[1,13]

A study by Guan et al. explored the mechanism of liver injury in COVID-19 patients through mouse models. They found that angiotensin-converting enzyme 2 (ACE2), the entry point into cells for SARS-CoV-2, is expressed in cholangiocytes, but scarcely expressed in hepatocytes. However, when there is inflammation in the liver, there is an up-regulation of ACE2 expression in the liver due to compensatory proliferation of hepatocytes derived from cholangiocytes which express ACE2 potentially allowing these hepatocytes to be infected by SARS-CoV-2.[70] In an unpublished study by Tian et al., autopsies of four patients who died from COVID-19, one of whom had abnormal liver enzyme values including elevated gamma-glutamyltransferase (GGT), revealed that the liver exhibited mild lobular infiltration by small lymphocytes, centrilobular sinusoidal dilation, and patchy necrosis. SARS-CoV-2 was also detected in liver tissue in one case.[71] Cytokine storm syndrome and drug-induced liver injury are common theories for mechanisms of liver injury in COVID-19 patients, however, histological evidence is lacking for these theories.

As there has been no direct confirmation of liver injury in COVID-19 patients, the abnormal biomarker values typically associated with the liver may have been caused extrahepatically. Elevated AST, ALT, and lactate dehydrogenase can be caused by muscle inflammation and hemolysis can account for elevated total bilirubin and lactate dehydrogenase.[72,73] Evidence exists for this alternative mechanism in COVID-19 patients; however, the evidence is not strong. Creatine kinase elevation likely indicates muscle inflammation, however, studies on COVID-19 patients have found varying results. A large study by Guan et al. found that creatine kinase was elevated in 19.0% of severe cases and 12.5% of non-severe cases, but statistical testing was not done to confirm the difference.[10] In a smaller study by Huang et al, creatine kinase was reported to have a median of 132.0 U/L (IQR: 82.0-493.0) in severe cases and 133.0 U/L (IQR: 61.0-189.0) in non-severe cases (p=0.31).[1] In another study, creatine kinase was found to be elevated 13% of cases, but also low in 23% of cases.[22] In a review, Zhang et al. reported that 54% of their cohort of 56 COVID-19 cases had elevated GGT levels, however, this result was unpublished.[26] In a detailed study of 3 patients with COVID-19 by Cao et al., one patient without a history of any liver disease had elevated GGT, AST, ALT, lactate dehydrogenase, low albumin, and normal total bilirubin. However, he also had a greatly elevated creatine kinase of 1081 U/L. This suggests that while this patient has evidence of mild liver injury, the muscle injury appears to contribute to the elevated ALT, AST, and lactate dehydrogenase.[74]

Additionally, a study by Zhou et al. found that 19% of cases had coagulopathy, a sign on potential liver injury.[23] And in other studies, low platelet count was reported in 36.2% of cases.[10]

This evidence suggests that true liver injury due to COVID-19 is likely occurring but the level of injury appears to be mild because while there are reports of abnormal liver function tests and coagulopathy, there were no reports of liver failure or signs of jaundice, ascites, hyperammonemia, or portal hypertension. While there have been reports of multiple organ failure, likely due to sepsis or acute respiratory distress syndrome, there have so far been no reports of severe liver injury such as acute-on-chronic liver failure or fulminant hepatitis caused directly by SARS-CoV-2.[22] As the liver and kidneys can be damaged in patients with COVID-19, considerations should be made on the dosage of drugs, especially those with known hepatotoxicity or renal toxicity risks. And liver and kidney functions should be monitored until the patient has cleared the virus.[75] For patients with pre-existing cirrhosis, especially those with decompensated cirrhosis, the hepatotoxicity of drug treatment options for COVID-19 must be highly considered as these patients have a high risk of developing a drug-induced liver injury. Remdesivir, a repurposed drug originally developed to treat Ebola, is currently one of the most promising drug treatments available for COVID-19.[76,77] Remdesivir has not been tested in patients with cirrhosis and due to its novelty, it is unknown whether this drug can cause hepatotoxicity.[78] Adeoye et al. predicted that remdesivir would be hepatotoxic, but this remains to be proven.[79] Liver function should be closely monitored in cirrhosis patients if remdesivir is administered. Chloroquine and hydroxychloroquine have been in use for decades and

have rarely been associated with liver injury according to the LiverTox database.[78] Baricitinib, another candidate drug for the treatment of COVID-19, may cause ALT elevations, but there have been no reports of hepatotoxicity associated with its use, thus, it is considered unlikely to be a cause of liver injury.[78]

Individuals without COVID-19 who are on immunosuppressive drugs for liver transplants or autoimmune-related conditions such as autoimmune hepatitis should continue taking their medications as the risk of organ rejection or autoimmune disease flares outweighs the chance acquiring SARS-CoV-2.[80] A case report by Qin et al. described an adult patient with COVID-19 who had liver transplantation within days of the viral infection. The patient managed to clear SARS-CoV-2 after 34 days of hospitalization while continuing to take immunosuppressive medication.[81] These patients and their caretakers should follow guidelines of the United States CDC for at-risk groups and they should avoid crowds, practice social distancing, and limiting travel.[82]

CONCLUSION

As COVID-19 becomes increasingly more widespread globally and within countries, increased precaution is a general trend across medical departments. Non-urgent and low priority surgeries and operations including endoscopy should be postponed. There is a risk of fecal-oral transmission of SARS-CoV-2 as the live virus has been found in the stool sample so endoscopies should be done with increased precaution and safety measures.

The current evidence suggests that there are indeed cases of true liver injury caused by COVID-19, however, the injury appears to be mild as severe injuries such as liver failure, independent of multiple organ failure, have not been reported. Histological evidence of liver injury has been reported. A plausible mechanism of liver injury is via the infection of hepatocytes derived from cholangiocytes which express ACE2 potentially allowing these hepatocytes to be infected by SARS-CoV-2. COVID-19 related liver injury was based on abnormal liver function tests or enzymes, which can have extrahepatic contributors such as muscle injury or hemolysis.

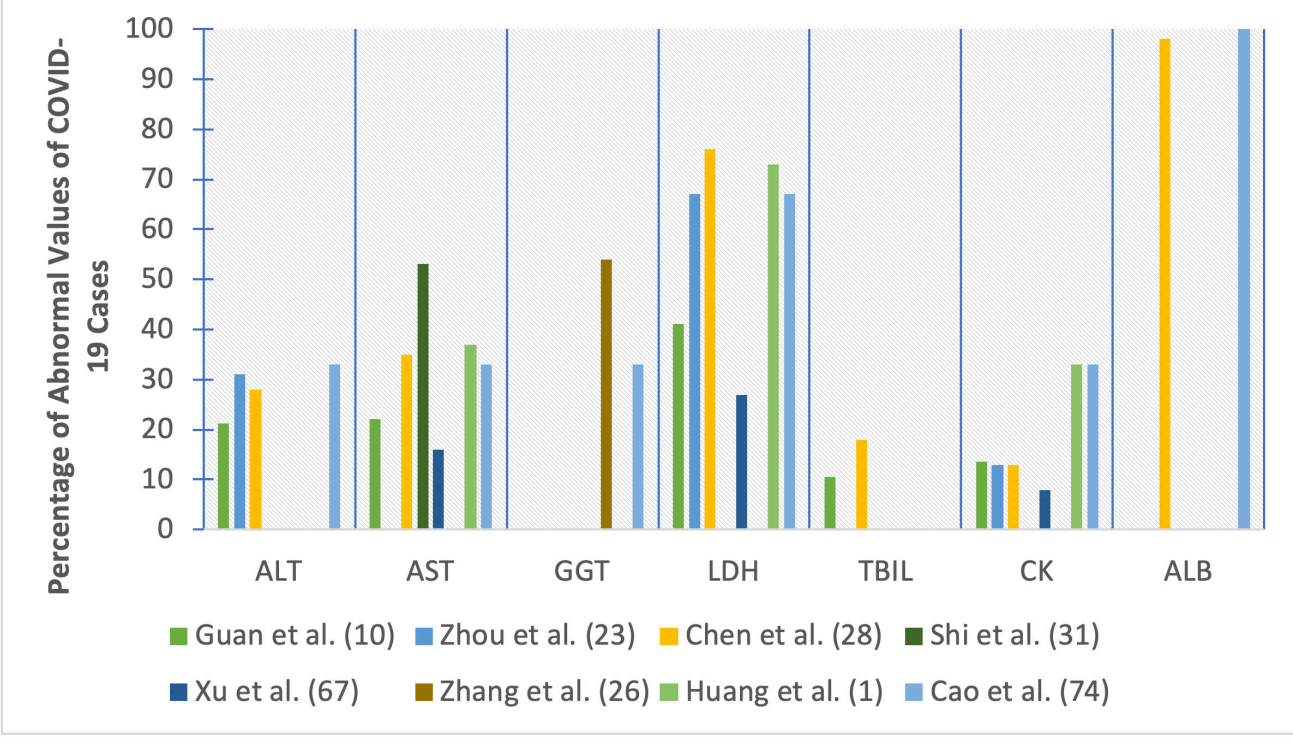

Fig 1. Frequency of hepatic panel and laboratory abnormalities in COVID-19 cases across multiple studies arranged from largest to smallest study.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Abnormal biomarker values were defined as having biomarkers values above the upper limit (or below the lower limit for albumin) of reference values specified by that particular study.
2. Some studies reported low creatine kinase levels, however, for the purposes of this figure, only elevated creatine kinase levels were concerned abnormal.

TABLE 1. Hepatic panel and laboratory values in overall COVID-19 cases.

Reference	Cohort Size, N	ALT (U/L) Overall	AST (U/L) Overall	GGT (U/L) Overall	LDH (U/L) Overall	TBIL (μmol/L) Overall	CK (U/L) Overall	ALB (g/L) Overall	Notes
Zhou et al.[23]	191	30.0 (17.0-46.0)	-	-	300.0 (234.0-407.0)	-	21.5 (13.0-72.4)	32.3 (29.1-35.8)	
Wang et al.[13]	138	24 (16-40)	31 (24-51)	-	261 (182-403)	9.8 (8.4-14.1)	14 (10-18)	-	
Chen et al.[22]	99	39.0 (22.0-53.0)	34.0 (26.0-48.0)	-	366.0 (260.0-447.0)	15.1 (7.3)*	85.0 (51.0-184.0)	31.6 (4.0)*	
Shi et al.[31]	81	46.2 (29.5)*	40.8 (17.9)*	-	-11.9 (3.6)*	-	32.9 (8.1)*		
Cai et al.[32]	80	22.5 (15.0-26.3)	25.1 (18.0-28.0)	25.5 (14-31.1)	-	-	-	-	Values were before intervention
Xu et al.[67]	62	22 (14-34)	26 (20-32)	-	205.0 (184.0-260.5)	-	69.0 (40.5-101.0)	-	
Huang et al.[1]	41	32.0 (21.0-50.0)	34.0 (26.0-48.0)	-	286.0 (242.0-408.0)	11.7 (9.5-13.9)	132.5 (62.0-219.0)	31.4 (28.9-36.0)	
Chen et al.[66]	21	26.0 (16.0-42.0)	27.0 (21.0-47.0)	-	336.0 (221.0-537.0)	8.8 (6.8-10.3)	73.0 (63.0-287.0)	33.7 (29.6-37.4)	
Cao et al.[74]	3	20 (15-52)	36 (25-54)	17 (15-87)	308 (163-651)	15.0 (8.4-15.5)	267 (46-1081)	33.4 (32.4-39.3)	Values were before immunoglobin intervention
Cui et al. J.[68]	1	84	100	-	-	33.7	46	-	Infant; DBIL=25.2 μmol/L

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Values are generally reported as medians with an interquartile range within parenthesis, however, some studies

TABLE 2. Hepatic panel and laboratory values in severe and non-severe subgroups of COVID-19.

Reference	Cohort Size, N	ALT (U/L)		AST (U/L)		LDH (U/L)		TBIL (μmol/L)		CK (U/L)		ALB (g/L)		Notes
		Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	
Zhou et al.[23]	191	40.0 (24.0-51.0)	27 (15.0-40.0)	-	-	521.0 (363.0-669.0)	253.5 (219.0-318.0)	-	-	39.0 (19.5-151.0)	18.0 (12.5-52.1)	29.1 (26.5-31.3)	33.6 (30.6-36.4)	Severe cases were deceased cases
Wang et al.[13]	138	35 (19-57)	23 (15-36)	52 (30-70)	29 (21-38)	435 (302-596)	212 (171-291)	11.5 (9.6-18.6)	9.3 (8.2-12.8)	18 (12-35)	13 (10-14)	-	-	
Yang et al.[65]	52	-	-	-	-	-	-	19.5 (4.3)*	13.1 (11.6)*	-	-	-	-	Severe cases were deceased cases
Huang et al.[1]	41	49.0 (29.0-115.0)	27.0 (19.5-40.0)	44.0 (30.0-70.0)	34.0 (24.0-40.5)	400.0 (323.0-578.0)	281.0 (233.0-357.0)	14.0 (11.9-32.9)	10.8 (9.4-12.3)	132.0 (82.0-493.0)	133.0 (61.0-189.0)	27.9 (26.3-30.9)	34.7 (30.2-36.5)	
Chen et al.[66]	21	42.0 (32.5-50.0)	16.0 (13.3-21.8)	47.0 (28.0-74.5)	24.0 (21.5-26.5)	537.0 (433.5-707.5)	224.0 (200.3-251.8)	8.8 (7.9-10.5)	7.8 (6.4-9.5)	214.0 (90.0-329.0)	64.0 (57.5-83.5)	29.6 (28.6-33.0)	37.2 (35.8-38.8)	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Values are generally reported as medians with an interquartile range within parenthesis, however, some studies or biomarkers have been reported as means with a standard deviation within parenthesis which we have indicated by * in the table cell.

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The Practice of Endoscopy during the COVID-19 Pandemic: Recommendations from the Thai Association for Gastrointestinal Endoscopy (TAGE) in collaboration with the Endoscopy Nurse Society (Thailand)

Pradermchai Kongkam, M.D.*, Kasenee Tiankanon, M.D.*, Siriporn Ratanalert, R.N., Vachira Janthakun, R.N**, Taya Kitiyakara, M.D.*, Phonthep Angsuwatcharakon, M.D.*, Tanyaporn Chantarojanasiri, M.D.*, Parit Mekaroonkamol, M.D.*, Wiriyaporn Ridtitid, M.D.*, Satimai Aniwan, M.D.*, Rapat Pittayanon, M.D.*, Siriboon Attasaranya, M.D.*, Sittikorn Linlawan, M.D.*, Nonthalee Pausawasdi, M.D.*, Thawatchai Akaraviputh, M.D.*, Thawee Ratanachu-ek, M.D.*, Rungsun Rerknimitr, M.D.**

**Thai Association for Gastrointestinal Endoscopy (TAGE), **The Endoscopy Nurses Society (Thailand): ENST*

ABSTRACT

For management of endoscopy units during the worldwide coronavirus disease 2019 (COVID-19) outbreak caused by the new coronavirus SARS-CoV-2 in Thailand, a working group of the Thai Association for Gastrointestinal Endoscopy (TAGE) in collaboration with the Endoscopy Nurse Society (Thailand) (ENST) has developed the following recommendations for Thai doctors and medical personnel working in gastrointestinal endoscopy (GIE) units.

Upper and lower GIE is considered as an aerosol generating procedure (AGP). Information regarding chance of infection in patients must be obtained before performing endoscopy to help determine the level of risk. Endoscopies should only be performed in emergency/urgency cases. Hospitals that have no confirmed cases with low incidences of infection in their coverage area may consider performing selective endoscopies.

For the confirmed infected patient, the recommendations are as follows; the endoscopist who performed the procedure must be an experienced one, wear the enhanced personal protective equipment (PPE) with correct practice how to wear and take off PPE, and strict hand hygiene. The endoscopic procedure should be performed in a negative pressure room; however, If not available, a bedside procedure in the cohort ward should be performed. Endotracheal tube intubation and removal should be done by an anesthesiologist. Most enzymatic detergent solutions can eliminate SARS-CoV-2. The use of an additional pre-cleaning process in order to prevent AGP from occurring during endoscope reprocessing is recommended.

Patient(s) under investigation (PUI) should wait for the test result before considering endoscopic procedure. For the low risk patient for COVID-19 infection who needs an endoscopic procedure, standard PPE is recommended. Due to the limitation of medical resources, only medical personnel who are necessary for the procedure and at risk of COVID-19 infection should be allowed to use the recommended PPE.

Keywords: COVID-19; endoscopy, coronavirus SARS-CoV-2; Thailand; aerosol generating procedure; Thai Association for Gastrointestinal Endoscopy (TAGE); enhanced personal protective equipment (PPE), patient(s) under investigation (PUI); Endoscopy Nurse Society (Thailand) (ENST) (Siriraj Med J 2020; 72: 283-286)

Corresponding author: Rungsun Rerknimitr
E-mail: ercp@live.com
Received 3 April 2020 Revised 4 June 2020 Accepted 5 June 2020
ORCID ID: http://orcid.org/0000-0001-6866-6886
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INTRODUCTION

The following recommendations are for Thai doctors and medical personnel working in gastrointestinal endoscopy unit. This advice was written on 25th March 2020, based on data and suggestions from the experts in Thailand and other countries, as an appropriate guideline to the current situation in Thailand.

The spread of the new coronavirus SARS-CoV-2 has recently led to the worldwide coronavirus disease 2019 (COVID 19) outbreak.[1] In this article, infected patients refer to persons who have been infected with COVID-19, and include both those with and without symptoms. Current data shows that COVID-19 infected patients had 1-3% mortality rate. This virus can also be found from the oral cavity and stools of infected patients.[2-4] Patients with the highest risk of death include the elderly, those with chronic medical conditions and immunocompromised status.[5]

Recommendations

1. Upper gastrointestinal endoscopy is considered as an aerosol generating procedure (AGP).[1] This procedure can cause high risk of viral spreading to endoscopists and surrounding medical personnel (Fig 1).[6] Lower gastrointestinal endoscopy (Colonoscopy) is considered as AGP as well, produced by the expulsion of luminal gas per rectum during the procedure.[7]

2. Information that must be obtained before performing endoscopy to help determine the level of risk include: fever (body temperature >37.5 Celsius), travel history, risk occupation, history of contact to confirmed infected patients, and the history of close contact with unfamiliar people.

3. Due to limited resources in the hospital during the COVID-19 outbreak, endoscopies should only be performed in emergency/urgency cases. Elective endoscopies in suspected or confirmed infected patient must be postponed. Hospitals that have no confirmed cases with low incidence of infection in their coverage area may consider performing selective endoscopies. We propose a classification of endoscopic procedures according to the urgency of the indication in Fig 2.[8]

4. For the confirmed infected patient who needs an endoscopic procedure, the recommendations as follows must be practiced.

1. The endoscopist who performed the procedure must be an experienced one. To reduce the risk of infection and the consumption of PPE, no trainee should be allowed in the endoscopy room during the procedure.

2. The endoscopist must wear the enhanced personal protective equipment (PPE) (Fig 3), including

1. Respirator mask (N95, FFP2/FFP3, CAPR) if available
2. Medical protecting coverall
3. Double disposable gloves
4. Medical cap/hood
5. Goggles/ eyes-visors and face shield
6. Waterproof leg covers

3. Practice how to wear and take off PPE in the correct way, using a buddy system to check for and prevent any errors.[6]

4. Strict hand hygiene is necessary to reduce contamination while wearing and taking off PPE.[5]

5. The endoscopic procedure should be performed in a negative pressure room. If one is not available, a bedside procedure in the cohort ward should be performed.

6. Endoscopic retrograde cholangiopancreatoscopy (ERCP) can be performed in the endoscopic unit, the operating room or at the bedside in the cohort ward with a portable fluoroscopy machine. This depends on the circumstances of each hospital.

7. Endotracheal tube intubation and removal should be done by an anesthesiologist. Endoscopists and the surrounding endoscopic medical personnel should stay outside of the room during endotracheal tube intubation and removal.

8. The endoscopic unit should be disinfected before and after the procedure. Most enzymatic detergents solutions can eliminate SARS-CoV-2.

9. Standard endoscope reprocessing steps are sufficient for SARS-CoV-2 disinfection. However, we recommend the use of an additional pre-cleaning process in order to prevent AGP from occurring during endoscope reprocessing (Fig 4).

5. Patient(s) under investigation (PUI) should wait for the test result before considering endoscopic procedure. But in an emergency situation, endoscopy should be performed with caution in the same way as for a confirmed infected patient.

6. For the low risk patient for COVID-19 infection who needs an endoscopic procedure, standard PPE including hair net, goggles, surgical mask, waterproof gown, disposable gloves, and shoe covers is recommended (Fig 3).

7. The use of mask respirators including N95 will depend on the local prevalence of COVID-19 and the availability of masks and other medical resources in the hospital. However it should be noted that asymptomatic infected patients can also spread the infection.

8. Due to the limitation of medical resources, only medical personnel who are necessary for the procedure and at risk of COVID-19 infection should be allowed to use the recommended PPE.

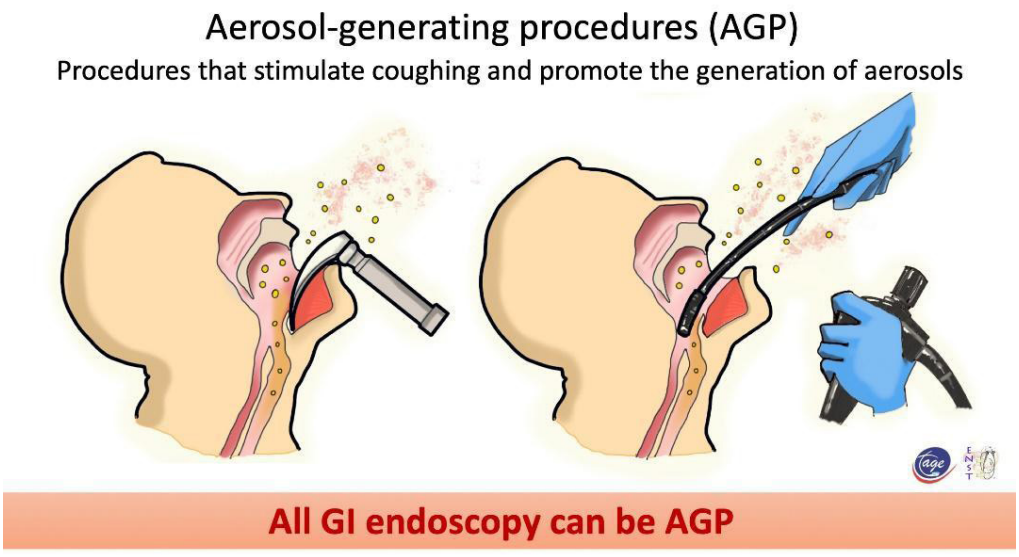

Fig 1. All GI endoscopies are considered as the aerosol generating procedures (AGP) and risk viral spreading

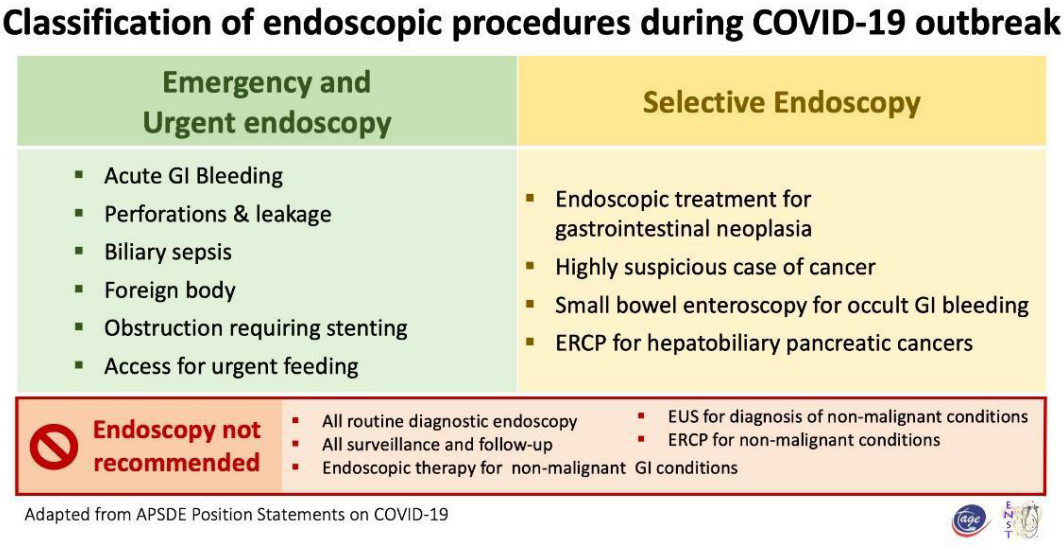

Fig 2. Classification of endoscopic procedures according to the urgency of indication

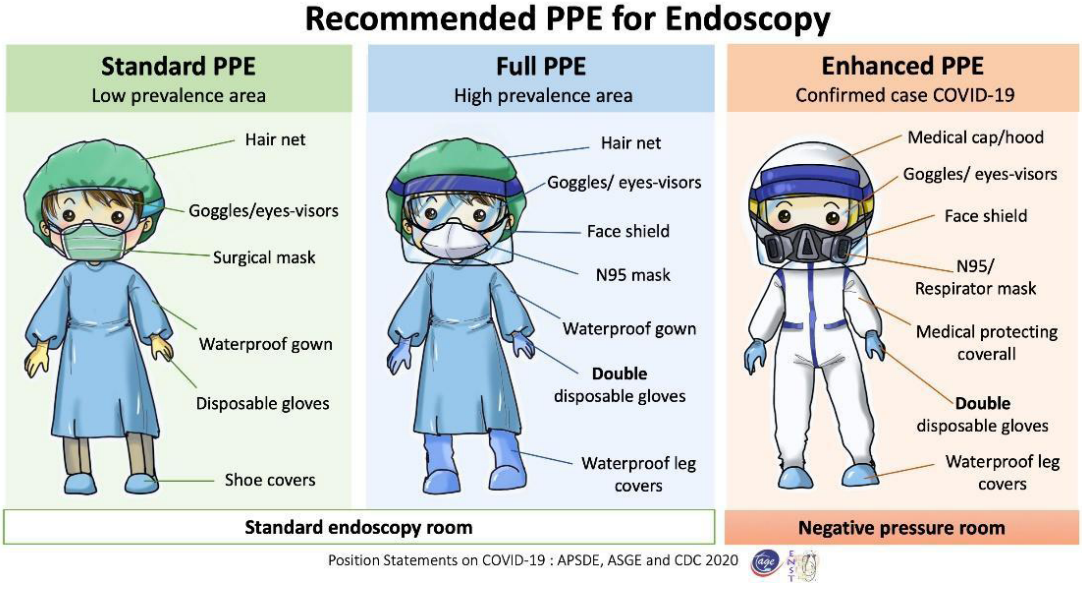

Fig 3. Three types of personal protective equipment (PPE) according to risk level of COVID-19 transmission

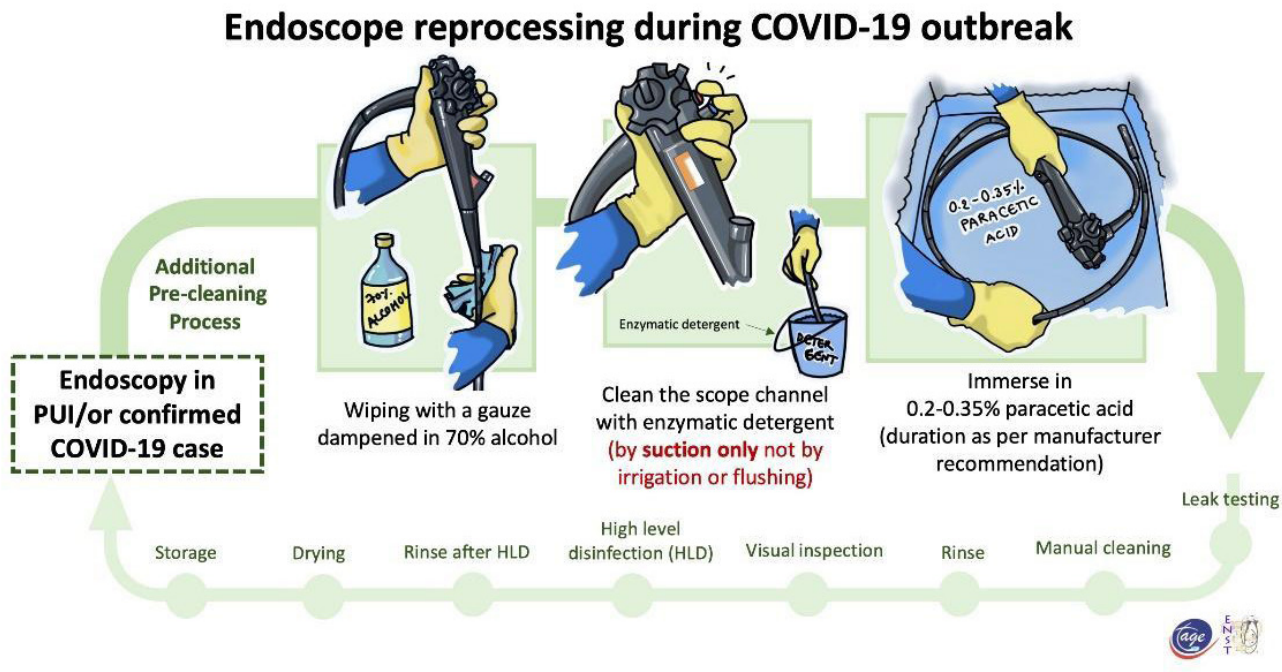

Fig 4. Recommended endoscope reprocessing steps during the COVID-19 outbreak

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Assessment of Prehospital Management of Patients Transported to a Thai University Hospital

Sattha Riyapan, M.D., MPH, Jirayu Chantanakomes, M.D., Onlak Ruangsomboon, M.D., Wansiri Chaisirin, M.D., Chok Limsuwat, M.D., Nattakarn Prapruetkit, M.D., Tipa Chakorn, M.D., Apichaya Monsomboon, M.D.

Department of Emergency Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To assess the quality of prehospital care given to patients transported to a Thai university hospital.

Methods: This prospective observational study collected data from EMS providers who transported patients to Siriraj Hospital during August 2017 to November 2017. Collected data was evaluated by at least 2 EMS medical directors for appropriateness of EMS dispatch and prehospital care. The primary outcome was to determine the quality of prehospital management among patients transported by EMS. Inter-rater variability in the evaluation of patient care between EMS medical directors and medical providers in the emergency department (ED) was performed using Cohen's kappa coefficient, with a value lower than 0.7 indicating significant variability.

Results: Data was collected from 246 EMS providers that transported patients to our center. Evaluation by EMS medical directors found EMS dispatch to be appropriate in 216 cases (87.8%), and patient management to be appropriate in 198 cases (80.5%). Inappropriate prehospital management was found most often in patients who presented with out-of-hospital cardiac arrest (OHCA) (87.5%), and with chest pain (63.6%). Medical providers in the ED rated prehospital management to be appropriate in 93.1% of cases. Cohen's kappa coefficient between EMS medical directors and ED providers was 0.2, which indicates significant variability between the two groups of assessors.

Conclusion: Quality assessment of the Thai EMS system revealed opportunities for improvement in prehospital management of patients dispatched by Thai EMS. Moreover, this study found variability in the evaluation of prehospital care between medical providers at the ED and EMS medical directors. Information from this study will help to influence and guide improvement in prehospital patient care in Thailand.

Keywords: Emergency medical services; quality assessment; prehospital management; emergency department (Siriraj Med J 2020; 72: 287-295)

INTRODUCTION

Emergency Medical Service (EMS) is a system that provides emergency care for patients during transport from incident sites to hospitals. An efficient EMS system was proven to reduce mortality and morbidity in several conditions.[1] Therefore, continuous quality improvement (CQI) in an EMS system is essential to accomplish desired outcomes.

The majority of CQI systems in pre-hospital care settings use the same concepts and methods of quality measurement as those used in in-hospital settings.[2-7] Many studies in recent years were done to find pre-hospital care quality measurements; however, the majority of studies focused on a specific disease, condition, or scenario. For example, a study in out-of-hospital cardiac arrest (OHCA) reported response time, presence of

Corresponding author: Sattha Riyapan
E-mail: sattha.riy@mahidol.ac.th
Received 24 June 2019 Revised 11 February 2020 Accepted 20 February 2020
ORCID ID: http://orcid.org/0000-0003-1867-0080
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bystander CPR, and presence of an AED as important quality indicators that were selected to be part of a CQI system.[3] Other studies that evaluated prehospital care performance in an acute coronary syndrome setting found use of a 12-lead EKG, providing initial treatment with aspirin and/or nitroglycerine, and transporting patients to appropriate hospitals to be indicators that guarantee quality in prehospital care.[9-12]

Thailand's EMS system has been developing a CQI system for 10 years. CQI-related projects have ranged from a small quality improvement project in one organization to the establishment of a national standard for EMS providers, equipment, and ambulances. To date, the national data used to evaluate EMS quality in Thailand has been data collected from Emergency Department (ED) providers. However, sometimes emergency department providers do not understand what to evaluate in a prehospital care setting, and this can make these assessments unreliable. To the best of our knowledge, no previous study from Thailand has collected data directly from arriving EMS teams, after which that data was evaluated for appropriateness by both ED providers and EMS medical directors at a national tertiary emergency department. Accordingly, the aim of this study was to evaluate the quality of pre-hospital care given to patients transported to a Thai university hospital. The secondary objective was to compare the assessments of prehospital care between ED providers and EMS medical directors.

MATERIALS AND METHODS

This prospective observational study collecting data from EMS teams who transported patients to the Department of Emergency Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Hospital during the August 2017 to November 2017 study period. Siriraj Hospital is a 2,300-bed university-based national tertiary center. We included EMS teams that transported patients to the ED or the trauma unit. This study included only EMS teams that were dispatched by the Bangkok EMS Center. EMS teams that did not agree to sign the informed consent document were excluded from the study. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (Si 375/2017).

Data collection

EMS teams dispatched by Bangkok EMS center came through the triage area of Siriraj Hospital. The triage nurse specified where the patient was to be sent according to ED protocol. If the patient needed emergency care, they were immediately transferred to the emergency room. The nurse waited until the EMS team communicated all appropriate information to the ED. The nurse then approached the team and asked them for their written informed consent to request, collect, and record data relating to prehospital care given to the patient that they just transported.

Outcome measurement

The record form was sent to 3 EMS medical directors for a review of the quality of prehospital care that was provided by the EMS team. The primary outcome was the appropriateness of both dispatch decisions and pre-hospital care. Appropriateness was determined based on evidence-based management data and protocols in pre-hospital care, and current resources available for use by Thai EMS teams. Appropriateness criteria were compiled in a check list form, as demonstrated in the appendix. A decision could be reached by agreement of two of three EMS medical directors, and this was the primary outcome. ED providers more broadly assessed prehospital management according to the following 4 categories: airway management, circulation management, bleeding control, and immobilization. Appropriateness among ED providers was defined as a judgment of appropriateness in all 4 categories. Inter-rater reliability between EMS medical directors and ED providers was the secondary outcome.

Sample size calculation

This research aimed to evaluate the quality of EMS prehospital patient care. Evaluation of EMS care in Thailand yielded a favorable prehospital care rate of over 90%. However, that evaluation was not performed by experts in prehospital care. The assessment for quality control was estimated using data from studies conducted in other countries that included evaluation by EMS medical directors that found only 80% adequacy of prehospital patient care by EMS teams.[13] The degree of accuracy required was 0.05 and the probability of a type 1 error was 0.05. The calculated sample size was 246 with a standard normal deviation (Z=1.96).

Statistical analysis

Statistical analysis was performed using SPSS Statistics (SPSS, Inc., Chicago, IL, USA). Demographic data were summarized using descriptive statistics. Categorical data are presented as number or number and percentage, and continuous data are presented as mean ± standard deviation. Inter-rater reliability was calculated by Cohen's kappa coefficient, and a difference in inter-rater agreement of less than 0.7 was defined as significant inter-rater variability.

RESULTS

During the study period, 286 cases were transferred by EMS to our center. Forty of those cases were excluded due to various reasons (Fig 1). The remaining 246 cases were included in our final analysis. The mean age of included patients was 67 years, and 43.1% were male. Most cases received care from advanced life support (ALS) EMS units (186 cases, 75.6%), and almost all cases that arrived were non-trauma cases (240 cases, 97.9%). Only 11 cases (4.5%) had physicians on scene, and 71 (29%) had pre-hospital notification. Table 1 describes the demographic data of patients transported by EMS to Siriraj Hospital.

In non-trauma cases, the chief complaint that led to a call for an ambulance was dyspnea (73 cases, 30.4%), followed by alteration of consciousness (57 cases, 23.7%). Other reasons included seizures (21 cases, 8.8%), weakness (13 cases, 5.4%), and chest pain (11 cases, 4.6%). Provisional diagnosis by EMS was most often dyspnea (29 cases, 12%), followed by alteration of consciousness (12 cases, 7%), hypoglycemia (19 cases, 7.9%), and seizure (18 cases, 7.5%). Regarding pre-hospital interventions, 136 patients (57%) had airway assistance, and most of those received oxygen cannula. Three cases had endotracheal tube intubation attempts, with successful intubation in all 3 cases. Intravenous access was performed in 85 cases (37%), and normal saline was the most often given initial fluid. Point-of-care testing (POCT) for glucose was performed in 150 cases (62.5%), and EKG monitoring was performed in 54 cases (22.5%) (Table 2).

Evaluation of dispatch and prehospital management by EMS medical directors demonstrated a Cohen's kappa coefficient for inter-rater agreement of 0.83 and 0.71, respectively. Final results showed appropriate dispatch in 216 cases (87.8%), and appropriate prehospital care in 198 cases (80.5%) (Table 3).

Fig 2 shows the proportion of inappropriate prehospital management classified by chief complaint. OHCA had the highest proportion of inappropriate treatment (7 out of 9 patients, 87.5%). This was due to no hospital notification in 3 patients, and no initial rhythm noted in 2 patients. The second highest inappropriately managed chief complaint was chest pain (63.3%), which was due to no EKG monitoring and no aspirin administered in ACS suspected patients. Presentation of weakness was the third most inappropriately managed chief complain (53.8%). All of those patients were suspected of having a stroke, but the EMS responders did not notify the hospital.

Only 131 cases (53%) had quality assessment performed by ED providers. Of those, 122 cases (93.1%) were judged to have received appropriate management in all 4 categories (Table 4). A total of 102 cases (78%) in this group had appropriate pre-hospital care evaluated by EMS medical directors. Cohen's kappa coefficient between EMS medical directors and ED providers was 0.2, which indicates significant variability between the two groups of assessors.

DISCUSSION

This prospective observational study collected data from EMS providers who transported patients to Siriraj Hospital. The objective was to evaluate the quality of prehospital care and dispatch. The results showed appropriate prehospital care and dispatch, as evaluated by EMS medical directors, to be 80.5% and 87.8%, respectively.

Our results showed that 80.5% of patients had appropriate care, which is lower than the recent report on EMS care in Thailand that reported appropriate care of over 90% in all categories.[14] The reason that our study found a lower result may be due to the following factors. First, the EMS directors and the ED providers did not use the same form to evaluate the patient. The research form included information that is not regularly collected from EMS providers, but it included key performance indicators in patient care. For instance, prehospital notification is essentially important in patients that are likely to require immediate urgent care upon arrival, like acute stroke patients and OHCA patients.[15] Secondly, our EMS medical directors assessed quality using a specific checklist classified by chief complaints. The checklist was created using performance indicators that were more specific and standardized. For example, POCT glucose in alteration of consciousness or hypoglycemic patients, bronchodilator in COPD/asthma exacerbation, EKG monitoring and ASA in suspected ACS, and IV fluids in sepsis patients. In contrast, medical providers in the ED evaluated cases using only primary survey assessment. So, the observed assessment variability between ED providers and EMS medical directors may be due to the different forms and using key performance indicators rather than primary survey assessments as an evaluation.

Out-of-hospital cardiac arrest had the highest proportion of inappropriate care (87.5%). Excessively long response time, no rhythm noted in the form, and no hospital pre-notification were some of the reasons for inappropriate care. Time documentation was noted in 5 patients, with a median response time of 7 minutes and a median total CPR time of 15 minutes. Response time is one of the key performance indicators in established

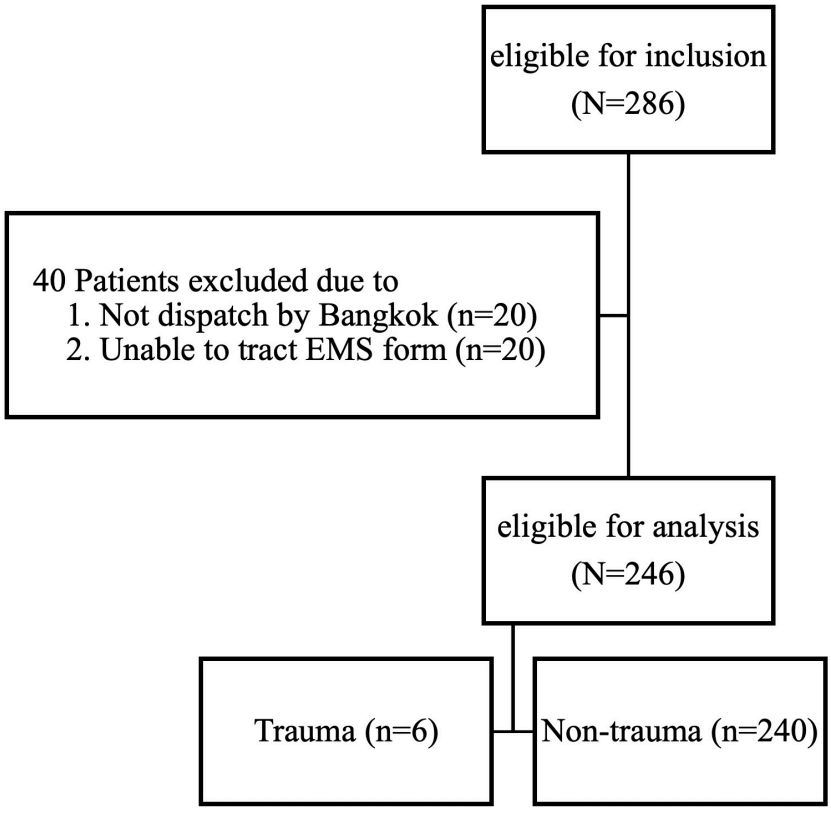

Fig 1. Flow diagram of patient enrollment
Abbreviation: EMS = Emergency medical services

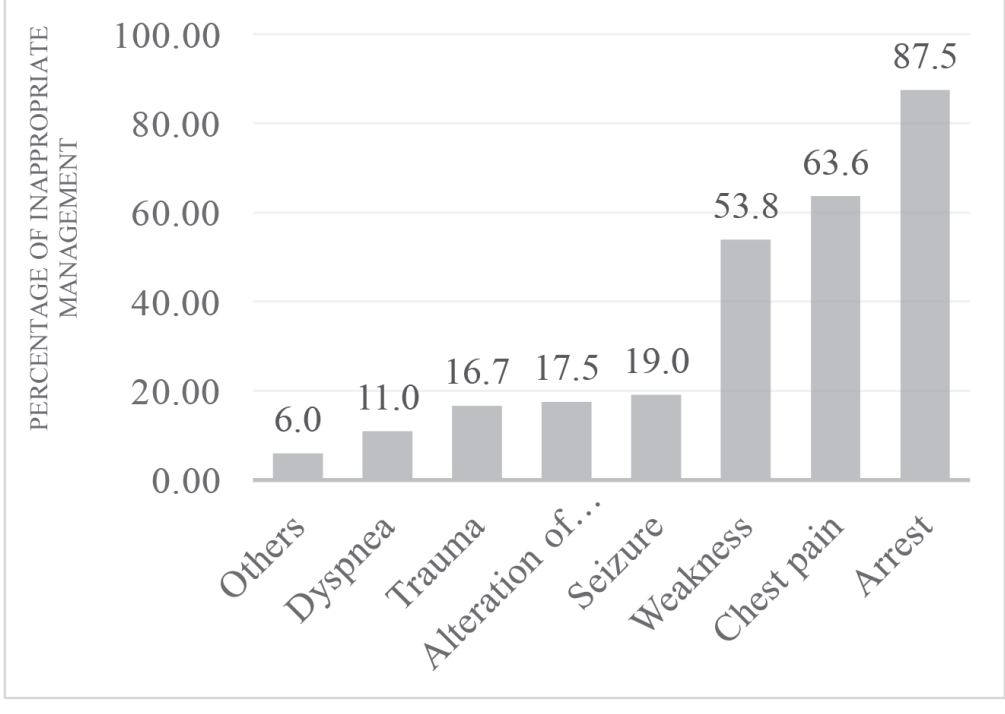

Fig 2. Proportion of inappropriate prehospital management of patients transported to Siriraj Hospital categorized by chief complaints

TABLE 1. Patient and transport characteristics.Abbreviation: SD = Standard deviation.

	Patients (N=246) Number of patients (%)
Male gender	106 (43.1)
Age (years), mean + SD	67 + 17.8
Underlying diseases	
Hypertension	123 (50)
Diabetes	94 (38.2)
Chronic obstructive pulmonary disease or asthma	19 (7.7)
Ischemic heart disease	34 (13.8)
Stroke (Ischemic/hemorrhagic)	34 (13.8)
Epilepsy	7 (2.8)
Others	80 (32.7)
Transfer by advanced life support team	186 (75.6)
Doctor on scene	11 (4.5)
Prehospital notification	71 (28.9)
Non-trauma patients	240 (97.9)

advanced EMS systems. In Thailand, the response time for OHCA should not be more than 10 minutes.[16,17] The data collected in the present study showed a median response time and call-to-arrival to the hospital time that was shorter than data from Asian populations that revealed a median response time of 11.8 minutes, and call-to-arrival to the hospital time of 41.8 minutes.[16] Only 33.3% of OHCA patients in this study had prehospital notification, which was lower than the rates reported from other Asia-Pacific countries.[16] Efforts should be made to improve EMS response or first medical contact time in cases with OHCA. Prehospital notification is also an important issue that should be emphasized to EMS teams.

Patients with chest pain that did not receive EKG monitoring or that did not receive ASA were found to have received inappropriate care. One or both of these treatment omissions was observed in 63.6% of patients that presented with chest pain. As stated in the guidelines[11], patients with suspected ACS should have an initial 12-lead EKG and EKG monitoring to detect arrhythmia or arrest. EKG monitoring was determined to be essential, and was included as a key performance indicator.[9,10] It is also recommended that patients with suspected ACS receive aspirin in prehospital settings. These are all key indicators in current international guidelines. Thai EMS systems should also apply these treatment guidelines in prehospital management to improve patient outcome. Our results showed that half of the patients that presented with weakness were prehospital diagnosed as acute stroke. All of these cases were judged to be inappropriately managed because the EMS provider did not notify the ED. Prehospital notification was shown to reduce time-to-CT and time-to-thrombolytic in patients with ischemic stroke.[18,19] Hospital prenotification, therefore, reduces morbidity and mortality in patients with suspected stroke. Hospital prenotification was reported to be a key performance indicator in an EMS CQI system.[20] Our result showed that 28.9% of EMS providers notified our center before arrival. Awareness of an incoming medical unit facilitated improved preparedness in the ED, especially in critical situations, such as trauma[21], OHCA, stroke, and myocardial infarction. Emphasis of the importance of prehospital notification by EMS units and creating a simple way to transmit patient information should be a key development objective.

Dispatch appropriateness was 87.8%, with dispatch inappropriateness defined as the patient being under-

triaged. Our number of under-triaged cases correlated with the latest 11% figure reported from the National EMS Registry.[14] The reason that patients were under-triaged was multifactorial. The type of provider that was sent depended on the decision of the dispatcher that relied on the information given by the caller. Furthermore, the availability or unavailability of ALS teams also influenced the type of ambulance sent. These findings highlight the need for improved dispatcher skills and decision making, and the need for more ALS units in our service area.

Limitations

This study has some limitations. First, this was a single-center study, which limits the number and demographics of the cases being transported to our center. Second, the number of non-trauma cases was significantly greater than the number of included trauma cases. The key reason for this difference between groups is likely that many (if not most) of the trauma cases that are transported to our center arrive by emergency medical responder, and this type of arrival was not included in our study. This highlights the questions – what are the conditions under which trauma patients are transported to our hospital, and are ALS teams being appropriately dispatched or not? Third, since the initiation of data collection was dependent on the triage nurse who was the first person in the ED to make contact with the EMS team, it is possible that some cases could have been missed. Fourth, some data were collected from patient charts due to the fact that patient data collection during real-time emergency situations is impractical. That retrospective factor means that some data could have been missing or incomplete. Fifth and last, the prospective data collected from the EMS team had to be recalled by the members of the EMS team. It is, therefore, possible that some data could be adversely affected by recall bias.

CONCLUSION

This study found that the EMS system that dispatches medical units to transport patients to the Emergency Department of Siriraj Hospital has room for improvement in several areas of prehospital patient care. Key areas of improvement that were identified include improvements in dispatcher decision making and increasing the number of ALS providers in the service area. Improved prehospital medical care provider knowledge, enhanced quality assurance data collection methods, and the implementation of a performance indicator-based system will improve prehospital care and patient outcomes.

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Conflict of interest declaration: All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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APPENDIX

Check list for EMS quality evaluation by EMS medical director
Check list for evaluator

Conditions	Inappropriate due to
OHCA	**Dispatch** ☐ Dispatch BLS team **Airway** ☐ No BVM and no supraglottic airway device and no intubation ☐ Intubation more than 2 attempts (Only for ALS team) **Circulation** ☐ No IV access if scene time more than 5 minutes (only for ALS team) **CPR** ☐ No note of initial rhythm ☐ No defibrillation if shockable rhythm **Others** ☐ Response time > 8 minutes ☐ No prehospital notification ☐ No EKG monitoring (only for ALS team)
Alteration of consciousness	**Dispatch** ☐ Dispatch BLS team if GCS < 8 **Airway** ☐ O_2sat < 94% and no airway intervention or oxygen therapy ☐ Intubation more than 2 attempts (Only for ALS team) **Circulation** ☐ No IV given if pulse > 120 or hypotension in suspected sepsis case (Only for ALS team) **Others** ☐ No POCT glucose ☐ No prehospital notification in suspected acute stroke

Dyspnea	**Dispatch** ☐ Dispatch BLS team **Airway** ☐ O_2sat < 94% and no airway intervention or oxygen therapy ☐ Intubation more than 2 attempts (Only for ALS team) ☐ No bronchodilator given in suspected exacerbation of COPD or asthmatic attack **Circulation** ☐ No IV given if pulse > 120 or hypotension in suspected sepsis case (Only for ALS team)
Chest pain	**Dispatch** ☐ Dispatch BLS team **Airway** ☐ O^2sat < 94% and no airway intervention or oxygen therapy **Others** ☐ No EKG monitoring ☐ No hospital notification in suspected ACS ☐ No aspirin if suspected ACS and no contraindication (Only for ALS team)
Weakness	**Dispatch** ☐ Dispatch BLS team if unilateral weakness **Airway** ☐ O_2sat < 94% and no airway intervention or oxygen therapy ☐ Intubation more than 2 attempts (Only for ALS team) **Circulation** ☐ No IV given if pulse > 120 or hypotension in suspected sepsis case (Only for ALS team) **Others** ☐ No POCT glucose ☐ No prehospital notification in suspected stroke
Seizure	**Dispatch** ☐ Dispatch BLS team if unilateral weakness **Airway** ☐ O_2sat < 94% and no airway intervention or oxygen therapy ☐ Intubation more than 2 attempts (Only for ALS team) **Circulation** ☐ No IV given if pulse > 120 or hypotension in suspected sepsis case (Only for ALS team) **Others** ☐ No POCT glucose
Other conditions	**Airway** ☐ O_2sat < 94% and no airway intervention or oxygen therapy ☐ Intubation more than 2 attempts (Only for ALS team) **Circulation** ☐ No IV given if pulse > 120 or hypotension in suspected sepsis case (Only for ALS team) **Others** ☐ No POCT glucose in suspected stroke ☐ No prehospital notification in suspected stroke

Trauma

Dispatch

☐ Dispatch BLS team if GCS < 8 or hypotension

Airway with C-spine

☐ No cervical collar in blunt mechanism with GCS < 15 or hypotension

Breathing

☐ O_2sat < 94% and no airway intervention or oxygen therapy

☐ No needle thoracostomy in tension pneumothorax (only for ALS team)

☐ No three side dressing in open pneumothorax (only for ALS team)

Circulation

☐ No IV fluid given in SBP < 70 mmHg (only for ALS team)

☐ Give IV and prolong scene time > 10 min

☐ No bleeding control if active bleeding

Immobilization

☐ No spinal board in blunt mechanism with GCS < 15 or hypotension

Others

☐ Scene time > 10 min

Autoverification Improved Process Efficiency, Reduced Staff Workload, and Enhanced Staff Satisfaction Using a Critical Path for Result Validation

Sairung Nuanin, B.Sc. (Med Tech)*, Panutsaya Tientadakul, M.D.*, Kanit Reesukumal, M.D.*, Sudarat Piyophirapong, M.D.*, Gerald J. Kost, M.D., Ph.D., Busadee Pratumvinit, M.D.***

**Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, **Point-of-Care Testing Center for Teaching and Research (POCT.CTR™), School of Medicine, University of California - Davis, Sacramento, California, USA.*

ABSTRACT

Objective: Continuous process improvements enhance accuracy and productivity in a clinical laboratory setting. This study aimed to investigate the accuracy and efficiency of a new autoverification (AV) system designed to improve the consistency and uniformity of reported laboratory test results.

Methods: Limit checks, delta checks, and consistency checks were established, and then retrospective data from 500 requested tests were used to evaluate the accuracy of AV rules compared to manual verification, which was performed by five experienced medical technologists. Efficiency was evaluated by comparing turnaround time (TAT), error rates, workload, and staff satisfaction between before and after AV implementation.

Results: AV had 100% sensitivity, 77.6% specificity, and a 22% false-positive rate. The AV passing rate was 95%, 85%, 42%, and 39% for chemistry, coagulation, microscopy, and hematology, respectively. The overall passing rate was 65%. After implementation, the mean overall TAT decreased from 54.2±26.6 to 52.4±24.2 min (p<0.001). However, TAT during peak hours increased (p<0.05). Incident reports decreased 8-fold (p<0.05), net workload decreased by 0.76 full-time equivalent, and overall staff satisfaction increased (p<0.001).

Conclusion: Our laboratory's new AV system demonstrated an overall passing rate of 65% with decreases in TAT, incident reports, and workload, and an increase in staff satisfaction.

Keywords: Autoverification; critical path; delta check; full-time equivalent; laboratory information system; turnaround time (Siriraj Med J 2020; 72: 296-306)

INTRODUCTION

Autoverification (AV) uses predetermined rules to direct the release of laboratory results, and verifies results by computer without staff review.[1,2] Previous studies reported that AV improved turnaround time (TAT)[3-7], reduced manpower requirements[4,5], decreased error rates[7], and enhanced physician satisfaction.[3] AV algorithms usually include instrument status flag, quality control (QC) checks, interference indices (hemolysis, icterus, lipemia), critical values, limit checks, delta checks, and consistency checks to filter unusual data.[8-10]

According to Clinical and Laboratory Standards Institute (CLSI) guideline[1], the criteria included in AV algorithms can be simple or complex comprising multiple data elements and multiple-step defined Boolean logic to validate clinical laboratory results. Computer-based actions could include immediate verification of a result, repeat analysis, reflexive testing, addition of comments,

Corresponding author: Busadee Pratumvinit
E-mail: busadee.pra@mahidol.ac.th
Received 23 March 2020 Revised 26 May 2020 Accepted 28 May 2020
ORCID ID: http://orcid.org/0000-0002-5220-0552
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or manual steps, including manual review of the results.[1] Previous studies described the use of AV in some sections or specific test groups of laboratories, including clinical chemistry[2,7,8,11-13], arterial blood gas[14], thyroid function[4,6], sex hormones[4], hepatitis B serological markers[15], urinalysis[7,16], hematology[17-20], and coagulation.[18, 21-24]

Our laboratory experiences a 3-9% annual increase in testing volume each year; however, the number of personnel that perform manual result verification has not increased. In response and in order to improve operational efficiency, we designed and implemented the AV system profiled in this report to improve TAT, improve the consistency of result verification, and to reduce the workload of staff in our laboratory. Here, we present a detailed description of the implementation of AV in clinical chemistry, microscopy, hematology, and coagulation. This study is the first to describe the implementation of an AV system that simultaneously incorporates multiple disciplines using a critical path concept.[25,26] This study aimed to investigate the accuracy of the AV rules, and the efficiency of a new AV system designed to improve the consistency and uniformity of reported laboratory test results. We evaluated the AV passing rate, and determined the impact of the AV system on laboratory personnel. We also compared TAT, requisition sheets per hour, laboratory staff survey, and error rates between before and after the implementation of the AV system.

MATERIALS AND METHODS

Setting and ethics

This study was conducted at the central laboratory of Siriraj Hospital, which is a 2,300-bed national tertiary referral center located in Bangkok, Thailand. This laboratory provides clinical chemistry, microscopy, hematology, and coagulation testing for both outpatient and inpatient services. Our laboratory performs approximately 6 million tests per year using a cobas 8000 (Roche Diagnostics, Mannheim, Germany) for clinical chemistry, a UX-2000 (Sysmex Corporation, Kobe, Japan) for urinalysis, an XN-3000 (Sysmex Corporation) for hematology, and the CA-1500 & CS-2100i systems (Sysmex Corporation) for coagulation analysis. The HCLAB system (Sysmex Corporation) is the laboratory information system (LIS) used in our laboratory. The protocol for this study was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University (Si 331/2015 EC2).

Study design

Fig 1 shows the study protocol for the design and implementation of our AV system. First, we defined the scope of the AV system, including selection of team members, tests, and tools. The tool used in this study was our laboratory information system (LIS). We then collected the information needed to set the AV rules, after which the rules were decided by consensus among the study team members. Next, we collected efficiency data before implementation of AV, and set up rules in the computer system. The accuracy of the AV rules was assessed before implementation into clinical service. After implementation, we collected efficiency data, surveyed laboratory staff, and calculated AV passing rate and full-time equivalent reduction (FTE).

Test selection

We selected tests that are performed on automated analytical systems and that are released automatically via the LIS, including 86 parameters in clinical chemistry (71 plasma/serum/blood parameters, and 15 urine parameters, 1 test in microscopy (urinalysis), 2 tests in hematology (complete blood count [CBC], and automated hematocrit [Hct]), and 5 tests in coagulation (Table 1).

Development of the autoverification algorithm

Fig 2 shows the multicomponent critical path for autoverification. The algorithm for the clinical chemistry and coagulation tests was developed according to the CLSI AUTO10-A guideline.[1] For clinical chemistry, the cobas® 8000 Data Manager was used to check instrument status flags, quality control (QC) results, and interference indices. If there were instrument flags or tests that failed QC, the test results would not be released. If interference indices exceeded the threshold for respective tests, the results would be released with comments to the LIS. For coagulation, the results would be released directly to the LIS.

After entering the AV system, the order of verification was limit checks, delta checks, and consistency checks. If the analytes had critical values, the critical values were used as their limit checks. If the results failed the limit checks, the delta checks were used. Delta checks compared the current data with previous data from the same patient to determine the differences. If the differences were within the range of delta check acceptability, consistency checks were followed. If the test results passed all of the above checks, they were reported by the AV system. If the test results failed any of the above checks, they were reported by manual verification (MV).

Criteria for hematology (complete blood count) and microscopy (urinalysis) tests derived from our previous studies were set in middleware before entering the LIS.[27,28]

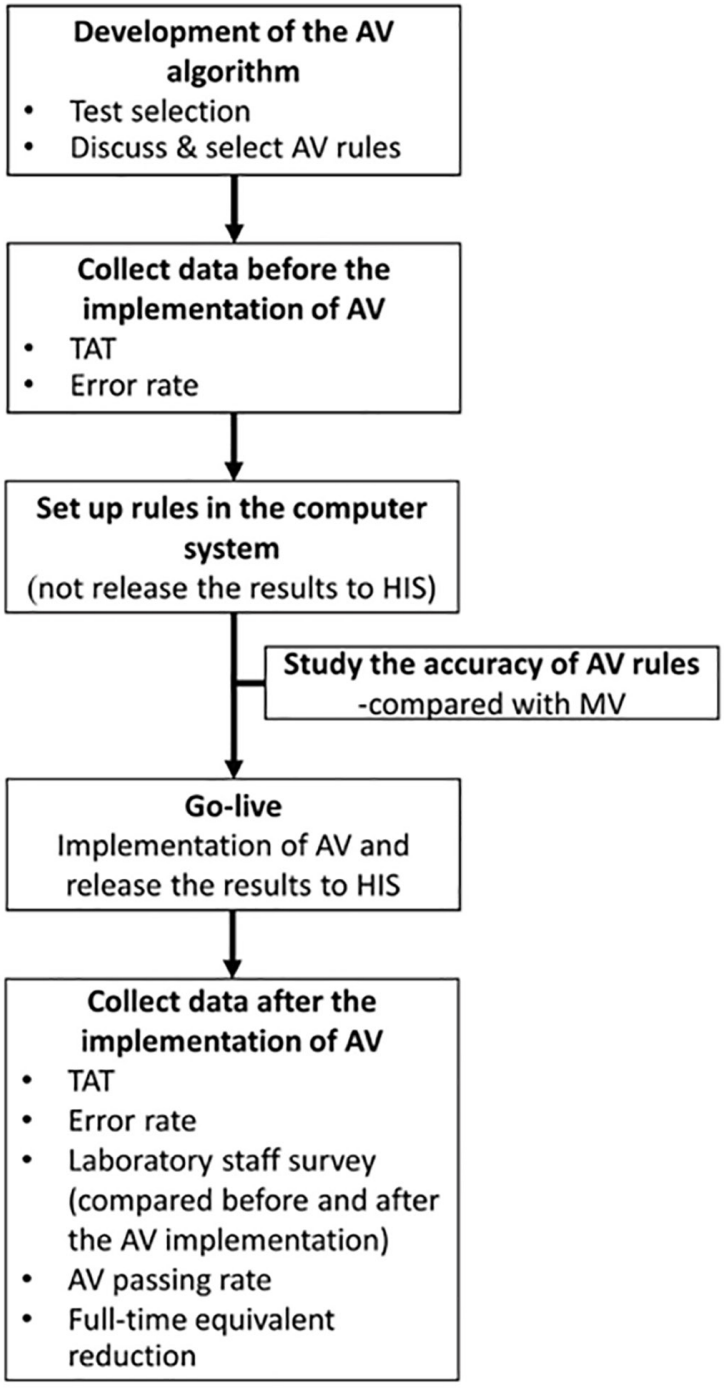

Fig 1. Flow diagram describing the study protocol for the design and implementation of the autoverification system (AV).
Abbreviations: AV, autoverification; HIS, hospital information system; MV, manual verification; TAT, turnaround time

Development of AV rules

Hematology tests

For complete blood count analysis, the first time test results were held in the presence of hemoglobin <7 or >19 g/dL, mean corpuscular volume <70 or >110 fL, red cell distribution width >22%, white blood cell (WBC) <1,500 or >30,000/µL, platelet <100,000/µL or >600,000/µL, no differential of WBC, absolute neutrophil counts <500/µL or >25,000/µL, absolute lymphocyte counts >7,000/µL, absolute monocyte counts >3,000/µL, absolute eosinophil counts >2,000/µL, absolute basophil counts >500/µL, absolute reticulocyte count >250/µL, or suspect flags.[27] In repeated samples, criteria included WBC <1,500 or >30,000/µL and delta WBC ≥10,000/µL within 3 days, platelet <100,000/µL and delta platelet >20,000/µL, and the presence of suspect flags. All automated hematocrit results were released by autoverification.

TABLE 1. List of tests in the autoverification system for clinical chemistry and coagulation.

Plasma/serum/blood in clinical chemistry		
25-hydroxyvitamin D	Follicle stimulating hormone	Placental growth factor
Alanine aminotransferase*	Free calcium	Potassium*
Albumin*	Free thyroxine	Potential of hydrogen (pH)
Alkaline phosphatase*	Free triiodothyronine	Prealbumin
Alpha-1 antitrypsin	Gamma-glutamyltransferase	Procalcitonin
Ammonia	Glucose*	Progesterone
Amylase	Haptoglobin	Prolactin
Anion gap	Hemoglobin A1c*	Sodium*
Aspartate aminotransferase*	High-density lipoprotein cholesterol*	Soluble fms-like tyrosine kinase-1
Beta-crosslaps	High-sensitivity C-reactive protein	Testosterone
Bicarbonate*	Insulin	Thyroid stimulating hormone
Carboxyhemoglobin	Lactate	Thyroxine
Ceruloplasmin	Lactate dehydrogenase	Total bilirubin*
Chloride*	Lipase	Total calcium
Cholesterol*	Low-density lipoprotein cholesterol*	Total procollagen type 1 amino-
terminal propeptide		
Cortisol	Luteinizing hormone	Total protein*
C-reactive protein	Magnesium	Transferrin
Creatine kinase	Methemoglobin	Triglyceride*
Creatine kinase-MB (mass)	N-mid osteocalcin	Triiodothyronine
Creatinine*	N-terminal pro-brain natriuretic peptide	Troponin-T (high-sensitivity)
Direct bilirubin*	Parathyroid hormone	Urea nitrogen*
Estradiol	Partial pressure of CO2 (pCO2)	Uric acid*
Ferritin Partial pressure of O2 (pO2)	Vitamin B12	
Folate Phosphorus		
Urine in clinical chemistry		
Albumin	Creatinine	Protein
Albumin/creatinine	Glucose	Protein/creatinine
Amylase	Magnesium	Sodium
Calcium	Phosphorus	Urea nitrogen
Chloride	Potassium	Uric
Coagulation tests		
Activated partial thromboplastin time*	Fibrinogen*	Prothrombin time*
D-dimer	International normalized ratio*	

*candidate tests incorporated during the trial of the autoverification system

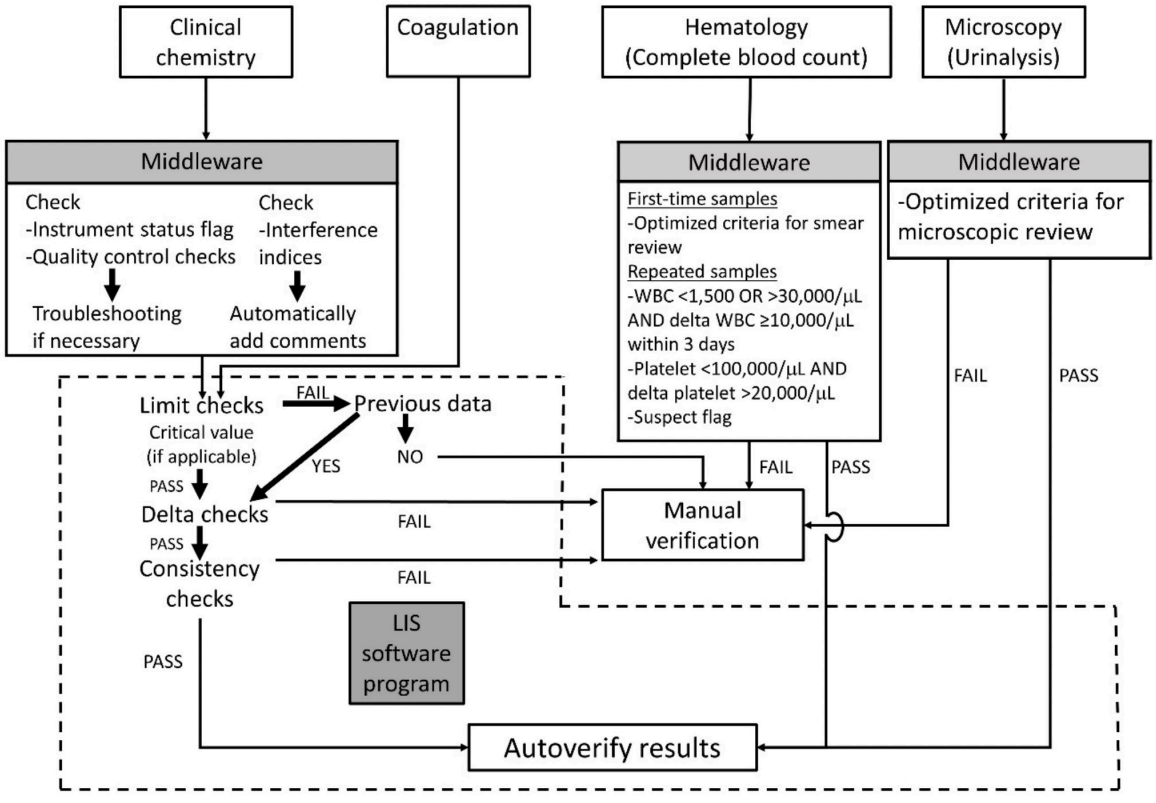

Fig 2. Flow diagram describing the critical path for autoverification (AV). Clinical chemistry tests were checked by middleware before entering the AV system established in the laboratory information system (LIS). Coagulation tests entered the AV system directly. AV rules were set in middleware for hematology and microscopy tests. For optimized criteria for smear review in first-time samples and microscopic review, please refer to the manuscript text.

Microscopy tests

For urinalysis, the results were held in the presence of red blood cells (RBC) >28.1/μL with negative blood tests from chemical strip, RBC 17-59/μL with positive blood tests, RBC >300/μL regardless the blood test results, WBC 50-120/μL, epithelial cells 56-120/μL, small round cells >10/μL, hyaline casts >3/μL, pathological casts >1.5/μL, crystals >10/μL, yeast like cells, sperms >3/μL, or flags.

Clinical chemistry and coagulation tests

The AV rules used in clinical chemistry and coagulation tests included limit checks, delta checks, and consistency checks. All D-dimer results were released by autoverification. The methods for developing the AV rules were, as follows:

1. Limit checks

Limit checks were developed using different methods, as follows:

1.1 Critical values

Critical values are potentially life-threatening laboratory results that require immediate medical attention. The critical values were derived from the literature[29,30] and discussed with clinicians. The analytes for which critical values were used as a limit check were free calcium, glucose, pCO_2, pO_2, potassium, pH, sodium, and troponin-T (high-sensitivity).

1.2 Other sources

We used different sources to employ limit checks. Limit checks were derived from a distribution interval of patient data between the 2.5th and 97.5th percentiles (modified from a previous study)[12], a near-midpoint between the median reference range value and the analyzer's linear analytical measurement limits[7], and the analytical measurement limits.

2. Delta checks

Delta check can be used to identify cases of patient specimen misidentification, specimen integrity issues, and analytical issues.[31] Our laboratory used this formula to calculate delta check:

Delta check (%) = [(current result-previous result)/previous result] *100

The acceptability limit of delta checks in this study was obtained from:

2.1 Reference change value (RCV)

RCV denotes the amount of change that would

indicate a significant difference between two sequential results. The simplified formula for RCV calculation includes variations associated with analytical variation and intra-individual biological variation, as follows:

Reference change value (RCV) = $2^{1/2}$*Z*(CV_A^2+CV_I^2)$^{1/2}$

(Z = Z score, CV_A = analytical variation, CV_I = intra-individual biological variation). In this study, a bidirectional Z-score was used (1.96 for a 95% probability), CV_A was derived from analytical variation during a 1-month period in our laboratory, and CV_I was obtained from the literature.[32]

2.2 Other sources

We applied delta checks from previous autoverification study[2], textbook[30], and delta check rules from another institute (Swedish Covenant Hospital, courtesy of Susan Dawson). The duration of delta checks was 120 days.

3. Consistency checks

The consistency checks were, as follows: (a) If triglyceride was above 800 mg/dL (9 mmol/L) and sodium was simultaneously requested, results would be held. Sodium would be analyzed by direct ISE method instead of indirect ISE method; (b) Direct bilirubin was more than total bilirubin; (c) Albumin was more than total protein; (d) T3 or FT3 or T4 or FT4 was more than the upper limit check for each test, but TSH was not less than the lower limit of the reference interval; and, (e) T3 or FT3 or T4 or FT4 was less than the lower limit check for each test, but TSH was not more than the upper limit of the reference interval.

Implementation

Initially, limit checks, delta checks, and consistency checks were applied to 24 candidate tests to test the system and detect errors in AV settings (Table 1). We then applied them to clinical chemistry and coagulation tests without releasing the results to physicians. Results that passed all AV rules would be labelled as auto-released, and then they were subjected to MV before delivery to clinicians. Results were checked retrospectively to detect discrepancies and errors using simulation program. When no errors occurred, we started to release the results to clinicians without MV.

Accuracy of the AV rules

Before implementing AV into clinical service, we validated the accuracy of AV rules and algorithms by comparing 500 patient reports between AV using simulation and MV by 5 experienced medical technologists (MT). If the verification results were not in agreement with at least 4 of the 5 MT, the decision would be made by consensus among 4 clinical pathologists. If AV rules were triggered and the results were held by MV, the report was graded as true-positive [TP]. If the report was released by both AV rules and MV, it was graded as true-negative [TN]. False-positive [FP] was defined as a report unvalidated by AV, but that was released by MV, and false-negative [FN] was graded as a report validated by AV, but that was held by MV.[33] Accuracy was defined as [TP + TN]*100/[all results].

Efficiency of the AV system

AV passing rates were obtained from each discipline and per requisition sheet using data from 24 h of 5 working days. Laboratory turnaround time (TAT) was defined as the time from specimen receipt to result reporting. We obtained laboratory TAT per hour for 20 days before and 20 days after implementation of the AV system. Error rates were gathered from non-conformities (NC), occurrence reports, and customer complaints during 1 month of each period.

A decrease in full-time equivalent (FTE) was calculated using the following formula: Decrease in FTE = (productive minutes/total work minutes) * the overall AV passing proportion per requisition sheet.

Productive minutes = MV time per day (minutes)* number of requisition sheets per day * 365 days.

MV time was obtained from the average time for MV in triplicate among 13 experienced MT. The total work minutes in our laboratory was calculated to be 96,600 minutes per year.

The questionnaire that we used in this study to determine laboratory staff satisfaction comprised 5 questions that were scored 1 to 10, as follows: (a) How would you describe your workload? (b) How much confidence do you have when reporting laboratory test results? (c) How many incident reports do you think the laboratory receives, either verbal communication or written document? (d) Describe your level of satisfaction with the speed with which laboratory results are reported. (e) What is your overall level of satisfaction with the laboratory reporting system?

Statistical analysis

AV passing rates from each discipline were compared using Pearson's chi-square test. Unpaired t-test was used to compare mean laboratory TAT each hour from 20 days before and 20 days after the implementation of AV. Mann-Whitney U test was used to compare the total number of requisition sheets per hour from 20 days before and 20 days after the implementation of the AV system, and TAT for only AV results versus manually

verified results after the implementation of AV. Error rates were compared using Fisher's exact test. Data from the survey of laboratory staff were compared using paired *t*-test. Statistical analyses were performed using PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Accuracy of autoverification rules

Using the data from a collection of 500 retrospective laboratory test requests, the TP rate was 76.4% (382/500), the TN rate was 1.6% (8/500), the FP rate was 22% (110/500), and the FN rate was 0% (0/500). The accuracy of AV rules was 78% (390/500), the diagnostic sensitivity was 100% (8/8), and the specificity was 77.6% (382/492).

Efficiency of the AV system

1. AV passing rate

To study the AV passing rate, 123,957 test results derived from 13,342 requisition sheets were collected from 5 working days. The highest AV passing rate was found in clinical chemistry at 95% (95% confidence interval [CI]: 94.9-95.1%), whereas the lowest AV passing rate was found in hematology at 39% (95% CI: 37.8-40.0, $p<0.001$). The AV passing rates in microscopy and coagulation were 42% (95% CI: 40.3-43.7) and 85% (95% CI: 83.7-86.2), respectively. The overall AV passing proportion per requisition sheet was 65% (95% CI: 64.2-65.8) (Fig 3).

2. Turnaround time (TAT)

Mean ± standard deviation (SD) laboratory TAT was reduced by 1.8 minutes (54.2±26.6 *vs.* 52.4±24.2 minutes, $p<0.001$) between 20 days before (n=63,813) and 20 days after (n=68,947) implementation of the AV system. The mean TAT after implementation of AV was significantly lower than the mean TAT before AV implementation at the 1st ($p=0.03$), 4th ($p=0.002$), 6th ($p<0.001$), 10th ($p=0.001$), 11th-21st ($p<0.001$), and 24th ($p=0.004$) hours. In contrast, the mean TAT before implementation was significantly lower than the mean TAT after implementation of AV at the 8th (59.4 *vs.* 61.9 minutes, $p<0.001$) and 9th (58.9 *vs.* 60.0 minutes, $p=0.004$) hours (Fig 4). The total number of requisition sheets per hour from 20 days was not different between before and after implementation of the AV process (n=24 hours, median = 2,014 *vs.* 2,151 sheets, $p=0.789$).

3. Error rates

Before implementation of the AV system, errors were found in 7 test results of 848,377 tests per month (0.0008%). After the implementation of AV, errors were detected in 1 of 870,511 tests per month (0.0001%) ($p=0.037$).

4. Impact of AV on laboratory staff

The average time for MV in triplicate by 13 MT was 6.98 seconds per 1 requisition sheet. The average number of requisition sheets per day (n=5 days, the same period we used to determine the AV passing rate) was 2,669 sheets/day. Therefore, the mean total time for MV was 310 minutes per day. The productive time (minutes) = 310 mins * 365 days. After the implementation of AV, the AV passing rate was 65%, which translates to a reduction of 0.76 FTE medical technician personnel needed for result verification.

5. Laboratory staff survey

From the perspective of laboratory staff (n=43), mean±SD score for workload was reduced from 83±18% to 52±21% ($p<0.001$). The confidence to report laboratory results was not different between before and after AV implementation ($p=0.234$). From a staff point of view, incident reports decreased about 9% ($p=0.045$), and the speed of the reporting of results improved by 31% ($p<0.001$). Overall staff satisfaction increased from 65±17% to 89±11% after the implementation of AV ($p<0.001$) (Fig 5).

DISCUSSION

The accuracy of AV rules and algorithms was 78% when compared to MV. The FP rate was 22%, and the FN rate was 0%. The sensitivity and specificity were 100% and 77.6%, respectively. Fuentes-Arderiu, *et al.* compared the Validation Assistée aux Laboratoires d'Analyses Biologiques (VALAB) Expert System to MV by nine clinical biochemists among 500 clinical laboratory reports. They found the diagnostic sensitivity of the VALAB Expert System to be 100%, and the diagnostic specificity was 95.7%.[11] Our study had lower specificity because we used thresholds of limit checks at 2.5th and 97.5th percentile of cumulative patient data so about 5% of results would be held by AV. We plan to decrease false-positive alerts through adjusting thresholds, and by modifying non-specific rules.

Our overall passing rate, which included several disciplines in the critical path, was 65%. For clinical chemistry, the AV passing rate was 95% compared to 84.8% in the study by Fuentes-Arderiu, *et al.*[11] Krasowski, *et al.* reported an increase in the passing rate for clinical chemistry from 40% in 2000 using the rudimentary rules set in the LIS to 99% in 2010 after the implementation of sophisticated rules in middleware[2]. For microscopy, the AV passing rate in this study was 42%, which is nearly the same as the 43% rate reported by Torke, *et al.*[7], and the

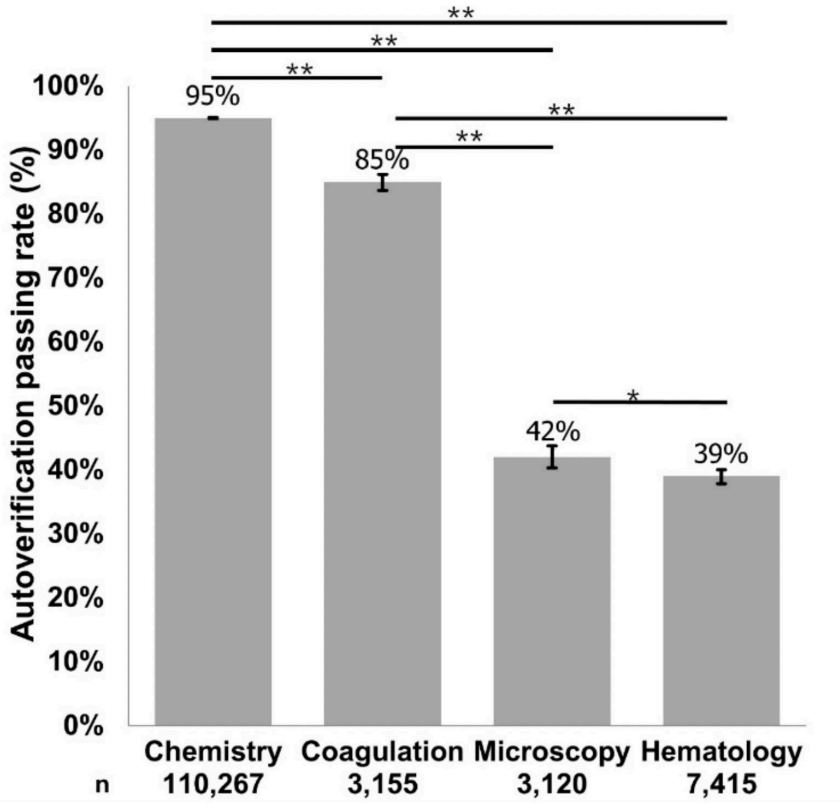

Fig 3. Autoverification (AV) passing rates (95% confidence interval). AV passing rates for chemistry, coagulation, microscopy, and hematology obtained from 5 working days (*p<0.05, **p<0.001).

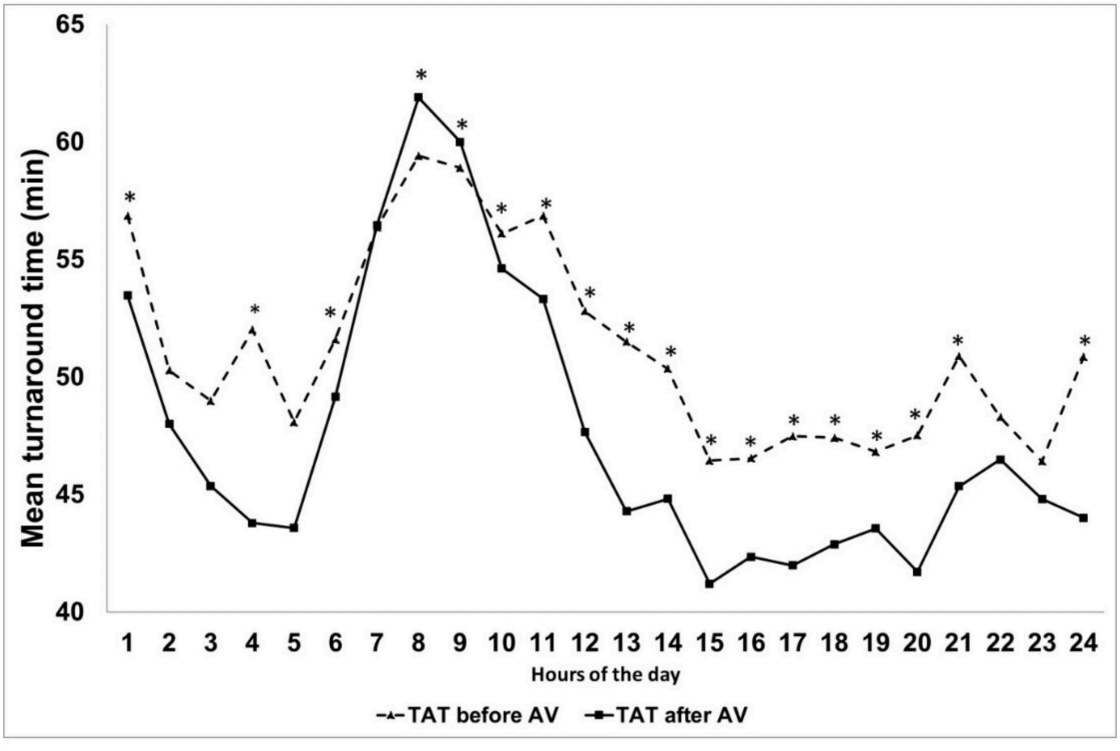

Fig 4. Turnaround time (TAT) before and after the implementation of autoverification (AV). Mean hourly TAT compared between 63,813 requisition sheets obtained during 20 days before and 68,947 requisition sheets obtained during 20 days after the implementation of AV (*p<0.05).

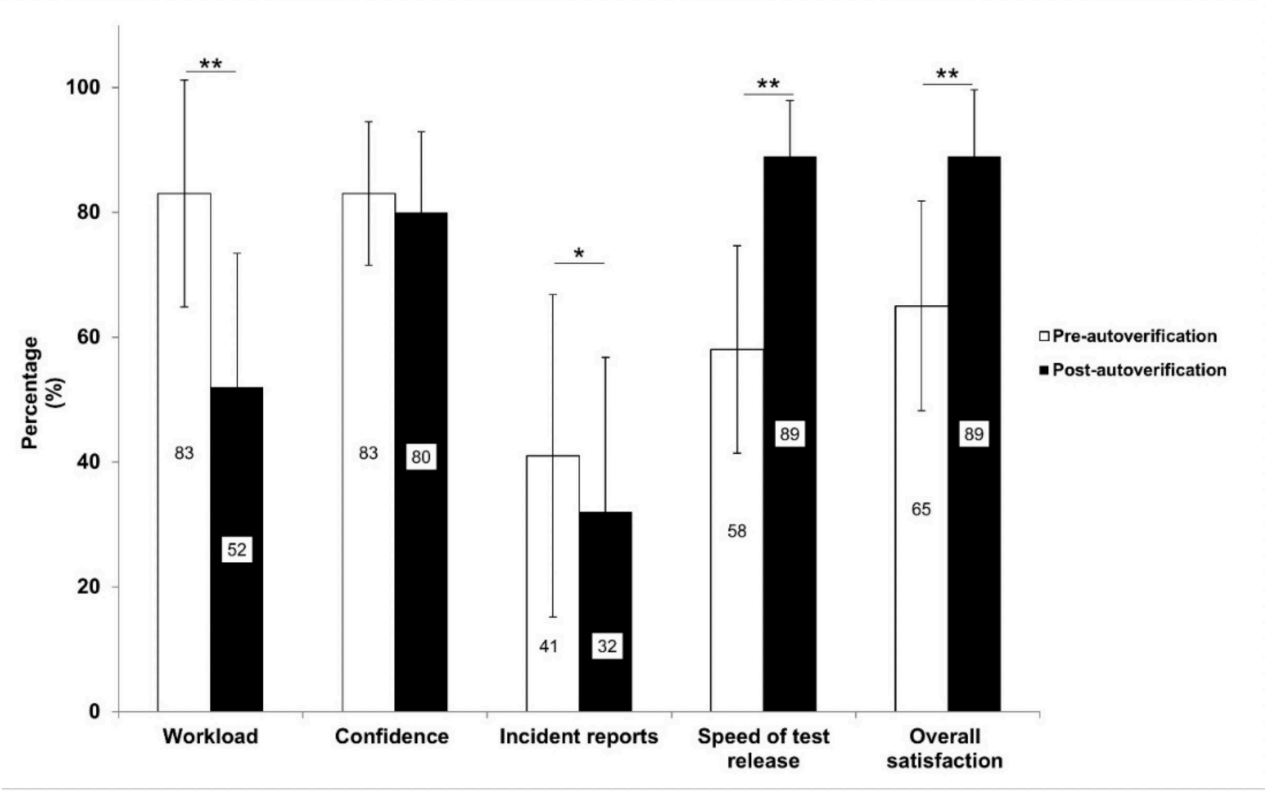

Fig 5. Laboratory staff survey. Mean ± standard deviation percentage of survey items (n=43) compared between before and after the implementation of the autoverification system (*p<0.05, **p<0.001).

47.6% rate reported by Palmieri, *et al.*[16] For hematology, the passing rate in this study was 39%. Martinez-Niteo, *et al.*[17] found a passing rate of 53.4% in pilot study, with a subsequent increase to 60% 18 months later – both of which were very high compared to our result. For coagulation, our passing rate was 85%, which is similar to the 82% result reported by Zhao, *et al.*[21]

Our study found that the overall TAT decreased from 54.2 to 52.4 minutes (3.3%) after the implementation of AV. However, the TAT during the peak hours (8th and 9th hours) was significantly increased. A possible explanation for this increase may be insufficient capacity of the computer server to manage the increased number of processing requests during the peak period. A previous study from a large, urban, tertiary acute care public hospital and trauma center showed that the TAT, calculated from time of specimen received to result released, was reduced by 22% (142 min *vs*. 112 min) after the implementation of AV.[7] However, the baseline TAT in our laboratory was about half of the baseline TAT in that study; therefore, the percent reduction might not be comparable.

The error rate in our study decreased from 0.0008% to 0.0001%. Previous study from John H. Stroger, Jr. Hospital of Cook County (JHSHCC) showed that error rates decreased from 0.06% to 0.009%.[7] We found that after implementation of AV, the number of laboratory staff needed for MV was reduced by 0.76 FTE. The study from JHSHCC found a much more dramatic reduction from 14 FTEs to 8.5 FTEs (a reduction of 40%) after implementation of AV.[7] Our laboratory had a lower reduction of FTE because criteria for manual review of complete blood count and urinalysis were already in place before the implementation of AV in all disciplines. After implementation of the AV system in our central laboratory, laboratory staff found the amount of workload and defects to be decreased, and the speed of test result reporting and overall satisfaction to be increased.

Although the AV system implemented at our center has many advantages, it also has some limitations. The software that our laboratory used to design our system was not specifically designed to build the rules and algorithms for the AV system. Software used to build AV rules and algorithms according to CLSI guideline should have the ability to use multiple data, to make changes to algorithms, and to provide an easy to use and flexible user interface that provides laboratory defined information in real time.[1] In some contrast, we were limited in our ability to set rules due to the functional limitations of our software. Moreover, large volume traffic during peak hours caused processing delays, which resulted in delays

in the reporting of results. Lastly, our software does not currently have a feature that facilitates comparison of result verification time between AV and MV.

CONCLUSION

Our new AV system demonstrated high sensitivity for error detection. The overall AV passing proportion per requisition sheet was 65%. This passing rate is similar to previous studies in clinical chemistry, microscopy, and coagulation tests. TAT time improved after implementation of the AV system, except during peak hours (8th and 9th hours), and this was likely due to a high traffic-related CPU slowdown. Overall staff satisfaction increased, and incident reports and workload decreased after the implementation of AV.

AV has many advantages relative to the reporting of test results; however, MV is still necessary to verify results after they fail AV. The improved efficiency of AV allows staff to spend more time on result verification. We will continue to evaluate rules to decrease false-positive alerts by modifying non-specific rules, and by addressing rules that triggered alerts that had no further action. If implemented broadly, this approach could enhance laboratory understanding and performance via successive critical path improvements.

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Authors' contributions

All authors contributed sufficiently to this study to be included as an author. All authors have read and approved the final version of this manuscript, and all authors are in agreement with the decision to submit this manuscript for journal publication.

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Conflict of interest declaration

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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Sleep Quality and Burnout Syndrome among Residents in Training at the Faculty of Medicine, Prince of Songkla University

Thirapath Chatlaong, M.D., Jarurin Pitanupong, M.D., Pakawat Wiwattanaworaset, M.D.

Department of Psychiatry, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Objective: To assess sleep quality, burnout syndrome and associated factors among residents in training.

Methods: A cross-sectional study surveyed all residents in training at the Faculty of Medicine, Prince of Songkla University; from August to October, 2019. The questionnaires were composed of 3 parts: 1) Personal and demographic inquiry 2) The Pittsburgh Sleep Quality Index (PSQI), Thai version 3) The Maslach Burnout Inventory (MBI), Thai version. All data were analyzed using descriptive statistics, and the results were showed as average, percentage, frequency, and standard deviation. Associated factors of sleep quality were analyzed by chi-square and logistic regression.

Results: There were 217 respondents. The majority of residents were female (57.1%), with a mean age of; 26.8±1.6 years. The participants reported their mean working hours, per week, as 67.8±28.5, and 78.3% of them had poor sleep quality. The problematic sleep subscales were subjective sleep quality, sleep duration, and daytime dysfunction. In addition, the disturbed factors for sleep quality were sleep disruption while being on call at 02.00-04.00am, temperature and noise in the bedroom while being on duty. The prevalence of burnout syndrome among residents was 95.4%, with the highest score revealed to be emotional exhaustion. Logistic regression showed that the associated factors of sleep quality were environmental problems in the bedroom while being on duty and emotional exhaustion.

Conclusion: Most residents had poor sleep quality; with associated factors of sleep quality being environmental problems in the bedroom and burnout syndrome.

Keywords: Resident; sleep quality; burnout syndrome (Siriraj Med J 2020; 72: 307-314)

INTRODUCTION

The number of doctors is proportionally much less in comparison to the population unit, as listed by the Ministry of Public Health. In 2018, data from the Ministry of Public Health showed that the ratio between medical personnel per population unit was 1:1,843. Then some doctors are required to practice for extended working hours, which may have negative effects on sleeping hours and quality; possibly leading to other undesired consequences, including medical errors[1], car accidents[2], job burnout[3] and depression.[1]

Residents are doctors who have graduated from their medical studies, and are attending specialization practices. During such specialization practices, residents are often subjected to high stress periods.[4,5] These stress factors include extended working hours and a high level of responsibility, with limited ability over the control of their working environment.[6]

Corresponding author: Jarurin Pitanupong

E-mail: pjarurin@medicine.psu.ac.th

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ORCID ID: http://orcid.org/0000-0001-9312-9775

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In the past, many studies have been conducted abroad on the sleep quality of residents. The prior studies found that most residents experienced sleep problems, which in turn affected their decision-making ability, medical procedures, increased the risks of car accidents[2] as well as job burnout.[3]

In Thailand, there has been no study conducted on the effects of poor sleep quality among doctors and residents. There were only two studies surveyed the effect of sleep problems and job efficiency among nurses.[7,8] However, a previous study was conducted on job burnout syndrome among medical doctors and residents, in the Regional Health District, that found the high prevalence of burnout syndrome (99.6%). Moreover, the related factors to emotional exhaustion were daily work hours, awareness of stress from work and awareness of a lack of sleep.[9] Furthermore, another previous study conducted at Songklanakarin Hospital found the prevalence of burnout syndrome among 244 residents was 100.0%, and the related factors to emotional exhaustion were daily work hours and the awareness of a lack of sleep.[10]

As mentioned before, sleep disturbance or poor sleep quality is associated to burnout syndrome. However, there are currently few studies that explore the sleep quality, and associated factors of sleep disturbance among residents in training at Prince of Songkla University. Therefore, the objective of this survey was to determine sleep quality and associated factors, so as to enhance the focus of these sleep problems, including burnout syndrome among residents.

Definition

Sleep quality is divided into two types; good sleep quality is having The Pittsburgh Sleep Quality Index (PSQI) score ≤ 5 and poor sleep quality is having The Pittsburgh Sleep Quality Index (PSQI) score > 5.

Burnout syndrome, according The Maslach Burnout Inventory (MBI) questionnaire, comprises of 3 parts 1) emotional exhaustion 2) de-personalization 3) reduced occupational accomplishment.

Major ward includes internal medicine, surgery, obstetrics and gynecology, orthopedic surgery and physical medicine, and pediatrics.

Minor ward includes anesthesiology, emergency, otolaryngology head and neck surgery, ophthalmology, radiology, family medicine and preventive medicine, and psychiatry.

MATERIALS AND METHODS

The Ethics Committee of the Faculty of Medicine, Prince of Songkla University approved this study (REC: 62-072-03-4). The study explored all residents that were in training at the Faculty of Medicine, Prince of Songkla University; from August to October, 2019. The inclusion criterions were being a resident and able to complete all of the questionnaires. Exclusion criterion was residents on a leave of absence.

Methodology

The residents were approached by a researcher in their classes beforehand. They were invited to participate, by introducing the rationale and given an overview on the information contained of the research. In cases of those who cooperated, the researcher distributed 3 self-reporting questionnaires; these were explained to the participants in detail. The participants were permitted to take a few minutes to deliberate whether or not to join the survey. So as to assure the participants' identities would be protected signatures of participants were not desired, and all participants had the right to withdraw from the study at any time.

All participants were allowed to finish, and return the questionnaires immediately or at a later time. They could submit the questionnaires via two options: drop it in the case at the front of the classroom, or return it and place it in the case located at the Psychiatry Department. Therefore, protecting respondent confidentiality was retained.

Instruments

The questionnaires consisted of 3 parts:

1) Personal and general demographic information comprising of: gender, age, training year, religion, income, marriage status, caffeine or alcohol drinking, substance usage, underlying diseases and working information.[11-13]

2) The Pittsburgh Sleep Quality Index (PSQI) Thai version. The PSQI is a self-rated questionnaire that evaluates sleep quality, and disturbances within a month time interval. Nineteen dimensions originate seven components: subjective sleep quality, sleep duration, sleep latency, sleep disturbances, habitual sleep efficiency, use of sleep medication and daytime dysfunction. Each component score ranges from 0 to 3 points. A score of "0" represents no difficulty, whilst a score of "3" represents severe difficulty. The seven component scores are collected to yield one "global" score, with a range from 0 to 21 points, total score >5 that means poor sleep quality.[11]

3) The Maslach Burnout Inventory (MBI) Thai version. This questionnaire comprised of 3 parts:

1) Emotional exhaustion (EE) subscale, Cronbach's alpha coefficient=0.9: never (score=0) to every day (score=6)

2) Depersonalization (DP) subscale, Cronbach's alpha

coefficient=0.7: never (score=0) to every day (score=6)

3) Personal accomplishment (PA) subscale, Cronbach's alpha coefficient=0.7): every day (score=0) to never (score=6)[14-16]

Statistical analysis

All data were analyzed, in order to describe the participants' behavior using descriptive statistics. The results are showed as: average, percentage, frequency, and standard deviation. The associated factors of sleep quality were analyzed using chi-square and logistic regression.

RESULTS

Demographic data

During August to October, 2019, residents that completed the questionnaires was 217 of 341; the response rate was 63.6%. Of the participants, 124 were female (57.1%) and 202 were unmarried (93.1%). Mean age was 26.8±1.6 years and the median income (IQR) was 35,000 (30,000-40,000) baht, per month. In addition, 168 participants drank coffee or tea (77.4%), 30 of them were drinkers (13.8%), and only 9 of them used sedative medication (4.1%), such as benzodiazepines or chlorpheniramine. Moreover, the majority of participants had no psychiatric disorders (93.5%); however, 44 of them had minor physical illness (20.3%), such as allergy, dyspepsia or migraine. (Table 1) In their field of work, the participants reported the mean working hours per week was 67.8±28.5.

Sleep data and quality

The majority of participants had poor sleep quality (78.3%). The mean Global PSQI score was 7.1±2.4. Among the sleep quality subscales, this study found sleep duration, subjective sleep quality, and daytime dysfunction were the problematic sleep subscale. (Table 2)

Among the participants, they reported the disturbed time period of sleep while being on call that affected or influenced sleep quality, was 02.00-04.00 am and 00.00-02.00 am (43.8% and 22.1%, respectively). (Table 3) In addition, the majority determinants disturbing sleep quality were environmental factors in the bedroom while being on duty, such as temperature and noise (70.5% and 64.5%, respectively). (Table 4)

Burnout syndrome

According to this survey, the prevalence of burnout syndrome (BS) among residents was 95.4%, and 56.2% of participants had a high level of EE, whereas 94.0% of them had a high level of PA. The mean score of EE, DP and PA were 26.9±13.1, 8.5±7.0, 15.8±10.2, respectively. (Table 5)

The association between demographic characteristics, burnout syndrome and sleep quality

Variables whose p-values from the univariate analysis were lower than 0.2 were included in the chi-square test. (Tables 1, 3, 5) From the multivariate analysis, emotional exhaustion and environmental problems in the bedroom were statistically significant associated factors related to sleep quality. (Table 6)

DISCUSSION

This survey showed the prevalence of poor sleep quality among residents was 78.3%, this rate was lower than the findings among nurses in Thailand.[8] However, this rate was higher than the findings in other countries that found 54.3% of residents had poor sleep quality.[17] According to work dysfunction, from poor sleep quality, the previous study reported the level of vigilance tasks among medical nurses during a night-shift work period was lower than other periods.[7] Among daytime work efficacy, this study concurred with the previous study, in that daytime dysfunction was subscale from poor sleep quality.

In addition, the prevalence of burnout syndrome among residents (95.4%) was agreeable to the previous study, which found that residents in training at the Faculty of Medicine, Prince of Songkla University had a high level of EE.[8] From this useful information, the Faculty of medicine should be aware of health-cover providers work-loads and work-hour estimations, as they may be significant keys for quality of life, for both residents, and inevitably Thai patients. Additionally, it will be useful for promoting residency health, and enhancing preventive programs for dropout risk among residents.

According to the associated factors of sleep quality, this study found the amount of working hours, environmental problems in the bedroom while being on duty, emotional exhaustion or burnout syndrome were significantly associated with poor sleep quality. Furthermore, most residents worked more than 55 hours per week, these prolonged working hours or exhaustion, caused by this burden, may affect their sleep quality. As a previous study found, working more than 55 hours per week was related to abnormal sleep latency, sleep duration and habitual sleep efficiency.[18] In addition, prolonged daytime work may produce stress, job burnout,[16,19] emotional exhaustion[13,20] and poor sleep quality; as demonstrated by a previous study conducted in India.[3]

TABLE 1. Association between general characteristics and sleep quality (n=217).

Demographic characteristics	Number (%) Good sleep (n=47)	Poor sleep (n=170)	Total (n=217)	Chi2 *P*-value
Gender				0.03
Male	27 (57.4)	65 (38.2)	92 (42.4)	
Female	20 (42.6)	104 (61.2)	124 (57.1)	
Not answered	0 (0.0)	1 (0.6)	1 (0.5)	
Marriage status				0.01[a]
Single	40 (85.1)	162 (95.3)	202 (93.1)	
Couple	7 (14.9)	7 (4.1)	14 (6.5)	
Not answered	0 (0.0)	1 (0.6)	1 (0.5)	
Academic training				0.55
1st	17 (36.2)	51 (30.0)	68 (31.3)	
2nd	15 (31.9)	61 (35.9)	76 (35.0)	
3rd	12 (25.5)	34 (20.0)	46 (21.2)	
4th	3 (6.4)	20 (11.8)	23 (10.6)	
Not answered	0 (0.0)	4 (2.3)	4 (1.8)	
Coffee or tea drinking (within 1 month)				0.12
Yes	32 (68.1)	136 (80.0)	168 (77.4)	
No	15 (31.9)	34 (20.0)	49 (22.6)	
Alcohol drinking (within 1 month)				0.63
Yes	5 (10.6)	25 (14.7)	30 (13.8)	
No	42 (89.4)	145 (85.3)	187 (86.2)	
Substance usage (within 1 month)				1[a]
Yes (cigarette)	0 (0.0)	1 (0.6)	1 (0.5)	
No	46 (97.9)	169 (99.4)	215 (99.1)	
Not answered	1 (2.1)	0 (0.0)	1 (0.5)	
Medication for sedation (within 1month)				1[a]
Yes	2 (4.3)	7 (4.1)	9 (4.1)	
No	45 (95.7)	163 (95.9)	208 (95.9)	
Physical illness				0.21
Yes	6 (12.8)	38 (22.4)	44 (20.3)	
No	41 (87.2)	132 (77.6)	173 (79.7)	
Psychiatric illness				0.21[a]
Yes	0 (0.0)	8 (4.7)	8 (3.7)	
No	45 (95.7)	158 (92.9)	203 (93.5)	
Not answered	2 (4.3)	4 (2.3)	6 (2.8)	

[a] Fisher's exact test

TABLE 2. The Pittsburgh Sleep Quality Index (PSQI) subscales (n=217).

PSQI subscales	Mean ± S.D. (Min-Max)
Subjective sleep quality	1.4±0.7 (0-3)
Sleep latency	0.7±0.8 (0-3)
Sleep duration	2.1±0.2 (2-3)
Habitual Sleep efficacy	0.3±0.7 (0-3)
Sleep disturbance	0.8±0.5 (0-3)
Use of sleeping medication	0.1±0.5 (0-3)
Daytime Sleep dysfunction	1.8±0.9 (0-3)
Mean ± S.D. (Min-Max)	7.1±2.4 (0-15)

TABLE 3. Association between working information and sleep quality (n=217).

Working information	Number (%) Good sleep (n=47)	Poor sleep (n=170)	Total (n=217)	*Chi2* *P*-value
Department				0.59
Major ward	23 (48.9)	93 (54.7)	116 (53.5)	
Minor ward	24 (51.1)	77 (45.3)	101 (46.5)	
Amount of working hour/week				0.02
≤40	12 (25.5)	26 (15.3)	38 (17.6)	
41-55	10 (21.3)	19 (11.2)	29 (13.4)	
>55	24 (51.1)	124 (72.9)	148 (68.2)	
Not answered	1 (2.1)	1 (0.6)	2 (0.9)	
Period of sleep cycle disruption				0.75
22.00-00.00 pm	7 (17.5)	20 (12.4)	27 (12.5)	
00.00-02.00 am	10 (25.0)	38 (23.6)	48 (22.1)	
02.00-04.00 am	16 (40.0)	79 (49.1)	95 (43.8)	
04.00-06.00 am	5 (12.5)	22 (13.7)	27 (12.4)	
Not answered	2 (5.0)	2 (1.2)	4 (1.8)	
Environmental problems in the bedroom while being on duty				<0.01
Not disturb	14 (30.4)	21 (12.4)	35 (42.8)	
Disturb	32 (69.6)	148 (87.6)	180 (157.2)	

Note: There were missing values for some variables.

TABLE 4. Disturbing environmental factors in the bed room while being on duty (n=217).

Disturbing environmental factors	Disturb	Not disturb	Not answered
Bright light	105 (48.4)	107 (49.3)	5 (2.3)
Noise	140 (64.5)	75 (34.6)	2 (0.9)
Temperature	153 (70.5)	59 (27.2)	5 (2.3)
Inconvenience of bedding	118 (54.4)	91 (41.9)	8 (3.7)
Smell	115 (53.0)	93 (42.9)	9 (4.1)

TABLE 5. Burnout syndrome (n=217).

Burnout subscale	Number (%) Good sleep (n=47)	Poor sleep (n=170)	Total (n=217)	Chi2 *P*-value
Emotional exhaustion				< 0.001
Low (0-16)	15 (31.9)	23 (13.5)	38 (17.5)	
Moderate (17-26)	13 (27.6)	34 (20.0)	47 (21.7)	
High (≥27)	14 (29.8)	108 (63.5)	122 (56.2)	
Not answered	5 (10.6)	5 (2.9)	10 (4.6)	
Mean ± S.D. (Min-Max)	26.9±13.1 (0-51)			
Depersonalization subscale				0.16
Low (0-6)	24 (51.1)	71 (41.8)	95 (43.8)	
Moderate (7-12)	10 (21.3)	39 (22.9)	49 (22.6)	
High (≥13)	8 (17.0)	55 (32.4)	63 (29.0)	
Not answered	5 (10.6)	5 (2.9)	10 (4.6)	
Mean ± S.D. (Min-Max)	8.5±7.0 (0-30)			
Personal accomplishment				0.04[a]
Low (≥39)	2 (4.3)	0 (0.0)	2 (0.9)	
Moderate (32-38)	0 (0.0)	1 (0.6)	1 (0.5)	
High (0-31)	40 (85.1)	164 (96.5)	204 (94.0)	
Not answered	5 (10.6)	5 (2.9)	10 (4.6)	
Mean ± S.D. (Min-Max)	15.8±10.2 (0-48)			

[a] Fisher's exact test

TABLE 6. The association between demographic data, burnout syndrome and sleep quality (n=217).

Factors	Crude odds ratio (95% Confidence interval)	Adjusted odds ratio (95% Confidence interval)	*P*-value LR test
Emotional exhaustion			<0.01
Low	1	1	
Moderate	1.66 (0.66,4.13)	1.58 (0.62,4.02)	
High	5.32 (2.23,12.68)	5.25 (2.17,12.72)	
Having disturbing factors in the bedroom			0.02
No	1	1	
Yes	2.78 (1.23,6.27)	2.8 (1.18,6.64)	

This study showed environmental problems in the bedroom while being on duty (temperature and noise) and sleep disruption while being on call, especially between 02.00-04.00am, were significant factors of poor sleep quality. Because, in normal human circadian rhythm, deep sleep or Non-REM periods commonly occur at this time. Then, the disruption during Non-REM periods may produce confusion, amnesia, poor judgement,[21] dysfunctions,[22] which in turn affects sleep quality in the next phase.[23] This point should be highlighted to the Faculty of medicine, for awareness and focus on residency quality of life or health promotion, because it may be useful for preventing harmful patient care; as well as decreasing the training risk from exhaustion or burnout.

Limitations

This study was a cross-sectional survey, and employed self-reporting questionnaire for individual evaluation. Besides its response rate (63.6%), the information might have led to bias in addition the study was quantitative, and the sample size was restricted to only residents in lower, southern Thailand. Thus, it is too soon to generalize nation-wide, or cannot be used for summing up all Thai residents.

Future recommendations and implications

Henceforward studies should include additional Faculty of medicines, within Thailand; in other words, a multi-center study is introduced. Moreover, other studies should retain a more qualitative method.

CONCLUSION

Most residents had poor sleep quality. The associated factors of sleep quality were environmental problems in the bedroom, emotional exhaustion or burnout syndrome.

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Effect of Home-Based Rehabilitation Exercise Program for Elderly Patients with Femoral Neck Fracture after Bipolar Hemiarthroplasty

Chantanee Ninlerd, B.Sc., Sangarun Dungkong, B.Sc., Gonrada Phuangphay, B.Sc., Chutikarn Amornsupak, B.Sc., Rapeepat Narkbunnam, M.D.

Department of Orthopaedic Surgery, Faculty of Medical Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: This study aimed to investigate the effectiveness of a home-based rehabilitation program by examining recovery time, the risk of falling, improvement in mobility, and improvement in quality of life.

Methods: This prospective cohort study included elderly patients who sustained a primary femoral neck fracture that required cement less bipolar hemiarthroplasty using posterior approach at the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Time to return to pre-injury status was the primary outcome. Patient quality of life was evaluated using Short Physical Performance Battery (SPPB) and EQ5D-5L at three and six months after surgery.

Results: Forty-one patients were included in the final analysis. All patients could return to pre-injury ambulatory status within six months. The mean SPPB score at six months was significantly higher than the mean score at three months after surgery. The results of EQ5D-5L showed that quality of life improved from three to six months after surgery. No postoperative complications were observed, including infections, secondary fractures, or hip dislocations.

Conclusion: The home-based rehabilitation program evaluated in this study was found to be safe and effective for improving recovery, physical performance, and quality of life. All participating patients could return to their pre-injury ambulatory status within six months.

Keywords: Femoral neck fracture; bipolar hemiarthroplasty; home-based rehabilitation exercise program; short physical performance battery (SPPB); EQ5D-5L (Siriraj Med J 2020; 72: 315-320)

INTRODUCTION

Since the proportion of elderly population continues to increase, the issues that affect aging and aged societies are attracting attention in many countries around the world. In 2015, 15.8 percent of Thai population were people aged 60 years and over. That number is projected to increase to 23.1% by 2025, and 37.1% by 2050.[1] Accordingly, Thailand has one of the fastest growing older adult populations in Asia.[2] Health and healthcare are major concerns of older people. Consistent with that, osteoporosis has been raised as one of the most important diseases because it occurs in most elderly people. Osteoporosis associates with a decrease in muscle strength and an increase in fall risk, which increases the risk of osteoporotic fractures.[3] The literature shows that approximately 20 percent of elderly people could experience a femoral neck fracture, which

Corresponding author: Rapeepat Narkbunnam
E-mail: mai_parma@hotmail.com
Received 7 May 2019 Revised 30 September 2019 Accepted 30 October 2019
ORCID ID: http://orcid.org/0000-0002-3564-1700
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can cause serious health consequences with approximately 10 to 20% mortality within six months and significant loss of mobility.[4,5] A standard of treatment that is now used to treat displaced osteoporotic femoral neck fracture is bipolar hemiarthroplasty.[5]

After undergoing this surgical procedure, patients have to attend a rehabilitation program to improve their ability to physically perform daily activities to the same level they did prior to their fracture, and to minimize their risk of falling and mortality.[6,7] General resistance exercise and aerobic practice can improve patient mobility.[8] However, participation in a rehabilitation program may be inconvenient for some patients for several possible reasons. For instance, most rehabilitation programs require a patient to travel to the hospital or rehabilitation center, and this involves higher cost of rehabilitation, travel-related expenses, the inconvenience of travel, and often the need for a caregiver. Home-based exercise programs were established to reduce the cost of rehabilitation, and to help patients regain physical functions.[9,10] Many studies support the benefit of having exercise at home – particularly for patients with femoral neck fractures.

In Thailand, various exercise programs have been implemented. A few studies have evaluated the effectiveness of home-based rehabilitation for stroke patients.[11,12] For patients with knee osteoarthrosis, Chaipinyo and Karoonsupcharoen studied home-based strength and balance training.[13] Our review of the literature revealed that no studies have assessed the effectiveness of home-based program for elderly patients with femoral neck fracture who received bipolar hemiarthroplasty. Accordingly, the aim of this study was to investigate the effectiveness of a home-based rehabilitation program for elderly patients with femoral neck fracture who received bipolar hemiarthroplasty by examining recovery time, the risk of falling, improvement in mobility, and improvement in quality of life.

MATERIALS AND METHODS

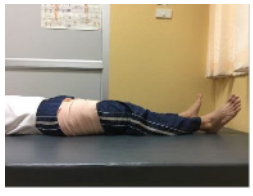
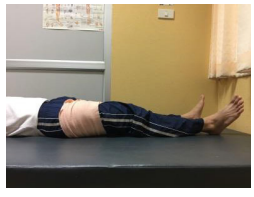
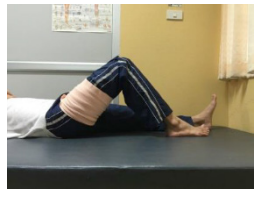
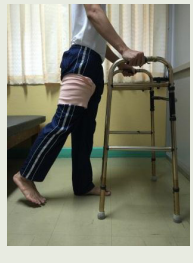
This study was approved by Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 400/2016). Patients aged from 60 to 85 years who required treatment for primary femoral neck fracture and who underwent cementless bipolar hemiarthroplasty using posterior approach were enrolled starting in January 2016. Included patients had to have had the ability to walk independently or walk with a gait aid for at least 10 meters prior to sustaining their fracture. Patients were excluded from this study if they had a disease that affects exercise, such as severe cardiovascular disease, severe respiratory disease, psychiatric disease, dementia, or cognitive impairment. Patients with post-operative complications that adversely affect the ability to exercise were also excluded.

Before undergoing surgery, all patients were instructed in how to perform a home-based rehabilitation program for femoral neck fractures by a physiotherapist. The program was designed to help patients recover and to improve their mobility so they can return to their pre-fracture status. Each patient had to perform the postoperative exercise once a day for six months. The rehabilitation program includes both lying and standing exercises. Lying exercises consisted of hip abduction and hip flexion. Standing exercises included hip abduction, hip extension, and hip flexion.[14] Patients were advised to perform each exercise 10-15 reps/set, 2 sets/time, 3 times per day (Table 1). Each patient received an exercise booklet and daily record sheet. From six weeks to the three month after surgery, participants would receive a phone call every week to encourage the rehabilitation program and to assess their pain level and their ability to walk. From the three months to the six months after surgery, patients would get a phone call once every two weeks.

Data collection

Demographic and clinical data of recruited patients were collected, including age, gender, side, number of days before surgery, weight, height, and body mass index (BMI). Patients were appointed for follow-up at six weeks, three months, and six months after receiving the operation. At follow-ups, postoperative complications, such as fracture, dislocation, and wound complication, were investigated. Time to return to pre-injury ambulatory status was measured as the primary outcome. Time to return to pre-injury status was indicated as six weeks, three months, or six months after the operation date. Physical performance and quality of life was assessed using Short Physical Performance Battery (SPPB) and EQ5D-5L, respectively. The SPPB test consists of three sections, including the ability to rise from sitting on a chair, standing balance test, and walking speed test, with scores that range from 0 (worst performance) to 12 (best performance).[15] The EQ5D-5L is a standardized tool used for describing health-related quality of life. It consists of two parts associated with health status: EQ5D and a visual analogue scale (EQ-VAS), which range from 0 to 100. The maximum score indicates the best health status.[16,17] This tool was proven to be reliable and valid for assessing the health status of elderly patients with femoral neck fractures.[18]

TABLE 1. The rehabilitation program for patients with femoral neck fracture after bipolar hemiarthroplasty

Lying position · Repeat 10-15 reps/set, 2 sets/time, and 3 times per day	Hip abduction exercise	Move your leg out to the side as far as you can and then back to the starting position.  
	Heel slide	Bend your knee while keeping your heel on the bed. Do not let your knee roll inward or bend over 90˚.  
Standing position · Repeat 10-15 reps/set, 2 sets/time, and 3 times per day	Hip flexion exercise	Lift your operated leg toward your chest. Do not lift your knee higher than your hip.  
	Hip abduction exercise	Keep your body straight and lift your leg out to the side.  
	Hip extension exercise	Lift your operated leg backward slowly, keep your body straight and then return your foot.  

Statistical analysis

Patient demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as frequency and percentage. Chi-square test was used to compare time to return to pre-injury ambulatory status. Paired *t*-test was used to compare the results of SPPB, EQ5D, and EQ-VAS. All data was analyzed using SPSS Statistics (SPSS, Inc., Chicago, IL, USA). A *p*-value less than 0.05 was considered statistically significant.

RESULTS

There were 53 patients with femoral neck fracture who underwent cementless bipolar hemiarthroplasty, as shown in Fig 1. The first patient was recruited in January 2016, and the last followed-up patient visited our clinic in April 2018. Eleven patients were excluded due to one of the following reasons: age over 85 years, conservative treatment, or inability to walk more than 10 meters. One patient was withdrawn from the study because two follow-up visits were missed.

Patient demographic and clinical characteristics are shown in Table 2. The mean age of participants was 76.4 ± 8.4 years, and 34 patients (82.9%) were women. Average BMI was 22.2 ± 3.2 kg/m^2. No patients had postoperative complications, including infections, secondary fractures, or hip dislocations.

After evaluating the outcome parameters, the proportion of participants who returned to pre-injury ambulatory status within six weeks, three months, and six months after surgery was 24.4%, 82.9%, and 99.9%, respectively (Table 3). As a result of this rehabilitation program, all included patients were able to return to their pre-injury ambulatory status within six months.

As shown in Table 3, the mean SPPB scores was 6.7 ± 1.3 at three months, and 8.5 ± 1.9 at six months ($p < 0.000$). According to the EQ5D questionnaires, health-related quality of life was improved from the three months to the six months. EQ-health state scores were 0.9 ± 0.0 and 1.0 ± 0.0 at three and six months ($p < 0.000$), respectively. For the pain scores, the average of EQ-VAS was 69.4 ± 12.1 at three months, which was improved to 85.9 ± 8.5 at six months ($p < 0.000$). At six months, 39 patients (95.1%) had an EQ-VAS score of zero on the prosthesis side. No patients experienced any limitations of physical function after six months.

DISCUSSION

Bipolar hemiarthroplasty is a conventional surgery for treating elderly people with femoral neck fracture.[19] After undergoing this procedure, all patients need to participate in a rehabilitation program to leverage their recovery. Home-based exercise programs were developed to reduce the cost of treatment and improve the effectiveness of patient rehabilitation.[9,10]

This prospective cohort study showed the recovery of patient functions following bipolar hemiarthroplasty to be improved after performing the recommended rehabilitation program for six months. Patient physical functions, quality of life, and time to return to pre-injury status were evaluated using SPPB and EQ5D-5L. Similar to previous studies, we found the SPPB scores at six months to be significantly higher than the scores at three months after surgery.[10,20]

Several studies have evaluated new rehabilitation programs that associated with intensive supervision, equipment, and progressive resistance exercises at hospitals. Those programs were found to have improved the capacity of conventional rehabilitation.[21-23] In contrast, the present study evaluated a newly designed home-based rehabilitation program that involved patients following a prescribed program and three physical therapist follow-up visits within six months. The advantages of this home-based rehabilitation program are lower cost and no requirement for the patient to travel to the hospital.

Although older patients with femoral neck fractures had asymmetric strengths of lower extremities and impaired postural balance[24,25], the program evaluated in this study included standing exercises to improve strength and balance in elderly patients. The efficacy of this program was demonstrated by improvement in SPPB scores.

The results obtained from the EQ5D-5L show that quality of life was improved from three months to six months. Moreover, 39 participants in this study had an EQ-VAS score of zero at six months. Neither recurrent fracture nor dislocation occurred during the rehabilitation period. No evidence of falling case found in this study. Thus, it can be concluded that this home-based rehabilitation program could safely and effectively promote health-related quality of life.

The key limitation of this study is that although patients were instructed in the exercises to perform and when and for how long, there is no way to know for certain that the exercise program was strictly followed. To enhance the likelihood of compliance, we provided each patient with a logbook so they could record their daily rehabilitation exercises and activities. The strengths of this study are its prospective design, the six months duration of rehabilitation, and the fact that validated assessment tools were used to evaluate recovery.

In conclusion, the home-based rehabilitation program

TABLE 2. Patient demographic and clinical characteristics

Characteristics	Mean ± SD or % (n)
Age, year	76.4 ± 8.4
Gender, % (n)	
Male	17.1 (7)
Female	82.9 (34)
BMI, kg/m^2	22.2 ± 3.2
Affected side, % (n)	
Right	43.9 (18)
Left	56.1 (23)
ASA	
2	56.1 (23)
3	43.9 (18)
Days before surgery, day	10.3 ± 11.3

Abbreviations: ASA = American Society of Anesthesia Score, BMI = body mass index

TABLE 3. Results of the rehabilitation program

Variables	Mean ± SD or % (n)	*P*-value
Patients returned to pre-injury ambulatory status, % (n)		
Within 6 weeks	24.4 (10)	
Within 3 months	**58.4 (24)**	
Within 6 months	17.1 (7)	
Mean SPPB scores		
At 3 months	6.7 ± 1.3	<.000
At 6 months	8.5 ± 1.9	
EQ-health state scores		
At 3 months	0.9 ± 0.0	<.000
At 6 months	1.0 ± 0.0	
EQ-VAS scores		
At 3 months	69.4 ± 12.1	<.000
At 6 months	85.9 ± 8.5	

p-value < 0.05 indicates statistical significance

Abbreviations: SPPB = Short Physical Performance Battery; EQ5D-5L questionnaire = EQ-health state score and EQ-VAS score

evaluated in this study was found to be safe and effective for improving patient recovery, physical performance, and quality of life. All participating patients were able to return to their pre-injury ambulatory status within six months. The results of this study suggest that exercise program can be used as a standardized rehabilitation protocol for elderly patients with femoral neck fracture following bipolar hemiarthroplasty.

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Conflicts of interest: No conflicts of interest

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Short-term Postoperative Outcomes Before and After the Establishment of the Siriraj Upper Gastrointestinal Cancer Center: A Propensity Score Matched Analysis

Chawisa Nampoolsuksan, M.D.*, Thammawat Parakonthun, M.D.*,, Thikhamporn Tawantanakorn, M.D.*, Andres Mora, M.D., Ph.D.***, Jirawat Swangsri, M.D., Ph.D.*,**, Thawatchai Akaraviputh, M.D., Dr.Med*, Asada Methasate, M.D., Ph.D.*,**, Anusak Yiengpruksawan, M.D.****, Vitoon Chinswangwatanakul, M.D., Ph.D.***

**Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, **Siriraj Upper Gastrointestinal Cancer Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand, ***Hospital of Specialties "Carlos Andrade Marin", Quito, Ecuador, ****Capital Health Cancer Center, Pennington, New Jersey, USA*

ABSTRACT

Objective: To evaluate short-term postoperative outcomes compared between before and 1 year after the establishment of the Siriraj Upper Gastrointestinal Cancer Center (UGICC).

Methods: Medical records of 211 adenocarcinoma of stomach (GC) and esophagogastric junction (AEG) patients who underwent radical gastrectomy at Siriraj Hospital during January 2012-September 2018 were reviewed (before UGICC; B-UGICC). Data of 40 patients operated upon during October 2018-September 2019 were prospectively collected after the establishment of UGICC (A-UGICC). Propensity score (PPS) matched analysis was conducted, and short-term outcomes were compared. Enhanced Recovery After Surgery (ERAS) protocol was applied to some patients in A-UGICC. Results of conventional care (CC) were compared with ERAS protocol.

Results: PPS matched 78 patients (13 AEG, 65 GC) in B-UGICC, and 40 patients (6 AEG, 34 GC) in A-UGICC. Median postoperative length of stay (POS) was significantly shorter in A-UGICC than in B-UGICC; however, complications and time to oral diet tolerability were not significantly different between groups. In A-UGICC, median POS and time to toleration of oral diet were significantly shorter among 15 ERAS patients than among 25 CC patients. Intestinal recovery and time to ambulation trended to be earlier in ERAS. Regarding the ERAS outcomes, 103 CC and 15 ERAS patients were matched to 36 non-ERAS and 13 ERAS patients. Median time to toleration of oral water, liquid diet, and solid diet was significantly shorter in ERAS than in CC (all $P<0.001$). Median POS was significantly shorter in ERAS ($P<0.001$). Postoperative complications were non-significantly different between ERAS and CC. There was no mortality in this study.

Conclusion: UGICC with multidisciplinary team approach and application of ERAS protocol contributed to improvement of postoperative short-term outcomes.

Keywords: Gastric cancer; esophagogastric junction; gastrectomy; multidisciplinary team; centralization; Enhanced Recovery After Surgery (ERAS) (Siriraj Med J 2020; 72: 321-329)

INTRODUCTION

Gastric cancer is one of the cancers that is often diagnosed as late-stage at presentation. Radical surgical resection with systemic chemotherapy is a mainstay of treatment.[1-4] Radical surgical resection should be considered among those regarded as being fit for surgery.[5,6] An

Corresponding author: Thammawat Parakonthun
E-mail: t.parakonthun@gmail.com
Received 9 April 2020 Revised 21 April 2020 Accepted 22 April 2020
ORCID ID: http://orcid.org/0000-0002-2990-0649
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experienced multidisciplinary team is needed from the time of diagnosis to encourage, educate, and care for these patients.[7-9] Previous meta-analysis demonstrated the effect of a high volume center on postoperative mortality.[10] High volume center appeared to associate with more radical surgery and lymph node dissection, and this resulted in better overall survival.[11,12] In Thailand, the first Upper Gastrointestinal Cancer Center (UGICC) was established at the Faculty of Medicine Siriraj Hospital, Mahidol University in November 2017. The aim of the Siriraj UGICC is to be a center of excellence in esophageal and gastric cancer treatment and care. Our multidisciplinary team, which includes surgeons, medical oncologists, radiation oncologists, anesthesiologists, nutritionists, physical therapists, nurses, and researchers, was organized to provide intensive perioperative and surgical care. Since October 2018, which is when surgical and perioperative protocols were refined and fully implemented, esophageal and gastric cancer patients at Siriraj Hospital have been treated and cared for by this specialized multidisciplinary team.

Several studies have recently published the results of Enhanced Recovery After Surgery (ERAS) protocol for perioperative care in gastric surgery.[13,14] Significantly earlier recovery of intestinal function and shorter hospital length of stay were observed in ERAS patients.[15,16] A reduction in total medical costs was also found in patients that received ERAS protocol.[17] However, no statistically significant difference in postoperative morbidities was found in ERAS patients when compared to those who received conventional treatment.[18-20] These studies suggest the safety and efficacy of ERAS when applied to gastric cancer patients undergoing gastric surgery. Accordingly, the ERAS protocol was adopted and integrated into the Siriraj UGICC perioperative care protocol.

The primary aim of this study was to evaluate short-term postoperative outcomes compared between before and 1 year after the establishment of the Siriraj UGICC. The secondary objective was to compare short-term postoperative outcomes between patients who received ERAS and patients who received conventional care (CC).

MATERIALS AND METHODS

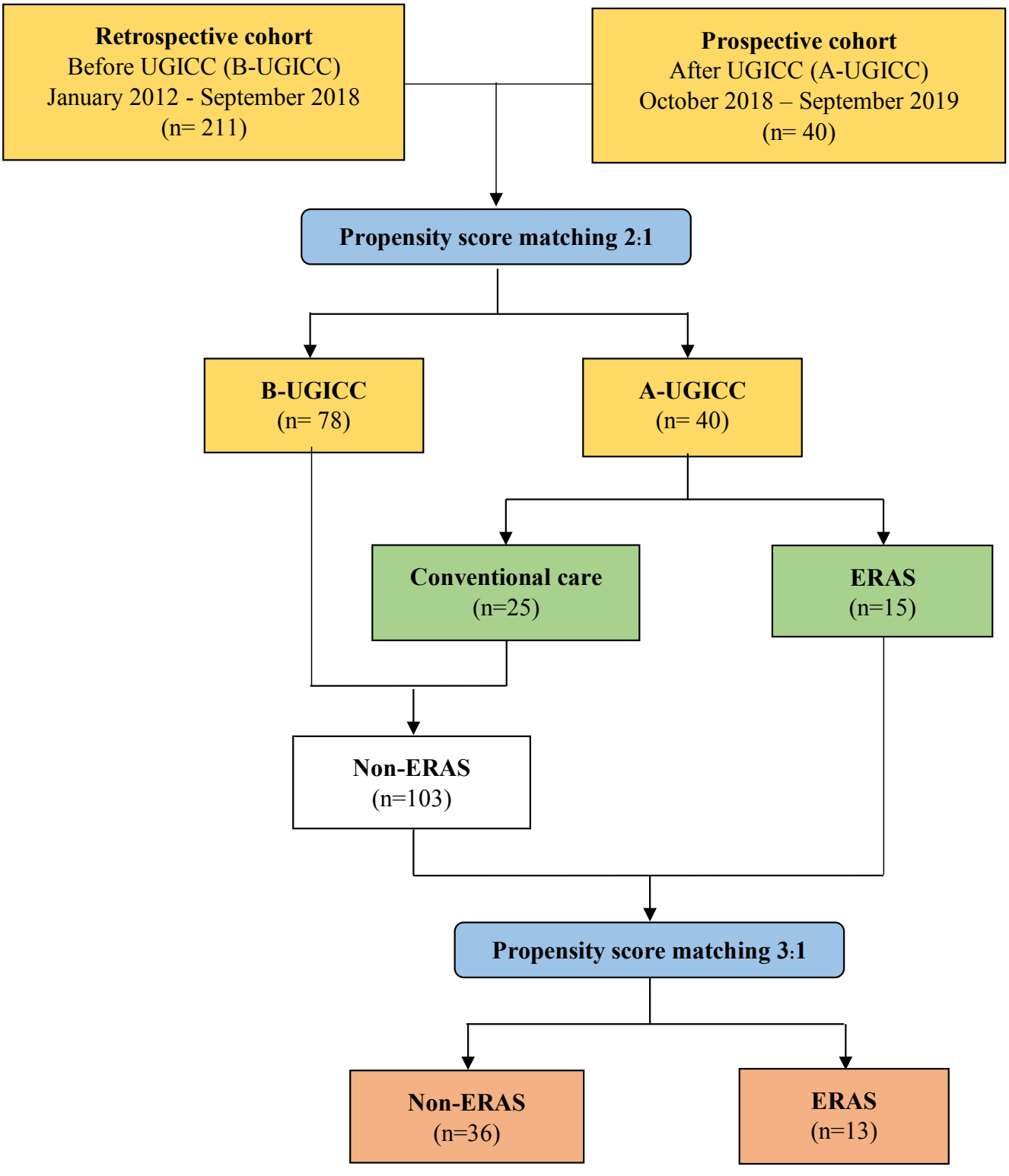
Patients

The medical records of 211 patients with adenocarcinoma of stomach or esophagogastric junction (Siewert type II and III) during January 2012 to September 2018 who underwent curative gastrectomy according to Japanese gastric cancer treatment guidelines[21,22] at Department of Surgery, Faculty of Medicine Siriraj Hospital were reviewed and classified as the *before UGICC group* (B-UGICC). Data of 40 new patients who underwent surgery for the same conditions during October 2018 to September 2019 were prospectively collected following the protocol record form of the Siriraj UGICC, and those patients were classified as the *after UGICC group* (A-UGICC). Propensity score matched analysis (approximately 2:1) with a caliper width of 0.2 using gender, age, American Society of Anesthesiology (ASA) grade, tumor location, operative approach, and extent of operation was conducted to compare between B-UGICC and A-UGICC groups, and to reduce selection bias. After establishment of the Siriraj UGICC, the ERAS protocol was applied in some patients who underwent upper gastrointestinal procedures whereas some patients received traditional care. Perioperative ERAS or conventional care protocols were applied depending on the patient-doctor discussion. Postoperative recovery and complications were compared between 25 patients who received conventional care and 15 patients who received ERAS protocol. Moreover, the short-term outcomes were compared between those in the B-UGICC and A-UGICC groups who received conventional care (non-ERAS group) and patients who received the ERAS protocol in the A-UGICC group (ERAS group) after propensity score matching (approximately 3:1) (Diagram 1).

Preoperative clinicopathological characteristics of patients, including age, gender, ASA grade, tumor location, operative approach and extent of resection were reviewed and recorded. Extent of gastric resection and lymphadenectomy were performed in accordance with Japanese gastric cancer treatment guidelines.[21,22] In this study, extended gastrectomy was defined as transabdominal gastrectomy with combined adjacent organ resection. Esophagogastrectomy was defined as a transthoracic esophagogastrectomy for adenocarcinoma of esophagogastric junction.

Perioperative protocols included preoperative clinical evaluation and laboratory investigations. Anesthesiologist was consulted to evaluate for patients at high risk for anesthesia. Nutritional status was assessed and improved to achieve the energy and protein requirements. Smoking and alcohol were strictly prohibited for at least 2-4 weeks before surgery. For patients receiving the ERAS protocol, breathing exercise and chest physical therapy were emphasized before admission. Clear liquid oral diet was allowed until 3 hours before surgery. Risk of postoperative nausea and vomiting was assessed and prevented. Postoperative pain was controlled by multimodal strategies. Early removal of all catheters and early ambulation were promoted. Oral fluid was started on the first day after surgery, and then soft diet was introduced on postoperative day 3

Diagram 1. Patients and propensity score matching for comparison.



Abbreviations: UGICC, Upper Gastrointestinal Cancer Center; ERAS, Enhanced Recovery After Surgery group

if tolerable. Patients were discharged as soon as they satisfied the discharge criteria.

This study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 119/2019).

Outcome measurements

The primary objective was to determine differences in short-term postoperative outcomes between before and after UGICC establishment. Study parameters were timing of intestinal function recovery, timing of ability to tolerate oral intake, postoperative complications and severity classified by Clavien-Dindo classification[23], postoperative length of hospital stay (POS), and postoperative mortality. In this study, we defined intestinal function recovery as time to first flatus and defecation. Severe complication was classified as a grade III and greater according to Clavien-Dindo classification. The secondary objective was to evaluate the benefits of the ERAS protocol compared to that of conventional care.

Statistical methods

All statistical analyses were performed using SPSS statistical software version 23.0 for Windows (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to characterize patients before and after the establishment of the Siriraj UGICC. Categorical variables were analyzed using chi-square test or Fisher's exact test, and continuous variables were compared using Student's *t*-test or Mann Whitney U test. Data are presented as number or number and percentage for categorical data, and as mean ± standard deviation (SD) for normally distributed continuous data (SD) or median and interquartile range for non-normally distributed continuous data. Propensity score match analysis was performed by PS matching for SPSS version 23.0. All statistical results were considered significant when the *P*-value was less than 0.05.

RESULTS

Demographic data

Two hundred and eleven patients in the B-UGICC group underwent curative gastrectomy. In the A-UGICC group, 40 new patients were prospectively recruited. There was no significant difference in age, gender, ASA grade, tumor location, or operative approach between groups. Most patients in the B-UGICC group underwent radical extended gastrectomy (86 of 211 patients, 40.8%), whereas radical total gastrectomy was the most common procedure in the A-UGICC group (18 of 40 patients, 45.0%). The extent of gastric resection was significantly different between groups (*P*=0.005). Propensity score matched 78 B-UGICC patients and 40 A-UGICC patients (Table 1). Propensity score match analysis revealed no statistically significant differences in any patient clinical characteristics or surgical procedures between groups. There were 19 patients with adenocarcinoma of the esophagogastric junction (13 in B-UGICC, 6 in A-UGICC), and 99 gastric cancer (65 in B-UGICC, 34 in A-UGICC) patients.

Therapeutic outcomes before and after establishment of the Siriraj UGICC

Of the 118 patients who underwent radical gastrectomy, there was no in-hospital or 30-day postoperative mortality in either group. The incidence of postoperative complications was 30 of 78 patients (38.5%) in B-UGICC, and 19 of 40 patients (47.5%) in A-UGICC. The morbidity rate was not significantly different between groups (*P*=0.628). Two patients (2.6%) in the B-UGICC group suffered from severe postoperative complications. In both cases, intra-abdominal collections, classified as grade IIIa, were successfully treated with non-operative management. In the A-UGICC group, one patient (2.5%) had postoperative bleeding at the esophagojejunostomy anastomosis, but this bleeding was observed to have spontaneously stopped at the time of endoscopy. This bleeding event was classified as grade IIIa. There was no significant difference between groups relative to postoperative time to tolerate oral intake. Median postoperative length of stay was longer in the B-UGICC group than in A-UGICC group (10 days vs. 9 days, respectively; P=0.026) (Table 2).

Impact of the ERAS protocol

Analysis of short-term outcomes compared between the conventional and ERAS protocols in the A-UGICC group is shown in Table 3. Median time to toleration of oral water, liquid diet, and solid diet was significantly shorter in ERAS patients than in CC patients (all *P*<0.001). Recovery of intestinal functions and time to mobilization and ambulation showed a non-significant trend toward being earlier in the ERAS group than in the CC group. Postoperative length of hospital stay was significantly shorter in the ERAS group (5 days vs. 10 days, respectively; *P*<0.001). The postoperative complication rate was not significantly different between ERAS and conventional care (53.3% vs. 44.0%, respectively; *P*=0.570).

To assure the benefit of the ERAS protocol beyond conventional perioperative care, we rearranged previously matched patients. Patients who received conventional care (78 patients in the B-UGICC group, and 25 patients that received the CC protocol in the A-UGICC group) were grouped into the non-ERAS group, and 15 patients who

received the ERAS protocol in the A-UGICC group were assigned to the ERAS group. Propensity score analysis (approximately 3:1) was performed and the patients were matched. Thirty-six patients in the non-ERAS group and 13 patients in the ERAS group were matched (Table 4). The results of that analysis were concordant with those of the previous analysis of ERAS in A-UGICC group. Specifically, significantly earlier time to toleration of oral intake (all $P<0.001$) and shorter postoperative length of stay ($P<0.001$) were observed in the ERAS group. Incidence of postoperative complication in ERAS was higher than in non-ERAS; however, the difference was not statistically significant (61.5% vs. 36.1%, respectively; $P=0.124$). No severe complication was observed in the ERAS group.

TABLE 1. Demographic and clinical characteristics compared between groups before and after propensity score matching.

Characteristics	Before propensity score matching			After propensity score matching		
	B-UGICC (n=211)	A-UGICC (n=40)	*P*-value	B-UGICC (n=78)	A-UGICC (n=40)	*P*-value
Gender, n			0.387			0.847
Male	118	19		39	19	
Female	93	21		39	21	
Age, mean±SD	62.8±14.0	61.6±15.3	0.490	62.9±13.5	61.6±15.3	0.253
ASA grade, n			0.709			0.673
0 – 2	149	27		56	27	
3 – 5	62	13		22	13	
Tumor location, n			0.821			1.000
AEG	38	6		13	6	
GC	173	34		65	34	
Operative approach, n			0.842			0.899
Transthoracic	10	1		4	1	
Open	173	32		59	32	
Laparoscopic	20	5		10	5	
Robotic-assisted	8	2		5	2	
Extent of operation, n			***0.005***			0.437
Proximal gastrectomy	2	0		2	0	
Distal gastrectomy	72	14		32	14	
Total gastrectomy	41	18		23	18	
Extended gastrectomy	86	7		17	7	
Esophagogastrectomy	10	1		4	1	
CRS with HIPEC, n	7	3	0.201	4	3	0.688

A *P*-value<0.05 indicates statistical significance

Abbreviations: AEG, adenocarcinoma of esophagogastric junction; ASA, American Society of Anesthesiologists physical status classification; A-UGICC, after establishment of the Upper Gastrointestinal Cancer Center; B-UGICC, before establishment of the Upper Gastrointestinal Cancer Center; CRS with HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; GC, gastric cancer; SD, standard deviation

TABLE 2. Short-term postoperative outcomes compared between before and after establishment of the Siriraj UGICC.

Postoperative outcomes	B-UGICC (n=78)	A-UGICC (n=40)	*P*-value
Oral intake (days), median (interquartile range)			
Water	4 (3-7)	4 (1.25-7)	0.825
Liquid	5 (4-9)	6 (2.5-8)	0.321
Solid	7 (5-10)	7 (4.25-9)	0.466
Complications, n (%)			0.628
No	48 (61.5)	21 (52.5)	
Mild (grade I-II)	28 (35.9)	18 (45)	
Severe (grade III-IV)	2 (2.6)	1 (2.5)	
Mortality, n (%)	0	0	N/A
Length of stay (days), median (interquartile range)			
Total length of stay	12 (9-16.25)	10 (7-14)	***0.023***
Postoperative length of stay	10 (8-14)	9 (6.25-11)	***0.026***

A *P*-value<0.05 indicates statistical significance

Abbreviations: A-UGICC, after establishment of the Upper Gastrointestinal Cancer Center; B-UGICC, before establishment of the Upper Gastrointestinal Cancer Center; N/A, not applicable

TABLE 3. Outcomes of treatment compared between protocols after establishment of the Siriraj UGICC.

Postoperative outcomes	Conventional care (n=25)	ERAS (n=15)	*P*-value
Oral intake (days), median (interquartile range)			
Water	7 (4.5-8)	1 (1-3)	***<0.001***
Liquid	7 (6-8.5)	2 (2-4)	***<0.001***
Solid	8 (7-10)	3 (3-5)	***<0.001***
Intestinal recovery (hours), median (interquartile range)			
Time to flatus	72 (55-86.5)	60 (24-86)	0.189
Time to defecation	96 (70-125.5)	88 (64-119)	0.401
Ambulation (hours), median (interquartile range)			
Time to in bed mobilization	28 (17-65.25)	22 (16-26)	0.442
Time to out of bed ambulation	63.5 (32.25-82.5)	44 (21-96)	0.682
Complications, n (%)			0.570
No	14 (56)	7 (46.7)	
Mild (grade I-II)	10 (40)	8 (53.3)	
Severe (grade III-IV)	1 (4)	0	
Mortality, n (%)	0	0	N/A
Length of stay (days), median (interquartile range)			
Total length of stay	13 (10.5-15.5)	6 (6-8)	***<0.001***
Postoperative length of stay	10 (9-12.5)	5 (5-7)	***<0.001***

A *P*-value<0.05 indicates statistical significance

Abbreviations: UGICC, Upper Gastrointestinal Cancer Center; ERAS, Enhanced Recovery After Surgery protocol; N/A, not applicable

TABLE 4. Outcomes of treatment compared between patients that did and that did not receive ERAS protocol after propensity score matching (approximately 3:1).

Postoperative outcomes	Non-ERAS (n=36)	ERAS (n=13)	*P*-value
Oral intake (days), median (interquartile range)			
Water	4 (3-7)	1 (1-2)	***<0.001***
Liquid	5.5 (4-8.75)	2 (2-3)	***<0.001***
Solid	7 (6-10)	3 (3-4.5)	***<0.001***
Complications, n (%)			0.124
No	23 (63.9)	5 (38.5)	
Mild (grade I-II)	11 (30.6)	8 (61.5)	
Severe (grade III-IV)	2 (5.6)	0	
Mortality, n (%)	0	0	N/A
Length of stay (days), median (interquartile range)			
Total length of stay	11.5 (9-14.75)	6 (6-7)	***<0.001***
Postoperative length of stay	10 (8-13)	5 (5-6.5)	***<0.001***

A *P*-value<0.05 indicates statistical significance
Abbreviations: ERAS, Enhanced Recovery After Surgery protocol; N/A, not applicable

DISCUSSION

Centralization is now recognized as a factor that improves postoperative mortality and treatment outcomes. High-volume centers and centers of excellence that specialize in certain types of cancer seem to have better short- and long-term survival outcomes. Nimptsch U, *et al.*[24] reported national hospital discharge data after complex gastric surgery in Germany. They found surgery in very high-volume hospitals (50 operations per year) to be associated with lower in-hospital mortality compared to treatment in very low-volume hospitals (5 surgeries per year) (10.6% vs. 12.0%, respectively). For cancer surgery, very high-volume hospitals (34 resections per year) had lower in-hospital mortality than that in very low volume hospitals (3 resections per year) (6.3% vs. 7.7% respectively). Iwatsuki M, *et al.*[25] analyzed the results of distal gastrectomy for gastric cancer from the National Clinical Database of Japan. Operative mortality was significantly higher in low-volume hospitals (1-22 cases per year) than in medium-volume (23-51 cases per year) and high-volume (52-404 cases per year) hospitals (1.9% vs. 1.0% vs. 0.5%, respectively; *P*<0.001). van Putten M, *et al.*[11] reported the short-and long-term outcomes before and after centralization of gastric cancer surgery in the Netherlands. The 30-day postoperative mortality rate was 6.5% before, and 4.1% after centralization (*P*=0.004). The 2-year overall survival rate was also improved from before to after centralization (55.4% vs. 58.5%, respectively; *P*=0.031). Hospital volume could have an impact on postoperative outcomes, and that centralization was associated with improved survival in the developed countries. However, data specific to the development and effectiveness of specialized esophageal and gastric cancer centers in developing countries is scarce. To the best of our knowledge, this is the first data of postoperative outcomes reported from the upper gastrointestinal cancer center in Thailand.

The Siriraj Upper Gastrointestinal Cancer Center was established in November 2017. To the best of our knowledge, this is the first specialized upper gastrointestinal cancer center organized by a multidisciplinary team in Thailand. The aim of the Siriraj UGICC is to be a center of excellence in esophageal and gastric cancer services. This center also aims to be a training center for medical personnel in all aspects of patient care for these two types of cancer. Research to identify ways to improve treatment and patient care is also an important component of the mission of the Siriraj UGICC. We arranged a multidisciplinary discussion to decide upon a pattern of perioperative and surgical care. Since this center's founding, management practices and clinical protocols have become more systematic and efficient. In the initial

period, ERAS protocol could be completely implemented for patients because of a strong multidisciplinary team. A prospectively maintained database is regularly reviewed and updated, and the quality of the documentation is more reliable to study and analyze.

This study reports short-term postoperative outcomes after radical gastrectomy compared between before and after the establishment of a UGICC. We applied propensity score matched analysis to reduce selection bias and improve the quality of comparison. Although our patients were treated by the same group of surgeons and the same surgical standard according to Japanese gastric cancer treatment guidelines, perioperative care was adjusted and refined by the multidisciplinary team after UGICC establishment. Patient recovery demonstrated a non-significant trend toward improvement in the A-UGICC group compared to the B-UGICC group; however, length of hospital stay was statistically significantly improved after the establishment of the Siriraj UGICC. The ERAS protocol is a strategy that can be applied during the perioperative and intraoperative period. Since the ERAS protocol is a new care strategy for esophageal and gastric cancer patients at our center and its reported superior postoperative results have never been proven at our hospital, it was applied in only some selected patients. Although the number of ERAS patients in our study was comparatively low, the postoperative short-term outcomes were promising. Significant improvement in patient recovery and length of hospital stay was clearly shown. In contrast, severe postoperative morbidity and mortality rates were not significantly increased. The identified safety and recovery benefits of the ERAS protocol suggest its benefit in other types of surgical patients in the future. After the Siriraj UGICC was established, the incidence of postoperative complications and mortality was not different from the pre-UGICC period. However and importantly, it should be noted that there was no postoperative mortality in this study. The high incidence of minor postoperative complications might be the result of better data collection.

Some limitations of this study have to be addressed. First, our data was derived from a single super-tertiary center in Thailand, which makes this a single-center study. Moreover, our center, which is a national super-tertiary referral center, is routinely referred complex cases that cannot be managed at a lower level center. This limitation suggests that our findings may not be generalizable to all other care settings. Second, the size of our study population was relatively small; however, the number of patients that undergo radical gastrectomy is generally quite low. In an attempt to mitigate this limitation and improve the quality of our analysis, we employed the use of propensity score matching to reduce selection bias and improve the quality of our comparisons. Further study is needed to compare the cost of treatment between pre- and post-UGICC, and to investigate the long-term outcomes of these patients.

In conclusion, Siriraj Upper Gastrointestinal Cancer Center aims to improve the quality of esophageal and gastric cancer care. This is the first specialized center organized by a multidisciplinary team in Thailand. High surgical standard and appropriate in-house perioperative protocol had significant positive impact on postoperative short-term outcomes. Multidisciplinary team in UGICC with the application of the ERAS protocol contributed to significant improvement in timing of ability to tolerate oral intake and postoperative length of hospital stay.

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Cutaneous Manifestations and Associated Systemic Findings of Patients with Zika Infections

Charussri Leeyaphan, M.D., Ploypailin Tantrapornpong, M.D.

Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: This retrospective study explored the clinical characteristics and laboratory results of ZIKV infections, and compared them with those of other viral exanthems.

Methods: The medical records of patients presenting with maculopapular viral exanthems between January 2017 and December 2018 were reviewed. The patients were divided into 2 two groups: ZIKV infections (confirmed by urine RT-PCR testing for ZIKV), and other viral exanthems. The clinical characteristics and laboratory results of complete blood counts of the two groups were compared.

Results: In all, 104 viral-exanthem patients were reviewed, with 35 patients diagnosed with a ZIKV infection (33.7%) and 69 with other viral exanthems (66.3%). The mean age of the ZIKV-infected patients was significantly higher than that of the other-viral-exanthem group (43.6 vs 36.2 years; p-value = 0.005). A multivariate analysis revealed that the incidences of a family/close contact cluster, conjunctivitis, and myalgia were significantly associated with ZIKV infections. However, there were no significant associations between the laboratory results of the ZIKV and other-viral-exanthem groups.

Conclusion: The ZIKV infection exhibits a prominent pattern recognition, including a family/close contact cluster, conjunctivitis, and myalgia, that can be used to distinguish it from other exanthematous viral diseases.

Keywords: Zika virus; viral exanthema; maculopapular rash (Siriraj Med J 2020; 72: 330-335)

INTRODUCTION

Maculopapular eruptions, or exanthems, are described as non-specific, erythematous, flat, and elevated lesions on the skin. They can develop on the face, trunk, and upper and lower extremities. While exanthems could be due to a variety of skin diseases, they are mostly the result of viral or bacterial infections and drug reactions.[1] The manifestations of virally caused exanthems may be non-specific, but they frequently involve fever, mucosal involvement, lymphadenopathy, myalgia, arthralgia, or arthritis. As the identification of the responsible viral pathogens can be a diagnostic challenge, pattern recognition and pathognomonic signs are needed to differentiate the various viral diseases.[2,3]

The Zika virus (ZIKV), a mosquito-borne flavivirus, caused a major outbreak in the State of Yap, the Federated States of Micronesia, in 2007. The ZIKV landed in the Americas as a result of immigration, and a major outbreak occurred throughout most of the Americas during 2015 and 2016.[4-6] ZIKV is transmitted by the bite of the Aedes aegypti mosquito species, sexual intercourse, and pregnancy, and it can cause serious complications such as Guillain–Barré syndrome and birth defects, especially microcephaly and other brain malformations (in the case

Corresponding author: Charussri Leeyaphan
E-mail: charussrilee@gmail.com
Received 1 August 2019 Revised 25 November 2019 Accepted 27 November 2019
ORCID ID: http://orcid.org/0000-0001-8430-376X
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of maternal-fetal transmissions).[7-9] Patients with ZIKV infections may have no symptoms or mild symptoms, such as fever and maculopapular eruptions like other viral exanthems.[10,11] This study aimed to differentiate the clinical manifestations, related factors, and laboratory results associated with ZIKV infections and other viral exanthems in order to diagnose ZIKV infections and prevent their spread prior to receiving confirmation by a specific laboratory investigation.

MATERIALS AND METHODS

Study population

Enrolled were adult patients (aged 18 years and above) who had been diagnosed with, or were suspected of having, a viral exanthem or ZIKV infection upon attending the Dermatology Clinic, Siriraj Hospital, Bangkok, January 2017-December 2018. Viral exanthems were diagnosed from the patients' histories and clinical manifestations (such as fever, skin eruptions, and lymphadenopathy), with drug eruptions or other infectious/inflammatory diseases being ruled out. The information collected on each included patient comprised (1) demographic data; (2) clinical features (fever duration, rash duration, family/close contact cluster, pattern of rash distribution, conjunctivitis, myalgia, arthralgia/arthritis, oral ulceration, genital ulceration, cough, coryza, pharyngitis, and lymphadenopathy); and (3) laboratory findings, with at least one complete blood count. In the ZIKV-infection group, urine RT-PCR testing for ZIKV was required as a confirmatory laboratory diagnosis. The study protocol was approved by the the Siriraj Institutional Review Board (Si 083/2019).

Statistical analysis

The statistical software, SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the data analyses. All continuous data were presented as means and standard deviations. The Chi-squared test was used to compare differences in the categorical data. A binary logistic regression was performed in a multivariate analysis to find the factors associated with the ZIKV and other viral exanthems. A probability value (p-value) of less than 0.05 was considered statistically significant.

RESULTS

Demographic data

Of the 104 enrolled patients, 35 had ZIKV infections while 69 had other viral exanthems resulting from measles, rubella, dengue infection, and nonspecific maculopapular eruptions. All patients had maculopapular eruptions as their chief complaint. The mean ages were 43.6 ± 14.5 years (ZIKV group) and 36.2 years (other-viral-exanthem group; p-value, 0.05). Most of the ZIKV-infected patients were female (n = 26; 74.5%). In the other-viral-exanthem group, 30 (43.5%) were male, and 39 (56.5%) were female. The mean fever duration before coming to hospital was shorter for the ZIKV-infection group than the other-viral-exanthem group, with 2.1 ± 1.1 days and 4.8 ± 3.2 days, respectively. The mean rash duration of the ZIKV-infection group (2.1 ± 1.1 days) was also shorter than that of the other-viral-exanthem group (3.9 ± 6.1 days).

Clinical manifestations

With a cut point of 35 years, the ZIKV infections were significantly associated with an age of more than 35 years (p = 0.007; OR, 3.3; 95% CI, 1.4–8.2). There were no significant differences in the sexual statuses of the patients in the ZIKV-infection and other-viral-exanthem groups. Of the 35 ZIKV-infected patients, most had fever (n = 27; 77.1%); a family/close contact cluster (n = 25; 71.4%); conjunctivitis (n = 22; 62.9%); and myalgia (n = 27; 77.1%). From the univariate analysis, the factors that were statistically significantly related to ZIKV infections rather than other viral exanthems were a family/close contact cluster (p < 0.001; OR, 8.8; 95% CI, 2.2–34.6); conjunctivitis (p < 0.001; OR, 6.1; 95% CI, 2.5–14.9); myalgia (p < 0.001; OR, 5.3; 95% CI, 2.1–13.2); and arthralgia/arthritis (p < 0.001; OR, 5.0; 95% CI, 2.1–12.6). By contrast, the following clinical features were not significantly related to ZIKV infections or other viral exanthems: fever, pattern of rash distribution, oral ulceration, genital ulceration, cough, coryza, pharyngitis, and lymphadenopathy (Table 1).

In a multivariate analysis adjusted for all related factors, a family/close contact cluster (p = 0.018; OR, 6.7; 95% CI, 1.4–32.7), conjunctivitis (p = 0.012; OR, 3.9; 95% CI, 1.3–11.2), and myalgia (p = 0.015; OR, 4.0; 95% CI, 1.3–12.5) were found to be statistically associated with ZIKV infections rather than other viral exanthems (Table 1).

Laboratory findings

From an analysis of the complete blood counts, hematocrits and platelets were not affected in most patients (Table 2). Leukocytosis (2.9%) was noted in one ZIKV-infected patient and 9 (13%) other-viral-exanthem patients. In both groups, a lymphocyte predominance was found in a small proportion of the patients. Atypical lymphocytes were present in 11.4% (n = 4) of the ZIKV-infected patients and 26.1% (n = 18) of the other-viral-exanthem patients. None of the ZIKV-infected patients had

TABLE 1. Clinical characteristics of patients with Zika and other-viral-exanthem infections.

Factors	ZIKV infections n (%)	Other-viral-exanthem infections n (%)	Univariate analysis Crude odds ratio (λ^2) (95% CI)	*P*-value	Multivariate analysis Adjusted odds ratio (95% CI)	*P*-value
Age			3.3 (1.4–8.2)	0.007*	1.8 (0.6–5.0)	0.294
< 35 years	9 (25.7)	37 (53.6)				
≥ 35 years	26 (74.3)	32 (46.4)				
Sexual status			0.5 (1.8–1.1)	0.077		
Male	9 (25.7)	30 (43.5)				
Female	26 (74.3)	39 (56.5)				
Fever			1.2 (0.5–3.1)	0.719		
Yes	27 (77.1)	51 (73.9)				
No	8 (22.9)	18 (26.1)				
Family/close contact cluster			8.8 (2.2–34.6)	< 0.001*	6.7 (1.4–32.7)	0.018*
Yes	25 (71.4)	3 (4.3)				
No	10 (28.6)	66 (95.7)				
Pattern of rash distribution				0.369		
Centripetal	10 (28.6)	12 (17.4)				
Centrifugal	16 (45.7)	33 (47.8)				
Generalized abruption	9 (25.7)	24 (34.8)				
Conjunctivitis			6.1 (2.5–14.9)	< 0.001*	3.9 (1.3–11.2)	0.012*
Yes	22 (62.9)	15 (21.7)				
No	13 (37.1)	54 (78.3)				
Myalgia			5.3 (2.1–13.2)	< 0.001*	4.0 (1.3–12.5)	0.015*
Yes	27 (77.1)	27 (39.1)				
No	8 (22.9)	42 (60.9)				
Arthralgia/arthritis			5.0 (2.0–12.6)	< 0.001*	1.1 (0.3–3.8)	0.846
Yes	17 (48.6)	11 (15.9)				
No	18 (51.4)	58 (84.1)				
Oral ulceration			0.4 (0.0–3.4)	0.364		
Yes	1 (2.9)	5 (7.2)				
No	34 (97.1)	64 (64.0)				
Genital ulceration			2 (0.1–33.0)	0.621		
Yes	1 (2.9)	1 (1.4)				
No	34 (97.1)	68 (98.6)				
Cough			1.4 (0.5–3.5)	0.529		
Yes	9 (25.7)	14 (20.3)				
No	26 (74.3)	55 (79.7)				
Coryza			1.3 (0.5–3.8)	0.605		
Yes	7 (20.0)	11 (15.9)				
No	28 (80.0)	58 (84.1)				
Pharyngitis			1.8 (0.8–4.3)	0.183		
Yes	13 (37.1)	17 (24.6)				
No	22 (62.9)	52 (75.4)				
Lymphadenopathy			0.5 (0.1–2.7)	0.448		
Yes	2 (5.7)	7 (10.1)				
No	33 (94.3)	62 (89.9)				

TABLE 2. Laboratory findings of patients with Zika and other-viral-exanthem infections.

Factors	ZIKV infections n (%)	Other-viral-exanthem infections n (%)	Univariate analysis Crude odds ratio (λ^2) (95% CI)	*P*-value
Anemia (Hct <35%)			0.5 (0.1–0.4)	0.508
Yes	1 (2.9)	4 (5.8)		
No	34 (97.1)	65 (94.2)		
Leukocytosis WBC (>10,000/ul)			0.2 (0.0–1.6)	0.096
Yes	1 (2.9)	9 (13.0)		
No	34 (97.1)	60 (87.0)		
Lymphocyte predominance (>40%)			2.0 (0.7–5.7)	0.201
Yes	8 (22.9)	9 (13.0)		
No	27 (77.1)	60 (87.0)		
Presence of atypical lymphocytes			0.4 (0.1–1.2)	0.084
Yes	4 (11.4)	18 (26.1)		
No	31 (88.6)	51 (73.9)		
Eosinophils (>7.5%)			1.0 (0.9–1.0)	0.211
Yes	0 (0)	3 (4.3)		
No	35 (100)	66 (95.7)		
Platelets (<200,000/ul)			0.4 (0.1–1.1)	0.082
Yes	6 (17.1)	23 (33.3)		
No	29 (82.9)	46 (66.7)		

Abbreviations: n, number; CI, confidence interval; Hct, hematocrit; WBC, white blood cell; ul, microliter

eosinophilia, whereas a few in the other-viral-exanthem group did. In addition, none of the laboratory findings were significantly associated with the ZIKV-infection or the other-viral-exanthem groups.

DISCUSSION

This retrospective cohort study evaluated factors related to ZIKV infections and compared them with the factors for other exanthematous viral diseases. The associated factors were characterized by demographic data; a history of a family/close contact cluster; signs and symptoms of fever, rash, and other flu-related symptoms (such as conjunctivitis and upper respiratory tract symptoms); arthralgia; arthritis; myalgia; and lymphadenopathy. We found that the ZIKV infections occurred in one-third (33.7%) of all of the viral-exanthem patients who presented with maculopapular eruptions. The age and sexual-status findings of the ZIKV patients were consistent with the patterns reported for other countries. For example, in Puerto Rico, ZIKV infections were more common among females than males.[12] In addition, the mean age of the ZIKV group in the Puerto Rico research was 43.6 years, which is in the same range as that of the present study (>35 years).

Due to the extensive Zika global outbreak that commenced in 2015, a clustering of cases among ZIKV-infected patients is more likely to be detected in many patterns, such as family, close contact, tour group, and immigrant.[13-15] In the case of Thailand, a number of travelers returning from rural areas within the country were found to have evidence of ZIKV infections.[16] Our study demonstrated that there was a strong association of cluster with ZIKV infection (an odds ratio of 6.7 compared with the other-viral-exanthem group). The fever duration was also longer than the rash duration for both the ZIKV-infection and the other-viral-exanthem groups. However, both the fever and rash durations of the ZIKV-infection group were shorter than those of the other-viral-exanthem group.

The classic manifestations of ZIKV infections include

fever, rash, conjunctivitis, and arthralgia/arthritis.[17,18] The outstanding feature that differentiates ZIKV infections from other-viral-exanthem infections is non-purulent conjunctivitis.[19] Nevertheless, this feature may not be reliably prominent in some populations, as was the case in a Malaysian study.[20] As to Bangkok, Thailand, the current study confirmed a statistically significant association between conjunctivitis and the ZIKV, with a 3.9 odds ratio. Myalgia was an additional clinical feature that the current study determined was significantly associated with the ZIKV among the viral-exanthem patients. This finding correlates with a study in the Brazilian State of Piaui that focused on patients infected with arboviruses (dengue virus, chikungunya virus, and ZIKV). Myalgia is one of the significantly associated features of the arboviruses group.[21]

On the other hand, the clinical manifestations that were not significantly different between the ZIKV-infection and the other-viral-exanthems groups were fever, the pattern of rash distribution, mucosal ulceration, arthralgia/arthritis, and lymphadenopathy. Aside from confirming a ZIKV-infection using a real-time RT-PCR analysis, a complete blood count is likely to be normal and show no differences between the two groups.

This study has the intrinsic limitations of retrospective studies. Moreover, ZIKV and other-viral-exanthem infections generally produce a wide range of clinical manifestations, from asymptomatic to viremic symptoms. The current study, however, focused on viral-exanthem populations presenting with a cutaneous sign (a maculopapular rash). A prospective cohort study utilizing a larger sample size with diverse clinical symptoms could be considered in further research.

CONCLUSION

The clinical manifestations associated with ZIKV infections were a family/close contact cluster, conjunctivitis, and myalgia. Discriminating these clinical features might be useful in differentiating between ZIKV and other-viral-exanthem infections.

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Conflicts of interest: This study had no conflicts of interest.

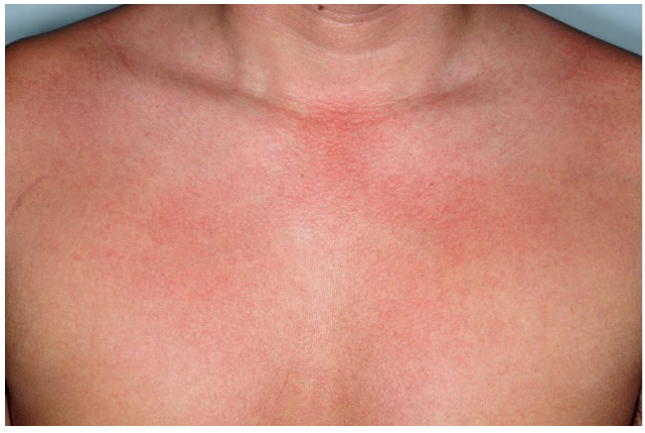

Fig 1. Maculopapular eruption which is commonly found in patients with zika infections.

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Dynamic Contrast-Enhanced Computed Tomography Findings that may Predict Poorly-Differentiated Hepatocellular Carcinoma Prior to Treatment

Chananwat Manyanon, M.D., Sopa Pongpornsup, M.D., Aphinya Charoensak, M.D.

Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To identify CT findings that predict poorly-differentiated hepatocellular carcinoma (p-HCC).

Methods: This retrospective study included pathologically proven HCC patients during January 2010 to December 2017 who underwent dynamic contrast-enhanced computed tomography (CT) imaging within 12 weeks before the pathological diagnosis. CT findings were reviewed and graded by consensus opinion of two abdominal radiologists. The relationship between imaging findings and histological differentiation of HCC was analyzed using chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for diagnosis of p-HCC were calculated.

Results: Of 200 HCCs during the study period, 18 were well-differentiated, 170 were moderately-differentiated, and 12 were poorly differentiated. Irregular rim enhancement in arterial phase (p<0.001) and presence of lymphadenopathy (p=0.003) were both statistically significantly different among the three types of histological differentiation of HCC. Sensitivity, specificity, PPV, NPV, and accuracy for prediction of p-HCC by the presence of irregular rim enhancement in arterial phase and lymphadenopathy were 58.3%, 97.3%, 58.3%, 97.3%, and 95%, and 50%, 88.8%, 22.2%, 96.5%, and 86.5% - all respectively.

Conclusion: The presence of irregular rim enhancement in arterial phase and lymphadenopathy are potentially useful CT findings for prediction of p-HCC prior to treatment.

Keywords: Computed tomography; histological differentiation; poor differentiation; hepatocellular carcinoma (Siriraj Med J 2020; 72: 336-342)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant hepatic tumor, and it is a huge contributor to the world's cancer burden.[1] The treatment options for HCC include curative therapies (hepatic resection, liver transplantation, and ablative techniques such as radiofrequency/microwave ablation (RFA), percutaneous ethanol injection therapy (PEIT)), and noncurative therapies (transarterial chemoembolization (TACE), radioembolization, stereotactic body radiation therapy (SBRT) and molecularly targeted therapy).[2-4] The type of treatment depends on tumor staging, patient performance status, and liver function reserve.

RFA has grown quickly during the last decade and currently considered the treatment of choice for HCC patients with Barcelona-Clinic Liver Cancer (BCLC)

Corresponding author: Aphinya Charoensak
E-mail: caphinya@gmail.com
Received 10 June 2019 Revised 16 December 2019 Accepted 20 December 2019
ORCID ID: http://orcid.org/0000-0001-5179-9279
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stage 0-A who are not suitable for surgery. However, small (<2.5 cm) single tumor that is easily located may be treated by either resection or ablation.[4] Forner *et al.*[5] suggested RFA instead of resection in patients with early HCC (<2 cm.). Several studies[6-8] reported that histological grading of HCC is an important prognostic factor after treatment, and that poorly-differented lesions have the worse prognosis. It has also been reported that poor differentiation is a risk factor for tumor seeding after RFA.[9,10] Fukuda *et al.*[11] suggested that even solitary small HCC (up to 2 cm.), when hepatic function is well preserved, hepatic resection should be the first choice especially in cases of moderately or poorly differentiated HCC due to high frequency of microscopic vascular invasion. Therefore, the prediction of poorly differentiated HCC before treatment has potential benefit for treatment planning and for safe RFA even in patients with small HCC.

Currently, non-invasive diagnosis of HCC can be made by imaging characteristics on dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).[2] Pathological diagnosis is reserved for suspicious lesions without characteristic imaging features. However, histological differentiation of HCC is not accurately obtained before surgery. Our review of the literature revealed that only a few studies[12-16] have investigated the relationship between imaging findings and histological grading of HCC.

Accordingly, the aim of this study was to investigate and identify dynamic contrast-enhanced CT findings that may predict poorly-differentiated hepatocellular carcinoma (p-HCC) prior to treatment.

MATERIALS AND METHODS

Study population

This retrospective single-center study was approved by the Siriraj Institutional Review Board (SIRB) (Si 226/2016) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The requirement to obtain written informed consent was waived. Patients with pathologically proven diagnosis of HCC during January 2010 to December 2017 were searched using pathological electronic database diagnosis. Patients who had no data relative to histological differentiation, who had not undergone dynamic CT within 12 weeks before the pathological diagnosis, who had received any prior treatment (e.g., RFA, TACE), and/or who had improper phases of dynamic CT were excluded. A flowchart showing the patient enrollment process is given in Fig 1. Our database search revealed 200 patients (151 males, and 49 females) with a pathologically proven diagnosis of HCC. The mean age of patients was 60.3±11.3 years (range: 30-93). The pathology diagnosis was obtained from core needle biopsy in 49 patients (24.5%), and from surgical resection in 151 patients (75.5%). The median time interval between CT imaging and pathological diagnosis was 31 days (range: 1-83).

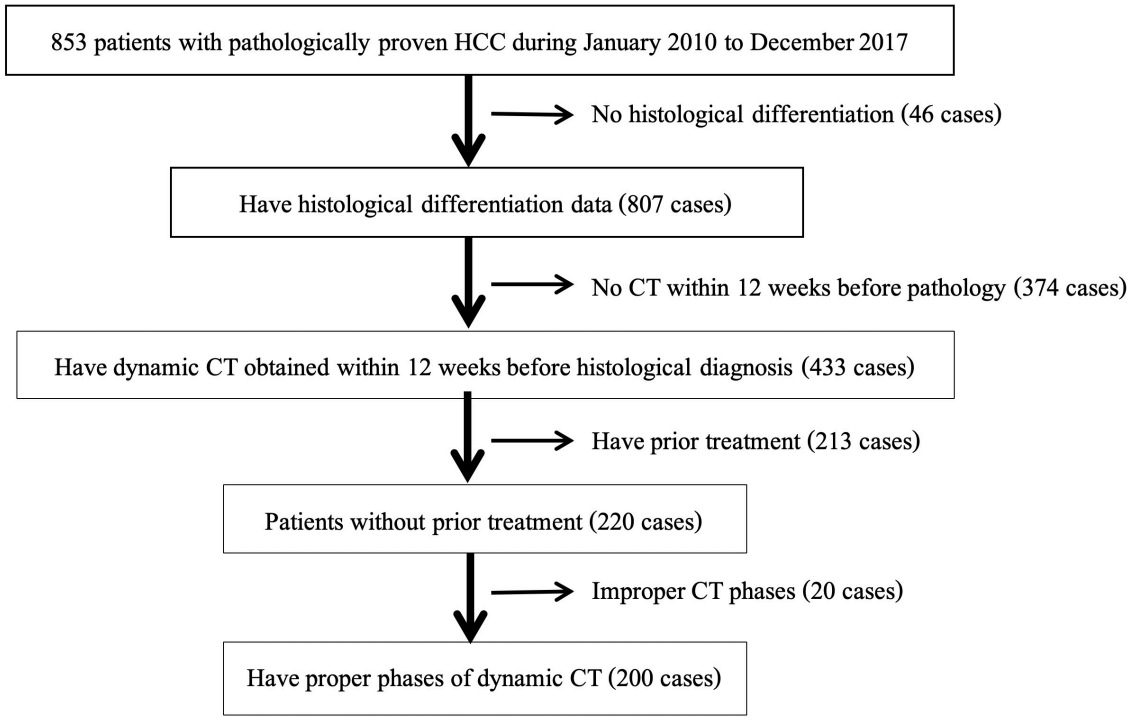


Fig 1. Flowchart describing the patient enrollment process.

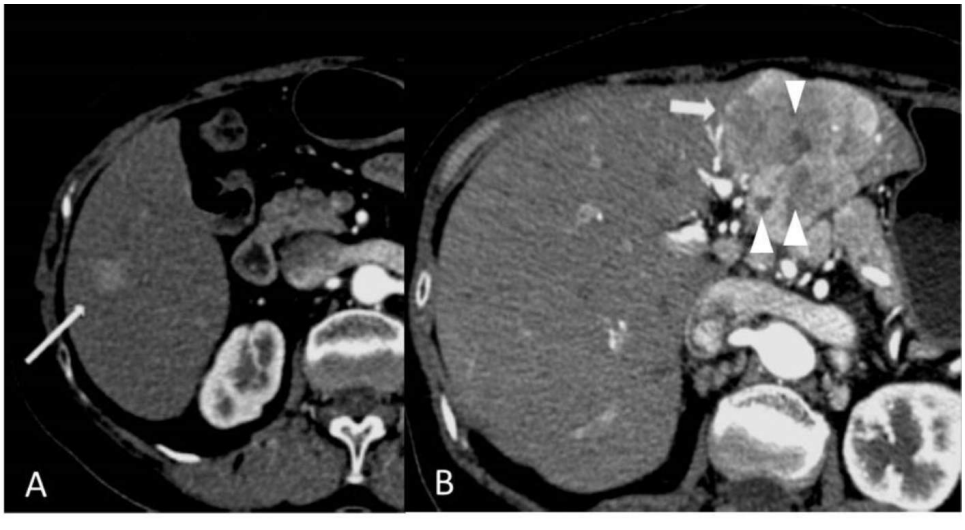
CT technique and interpretation

Dynamic CT scans of the liver were performed with a 16, 64, or 128 detector helical CT scanner (LightSpeed VCT, Discovery CT 750 HD and Optimal CT660; GE Healthcare, United States or SOMATOM Definition Dual Source, Siemens, Germany). The slice thickness was 1.25-1.5 mm (reconstructed at 5.0-7.0 mm). Dynamic contrast-enhanced CT scans were routinely performed during breath hold, including non-contrast, arterial dominant, and portovenous phases. Delayed phase was added in some patients. The arterial dominant, portovenous, and delayed phases were performed at 35 seconds, 80 seconds, and 5 minutes after initiation of contrast injection. Approximately 2 mL/kg of nonionic iodinated contrast agent followed by 20 mL of water was injected using a power injector at a rate of 2-3 mL/second.

CT images were retrospectively reviewed and graded by consensus opinion by two abdominal radiologists with 16 years and 13 years of experience, respectively. Types or levels of differentiation of HCC included well-differentiated (w-HCC), moderately-differentiated (m-HCC), and poorly-differentiated (p-HCC). Both readers were blinded to pathological differentiation data and other clinical characteristics, and knew only that the patient had been definitively diagnosed with HCC. For cases with multiple tumors, the largest lesion at the location of pathological diagnosis was assessed. CT findings were assessed, as follows: number of tumor(s) (single or multiple), tumor size (measurement of maximal diameter, including capsules), tumor margin (smooth, irregular, or infiltrative), tumor attenuation on pre-contrast images, degree of tumor enhancement (arterial enhancement, hypovascular enhancement), enhancement pattern on arterial phase (homogenous, heterogenous (Fig 2)), presence of non-enhanced area on arterial phase (Fig 2&3), presence of irregular rim enhancement on arterial phase (Fig 4), tumor stain washout on portovenous or delayed phases (Fig 3), capsular enhancement, lymphadenopathy (lymph node enlargement of >1 cm in short axis diameter), and vascular invasion.

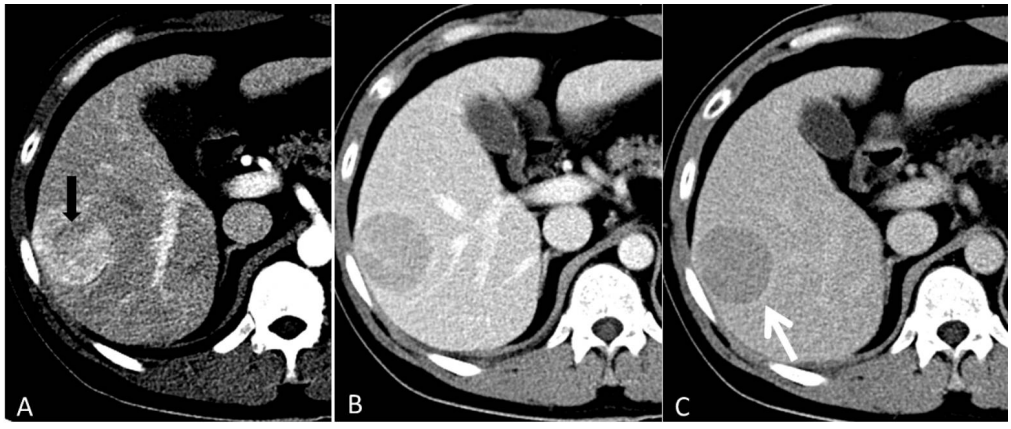
Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Normally distributed continuous data, including age and tumor size, are presented as mean ± standard deviation. Non-normally distributed continuous data, such as time interval between CT imaging and pathological diagnosis of HCC, are given as median and range. Categorical data are shown as frequency and percentage. The relationship of CT findings among the three types of histologic differentiation of HCC was analyzed using chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for diagnosis of p-HCC were calculated according to significant findings on dynamic contrast-enhanced CT. Statistical significance was defined as a *p*-value less than 0.05. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA).



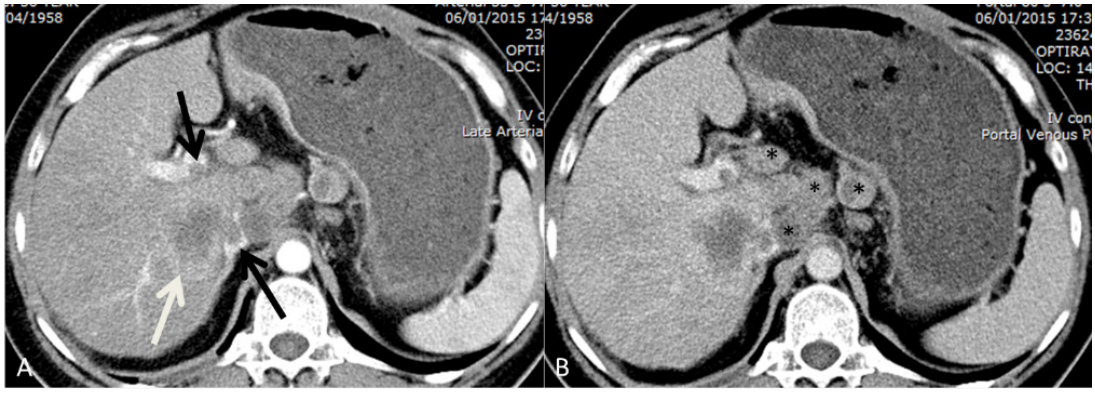
A. Axial CT image of arterial phase showing homogenous arterial enhanced HCC in right hepatic lobe without non-enhanced area (arrow).
B. Axial CT image of arterial phase (different case) showing heterogenous arterial enhanced HCC in left hepatic lobe (arrow) with presence of non-enhanced area (arrowhead).

Fig 2. Two different cases of arterial enhancement without non-enhanced area and arterial enhancement with non-enhanced area.



A. Axial CT image - arterial phase showing the presence of non-enhanced area on arterial phase (black arrow)
B. Axial CT image – portovenous phase showing tumor stain washout
C. Axial CT image – delayed phase showing tumor stain washout and the presence of capsular enhancement (white arrow)

Fig 3. Dynamic contrast-enhanced CT of a moderately-differentiated HCC case (pathological diagnosis from surgical resection).



Axial CT images of arterial phase (A) and portovenous phase (B) showing the presence of irregular rim enhancement on arterial phase (white arrow), and multiple abdominal lymphadenopathies (asterisk). Vascular invasion into portal vein and IVC was also demonstrated (black arrow).

Fig 4. Dynamic contrast-enhanced CT of a poorly-differentiated HCC case (pathological diagnosis from core needle biopsy).

RESULTS

Of 200 HCC cases, 120 cases (60%) had single lesion and 80 cases (40%) had multiple lesions. The histological classification was w-HCC in 18 cases (9%), m-HCC in 170 (85%) cases, and p-HCC in 12 cases (6%). There was no statistically significant difference in mean tumor diameter, type of tumor margin, tumor attenuation on pre-contrast image, pattern of tumor enhancement, presence of non-enhanced area on arterial phase, tumor stain washout, capsular enhancement, or vascular invasion among the three types of histological differentiation of HCC, as shown in Table 1. Hypovascular enhancement pattern was found in three cases (1.5%). All cases of p-HCC in the present study showed hypoattenuation on pre-contrast images, heterogenous arterial enhancement, presence of non-enhanced area on arterial phase, and tumor stain washout.

The present study found irregular rim enhancement (p<0.001) and presence of lymphadenopathy (p=0.003) to be statistically significantly different among the three types of histological differentiation of HCC (Table 1). The percentage of presence of irregular rim enhancement was significantly higher as the histological differentiation grade advanced. Lymphadenopathy was more commonly observed in p-HCC (50%) than in w-HCC (11.1%) and m-HCC (11.2%).

The sensitivity, specificity, PPV, NPV, and accuracy for the prediction of p-HCC by irregular rim enhancement and lymphadenopathy are shown in Table 2. Irregular rim enhancement had higher specificity, NPV, and accuracy (97.3%, 97.3%, and 95%, respectively) than lymphadenopathy (88.8%, 96.5%, and 86.5%, respectively) for p-HCC. The accuracy for prediction of p-HCC by combining these two findings did not significantly improve diagnosis compared to irregular rim enhancement alone, but the sensitivity was decreased to 33.3%.

TABLE 1. Correlation between CT findings and histological differentiation of HCC

CT findings	Histologically differentiation			*p*-value[a]	95% CI
	w-HCC (n=18)	m-HCC (n=170)	p-HCC (n=12)		
Tumor size; mean diameter ± SD	**6.5 ± 4.4 cm**	**5.3 ± 3.9 cm**	**6.3 ± 3.4 cm**	**0.524**	
Tumor margin				0.147	
Irregular	16 (88.9%)	132 (77.6%)	11 (91.7%)		
Smooth	1 (5.6%)	37 (21.8%)	1 (8.3%)		
Infiltrative	1 (5.6%)	1 (0.6%)	0 (0.0%)		
Tumor attenuation on pre-contrast images				0.232	
Hypoattenuation	13 (72.2%)	152 (89.4%)	12 (100%)		
Isoattenuation	2 (11.1%)	10 (5.9%)	0 (0.0%)		
Hyperattenuation	3 (16.7%)	7 (4.1%)	0 (0.0%)		
Fat content	0 (0.0%)	1 (0.6%)	0 (0.0%)		
Degree of tumor enhancement				1.0	
Arterial enhancement	18 (100%)	167 (98.2%)	12 (100%)		
Hypovascular enhancement	0 (0.0%)	3 (1.8%)	0 (0.0%)		
Enhancement pattern on arterial phase[b]				0.232	
Heterogeneous	17 (94.4%)	143 (85.6%)	12 (100%)		
Homogeneous	1 (5.6%)	24 (14.4%)	0 (0.0%)		
Non-enhanced area on arterial phase[b]				0.077	
Present	16 (88.9%)	125 (74.9%)	12 (100%)		
Absent	2 (11.1%)	42 (25.1%)	0 (0.0%)		
Irregular rim enhancement[b]				***<0.001***	
Present	0 (0.0%)	5 (3.0%)	7 (58.3%)		
Absent	18 (100%)	162 (97%)	5 (41.7%)		
Tumor stain washout[b]				0.858	
Present	17 (94.4%)	158 (94.6%)	12 (100%)		
Absent	1 (5.6%)	9 (5.4%)	0 (0.0%)		
Capsular enhancement				0.734	
Present	7 (38.9%)	55 (32.4%)	3 (25.0%)		
Absent	11 (61.1%)	115 (67.6%)	9 (75.0%)		
Lymphadenopathy				***0.003***	
Present	2 (11.1%)	19 (11.2%)	6 (50.0%)		
Absent	16 (88.9%)	151 (88.8%)	6 (50.0%)		
Vascular invasion				0.483	
Present	3 (16.7%)	22 (12.9%)	3 (25.0%)		
Absent	15 (83.3%)	148 (87.1%)	9 (75.0%)		

[a]Among the three different types of histologic differentiation in HCC, [b] Does not included three cases of hypovascular enhancement
Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma; w-HCC, well-differentiated HCC; m-HCC, moderately-differentiated HCC; p-HCC, poorly-differentiated HCC; SD, standard deviation

TABLE 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for prediction of p-HCC using CT findings.

CT findings	Sensitivity	Specificity	PPV	NPV	Accuracy
Irregular rim enhancement	58.3%	97.3%	58.3%	97.3%	95%
Lymphadenopathy	50.0%	88.8%	22.2%	96.5%	86.5%
Coexisting irregular rim enhancement and lymphadenopathy	33.3%	98.4%	57.1%	95.8%	94.4%

Abbreviations: p-HCC, poorly-differentiated hepatocellular carcinoma; CT, computed tomography

DISCUSSION

Histological grading of HCC is a relevant prognostic factor after treatment[6-8], and some studies found that poor differentiation is a risk factor of tumor seeding after RFA.[9,10] However, pathological diagnosis of HCC is not usually obtained before surgery, and needle biopsy is not routinely performed because of the risk of tumor seeding and the probability of diagnostic error due to tumor heterogeneity. Therefore, investigation into the correlation between imaging findings and histological grading of HCC might have some potential benefit for management of HCC patients.

Our study found that irregular rim enhancement on arterial phase had high specificity (97.3%) for prediction of p-HCC. This is similar to the findings of Kawamura, *et al.*[15] who found heterogeneous enhancement with irregular ring-like structures in the arterial phase to be an independent predictor of p-HCC. The explanation of this enhancement pattern may be combination of tumor necrosis and other factors, such as type II vessels[15]; however, the exact mechanism remains unknown. Nakachi, *et al.*[13] reported that arterial enhancement with non-enhanced areas, which included irregular rim enhancement pattern, was associated with p-HCC. Non-enhanced area on arterial phase and irregular rim enhancement on arterial phase were separately investigated in our study. Although non-enhanced area on arterial phase was present in all p-HCC in our study, this finding was not significantly difference among the three types of histological differentiation of HCC. This difference compared to prior study might be due to the small number of p-HCC and the relatively larger mean tumor size (5.5±3.9 cm. for all HCC cases) in our study. Tumor size is a factor that may affect enhancement pattern of HCC. Yoon SH, *et al.*[16] reported that tumor size <2 cm and w-HCC frequently had atypical enhancement patterns.

Irregular rim arterial enhancement pattern can also be found in other hepatic tumors, such as cholangiocarcinoma and fibrolamellar HCC. However, cholangiocarcinoma is rare in chronic hepatitis or cirrhotic patients when compared with HCC. Some imaging features can help in differentiating intrahepatic cholangiocarcinoma (ICC) from HCC.[17] ICC exhibits rim-like peripheral arterial enhancement with progressive centripetal enhancement, and it usually associates with peripheral biliary dilatation or capsular retraction. On the other hand, presence of intralesional fat and enhanced capsule are more suggestive of HCC than ICC. Fibrolamellar HCC, which is a rare primary liver tumor, has clinicopathologic features different from conventional HCC. It predominantly occurs in young patients without underlying hepatitis or cirrhosis, and serum alfa-fetoproteins are not elevated in most cases.[18] Calcification and central stellate scar are commonly seen in fibrolamellar HCC.[18] Presence of intralesional fat is more suggestive of conventional HCC than of fibrolamellar HCC.[18]

Abdominal lymph node is one of three most common sites of extrahepatic metastatic HCC.[19] In our study, lymphadenopathy was more commonly present in p-HCC (50%) than in w-HCC or m-HCC, and it had a specificity of 88.8% for prediction of p-HCC. This finding is similar to that reported by Lee, *et al.*[20] who found HCC with lymph node metastasis to be significantly associated with worse histological grade. However, the use of lymph node size criteria did not improve the accuracy of detection of metastatic nodes in our study. Enlarged lymph nodes can be either benign or metastatic nodes, and lymph node metastasis can be found in normal sized nodes. Further non-invasive imaging study for accurate evaluation of metastatic nodes is needed.

Tumor stain washout in the portovenous phase was reported to be associated with p-HCC in prior study.[13]

Lee, *et al.*[12] reported that early washout favored m-HCC and p-HCC more than w-HCC, and the presence of intratumoral aneurysm was highly specific finding for p-HCC. However, tumor stain washout was not found to be significant different among the three histological grades of HCC in our study.

Limitations

Our study has some limitations. First, this was a retrospective study and there was selection bias related to the inclusion criteria that only patients with pathological proof and CT images obtained within 12 weeks were selected. Second, the pathological diagnosis included patients with needle biopsy samples which can lead to diagnostic error due to heterogeneity of HCC tumors. Third, the small numbers of w-HCC (18 cases) and p-HCC (12 cases) in our study may reduce the reliability of the analysis. In the future, a larger scale cohort investigation should be conducted.

CONCLUSION

There is potential benefit of dynamic contrast-enhanced CT for prediction of p-HCC. The presence of irregular rim enhancement in arterial phase and lymphadenopathy are potentially useful CT findings for prediction of p-HCC prior to treatment.

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Factors Affecting Unfavourable Results from a Sinonasal Inverted Papilloma Surgery

Anan Bedavanija, M.D.*, Pongsakorn Tantilipikorn, M.D, Ph.D.*, Pichit Suksaranjit, M.D.*, Tawatchai Pongpruttipan, M.D.**, Pawin Keskool, M.D.*, Cheerasook Chongkolwatana, M.D.*, Choakchai Metheetrairut, M.D.*, Jate Lumyongsatien, M.D.*, Triphoom Suwanwech, M.D.***

**Department of Otolaryngology, **Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, ***Diamond Clinic, Bangkok 10240, Thailand.*

ABSTRACT

Objective: Sinonasal inverted papilloma (SNIP) is the most common nasal benign tumor, but locally invasive. The standard treatment is to identify origins of the tumor and total removal. Unfavourable results are finding postoperative residual or recurrent tumors. The aim of this study is to determine factors affecting postoperative residual or recurrent tumors and a rate of getting postoperative residual or recurrent tumors from SNIP surgeries.
Methods: A retrospective study in patients with SNIPs was conducted. Relationships between demographic data, tumor sites, tumor stages by Krouse classification, surgical approaches, surgeons' experience, using microdebrider assisted surgery, operative time, intraoperative blood loss, histopathology, Epstein Barr virus (EBV), human papillomavirus (HPV) infection, time to detect tumor after surgery and unfavourable results were evaluated. HPV and EBV were detected *by in situ hybridization*.
Results: 73 patients were included in this study. Unfavourable results were found in 27 patients (36.99%). 50% of patients received unfavourable results after postoperative duration of 115 months. 5 years of a disease-free survival rate was 64.3% (95% CI: 51.9% to 76.7%). The patients with external surgical approaches got worse results than those with endoscopic sinus surgery ($p = 0.01$, a hazard ratio of 3.88, 95% CI: 1.39 to 10.87). The patients operated without using microdebrider assisted surgery got worse results than those with using the device ($p < 0.001$, an adjusted hazard ratio of 5.09, 95% CI: 2.08 to 12.45). The patients with abnormal pathological changes (tissue dysplasia and malignant transformation) had worse results than those without changes ($p = 0.02$, an adjusted hazard ratio of 3.42, 95% CI: 1.24 to 9.38).
Conclusion: Non-endoscopic nasal surgery, non-using microdebrider assisted surgery, and abnormal pathological changes may be some of the causes of unfavourable results from SNIP surgeries. Long postsurgical surveillance should be done, because of 36.99% of patients received unfavourable results from SNIP surgeries.

Keywords: Sinonasal inverted papilloma; unfavourable results; relationship; sinus surgery (Siriraj Med J 2020; 72: 343-351)

INTRODUCTION

Sinonasal papillomas are nasal benign tumors developing from Schneiderian membranes, which are ectodermal remnants at boundary between nasal and sinus mucosa. They are classified into sinonasal inverted papilloma (SNIP), exophytic (fungiform) papilloma, and oncocytic (cylindrical cell) papilloma. The most common type of sinonasal papilloma is SNIP. SNIPs, which are found 0.2-1.5 cases per 100,000 populations[1,2], are the most common benign tumor of the nose and paranasal sinuses[13], but they are locally aggressive and usually recurrent. The tumors usually erode adjacent

Corresponding author: Pongsakorn Tantilipikorn
E-mail: ptantili@yahoo.com
Received 17 February 2020 Revised 20 April 2020 Accepted 22 April 2020
ORCID ID: http://orcid.org/0000-0003-1995-4798
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bones, extend to the orbit and intracranium. They have 5-15% risks of malignant transformation, and 5-15% risks of recurrence.[3-9] The main treatment is to identify all sites of tumor attachments, remove all tumors with affected mucosa, and drill out underlying bone in order to prevent tumor recurrence.[10] The standard treatment is an external approach with a medial maxillectomy via a lateral rhinotomy, or a midfacial degloving procedure.[11,41] Nowadays, an endoscopic surgery is usually performed, because it can reduce the morbidity of an external approach. An endoscope can help surgeons to visualize in the surgical field, even hidden sites such as an anterior wall of the maxillary sinus e.g., endoscopic Denker approach (anteromedial maxillectomy).[9,41] Therefore, some surgeons use an endoscope to assist an external approach to obtain complete tumor removal. A microdebrider is a powered rotary shaving device. It provides atraumatic dissection by resecting tissue precisely, minimizing unintended mucosal trauma. The using microdebrider assisted surgeries showed minimal bleeding, decreased surgical time, faster postoperative healing[19,22], and should reduce postoperative recurrences of SNIP surgeries. Postoperative recurrent rate of SNIP surgeries is lower in primary resections than secondary resections[10,12], so the patients with SNIPs should be operated as primary resections. Meta-analysis studies suggest HPV and EBV infection maybe potential causes of recurrence[2, 21,40], but no study in Thailand.

The risk factors affecting unfavourable results from SNIP surgeries, in literary reviews, are ages, genders, surgical approaches, tumor sites, tumor stages, histopathology, virus infection, and smoking[2,11-13]; however, they are still controversial. The purpose of this study is to determine the factors affecting postoperative residual or recurrent tumors and a rate of getting postoperative residual or recurrent tumors from SNIP surgeries.

MATERIALS AND METHODS

A retrospective study was conducted on patients, selected from 289 cases of SNIP surgeries, at Siriraj Hospital between January 2004 and December 2012. All patients, presenting as primary SNIPs, are more than 18 years old, postoperative tumor surveillance to December 2019. Exclusion criteria included partial or incomplete resection, revision surgery, and incomplete patient data. Demographic data, tumor sites, tumor stages by Krouse classification[14], surgical approaches, surgeons' experience, using microdebrider assisted surgery, operative time, intraoperative blood loss, histopathology, EBV, HPV infection, and a date of finding postoperative tumors were evaluated. The criteria of unfavourable result are finding postoperative residual or recurrent tumor by nasal endoscopic examination and pathological confirmation. The recurrent cases were defined as finding postoperative tumor after postoperative duration of 3 months. A total of 73 patients were selected in this study (Fig 1).

Hematoxylin and eosin-stained pathological slides were reviewed, and the diagnosis was confirmed by one pathologist (T.P.). Paraffin-embedded tissue blocks were selected for tissue microarray. The tissue microarray sections were hybridized separately with a target probe of Ventana Inform HPV II Family® 6 Probes, for low-risk HPV genotypes 6,11, then Ventana Inform HPV III Family® 16 Probes, for high-risk HPV genotypes 16, 18, 31, 33, 35 45, 51, 52, 56, 58, 66, and Epstein Barr virus encoding RNA (EBER).

This study protocol was approved by the Institutional Review Board Committee of the Siriraj Hospital. The sample size calculation was based on the study of Busquets et al.[8], found 15 % of postoperative SNIP recurrences. Sixty-one patients were required to get 95% confidence level with a type I error at 0.05.

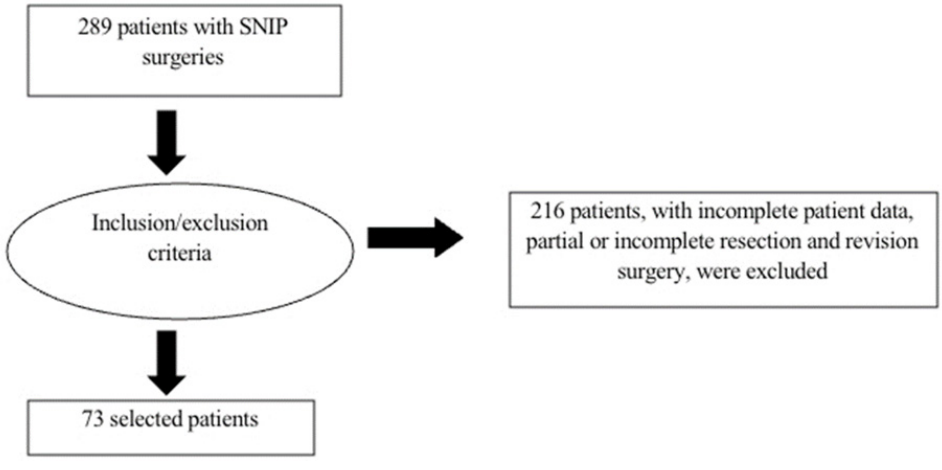

Fig 1. Flowchart of this study

Statistical analysis

The data was presented as numbers and percentages. If quantitative variables were normally distributed, the results were expressed as mean values and standard deviation, otherwise as median. A difference between two groups was analyzed by using t-test, or Mann-Whitney U test. Qualitative data are reported as counts and frequencies, and differences between two groups were analyzed by using Pearson Chi-Square test or Fisher's exact test, and receiver operating characteristic (ROC) curve. Cox regression was used to analyze the association of factors of unfavorable results. Kaplan-Meier curve and log rank test were used to analyze a disease-free survival. A p value of 0.05 was considered as a statistical significance. All calculation was performed by using SPSS, PASW statistics for windows, version 18.0.

RESULTS

General data

The age of the 73 patients ranged from 24 to 87 years, with a mean of 54.90 ± 13.27 years. There were 37 males and 36 females. The most common presenting symptom was nasal obstruction (71.60%). Other presenting symptoms were rhinorrhea/postnasal drip (11.24%), epistaxis (6.51%), smell dysfunction (2.96%), facial pain (2.96%), headache (1.78%), blocked ear (1.18%), toothache (1.18%), and oropharyngeal pain (0.49%).

Sixty-three patients had multiple tumor sites (86.30%). All SNIPs were unilateral sites, found 37 right-sided tumors, and 36 left-sided tumors. Tumors were located at lateral nasal wall (34.72%), maxillary sinus (23.83%), ethmoid sinus (19.17%), sphenoid sinus (5.70%), frontal sinus (7.25%), middle turbinate (4.66%), superior turbinate (2.07%), nasal septum (1.55%), and inferior turbinate (1.04%). Tumor stages by Krouse classification[14] revealed 4 groups as T1 (5.48%), 20 patients as T2 (27.40%), 47 patients as T3 (64.38%), and 2 patients as T4 (2.74%).

Endoscopic sinus surgeries were performed in 49 patients (67.12%). 6 patients (8.22%) underwent external surgical procedures and 18 patients (24.66%) were operated by combined approaches. Microdebriders were used in 28 of all cases (61.64%). SNIPs with tissue dysplasia without malignant change were found in 3 patients (4.11%). All of them were gotten postsurgical recurrences. Malignant transformations to squamous cell carcinoma occurred in 3 patients (4.11%). All of them were synchronous malignancy, no regional or distant metastasis, and recurrent tumors were found in 2 patients. All patients with malignant transformations were received postoperative radiation therapy, and 2 patients were received concurrent chemotherapy. A surgical margin was not free in one patient; however, all patients with malignant changes had survived.

Analysis of unfavorable results

The unfavourable results were found in 27 patients (36.99%) (7 residual cases, and 20 recurrent cases) and 50% of patients received unfavourable results after postoperative duration of 115 months. 5 years of a disease-free survival rate was 64.3% (95% CI: 51.9% to 76.7%). A mean time of unfavourable results was 30.23 months (ranging from 0.82 to 115.31 months).

Genders, ages, and onset of disease

An average age of the patients with unfavourable results was 50.82 years old, which is lower than a mean age of 57.30 years old in the successful group. There was a statistically significant difference between the two groups (p = 0.04). However, no relationship was found between genders, onset of disease and unfavourable results (p = 0.52, 0.27, respectively) (Table 1).

Tumor sites and stages

No statistical significances were found between each of the tumor sites (lateral nasal walls, ethmoid sinuses maxillary sinuses, sphenoid sinuses, frontal sinuses, superior turbinates, middle turbinates, inferior turbinates, and nasal septums), multiple tumor sites, tumor stages and unfavourable results (p = 0.19, 0.52, 0.61, 0.52, 0.61, 0.14, 0.28, 1.00, 0.55, 0.74, and 0.82, respectively) (Table 1).

Surgical approaches, intraoperative time, techniques, and blood loss

A significantly difference was found between three surgical approaches (p = 0.04) (Table 1). Both an endoscopic sinus surgery and an endoscopic assisted external surgical procedure offered better outcome than an external surgical procedure (p = 0.007, 0.04, respectively). However, no different in treatment outcome was found between the two groups using endoscope (p = 0.60). The patients with external surgical approaches had worse results than those with endoscopic sinus surgery (p = 0.01, a hazard ratio of 3.88, 95% CI: 1.39 to 10.87) (Fig 2).

No difference in surgical treatments was found between experienced and training surgeons (resident and/or fellow under supervision) (p = 0.45) and no relationships between intraoperative time, blood loss and unfavourable results were found (p = 0.16, 0.39, respectively) (Table 1).

Microdebrider is an assisted surgical device in nasal surgery and can be used for cutting and removing

TABLE 1. Factors affecting unfavourable results from SNIP surgeries in univariate analysis.

Factors	Successful treatments (n = 46)	Unfavorable treatments (n = 27)	*P*-value
Genders			0.52
Male	22	15	
Female	24	12	
Mean of ages (years)	57.30	50.82	**0.04*** **
Median of disease onset (months)	7.5 (3,12)	12 (3,24)	0.27
Tumor sites:			
Lateral nasal walls			0.19
No	2	4	
Yes	44	23	
Ethmoid sinuses			0.52
No	24	12	
Yes	22	15	
Maxillary sinuses			0.61
No	16	11	
Yes	30	16	
Sphenoid sinuses			0.52
No	40	22	
Yes	6	5	
Frontal sinuses			0.61
No	38	21	
Yes	8	6	
Superior turbinates			0.14
No	45	24	
Yes	1	3	
Middle turbinates			0.28
No	42	22	
Yes	4	5	
Inferior turbinates			1.00
No	45	26	
Yes	1	1	
Nasal septums			0.55
No	45	25	
Yes	1	2	
Multiple sites			0.74
No	7	3	
Yes	39	24	
Tumor stages			0.82
T1	3	1	
T2	12	8	
T3	30	17	
T4	1	1	

TABLE 1. Factors affecting unfavourable results from SNIP surgeries in univariate analysis. (continued)

Factors	Successful treatments (n = 46)	Unfavorable treatments (n = 27)	*P*-value
Surgical approaches			**0.04*** **
Endoscopic sinus surgery	34	15	
External surgical procedure	1	5	
Endoscopic assisted external surgical procedure	11	7	
Median of intraoperative time (minutes)	120 (90,150)	140 (100,180)	0.16
Median of intraoperative blood loss (ml)	225 (80,450)	300 (100,550)	0.39
Using microdebrider assisted surgery			**0.005*** **
Non-using	12	16	
Using	34	11	
Surgeons' experience			0.45
Experience	36	19	
Training	10	8	
Tissue dyplasia and malignant transformation			**0.05*** **
No dysplasia and malignant transformation	45	22	
Dysplasia and malignant transformation	1	5	
HPV infection			0.37
No HPV infection	46	26	
HPV infection	0	1	

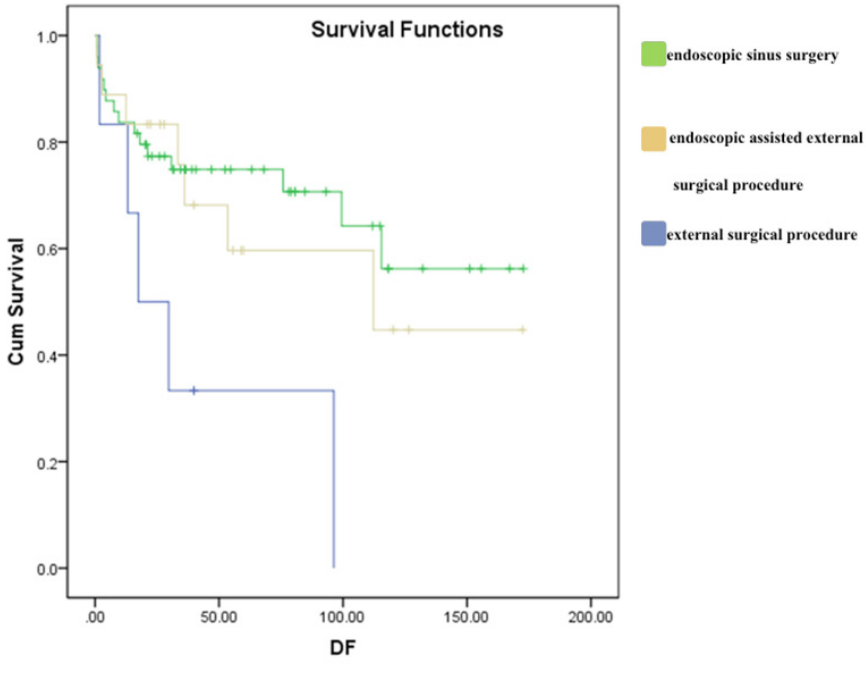

Fig 2. Disease free survival and surgical approaches

tissues, together. The patients with using microdebrider assisted surgery got better surgical outcomes than those without using the device (p =0.005) (Table 1).The patients operated without using microdebrider assisted surgery got worse results than those with using the device (p = 0.001, a hazard ratio of 4.51, 95% CI: 1.88 to 10.81, and p < 0.001, an adjusted hazard ratio of 5.09, 95% CI: 2.08 to 12.45, in multivariate backward cox regression analysis with abnormal pathological changes (tissue dysplasia and malignant transformation) (Fig 3).

Histopathology

The relationship was found between abnormal pathological changes (tissue dysplasia and malignant transformation) and unfavorable results (p = 0.05) (Table 1). The patients with the changes got worse unfavourable results than those with no pathological change (p = 0.05, a hazard ratio of 2.59, 95% CI: 0.97 to 6.90, and p = 0.02, an adjusted hazard ratio of 3.42, 95% CI: 1.24 to 9.38, in multivariate backward cox regression analysis with using microdebrider assisted surgery) (Fig 4).

Virus infection

Only one patient in the unfavourable group was positive for HPV type 6 by *in situ* hybridization and no EBV was detected in all patients. No relationship was found between HPV infection and unfavorable results (p = 0.37) (Table 1).

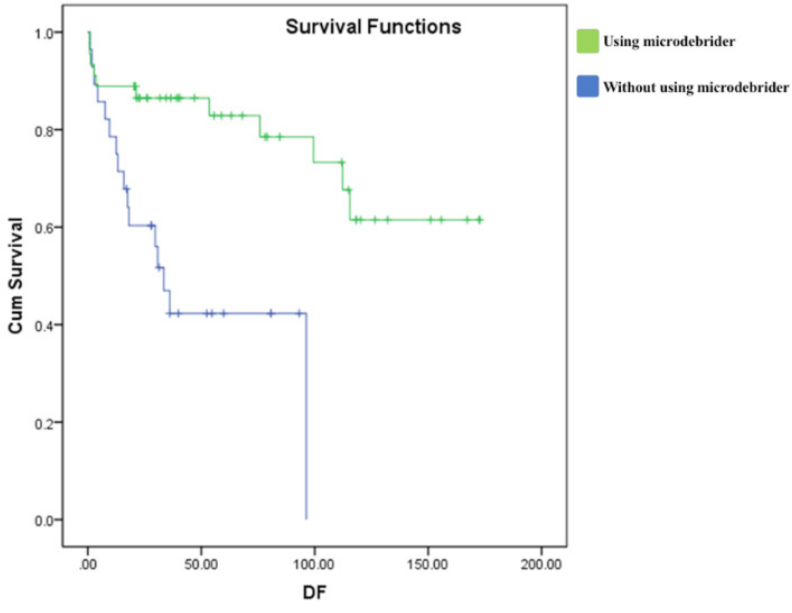

Fig 3. Disease free survival and using microdebrider assisted surgery

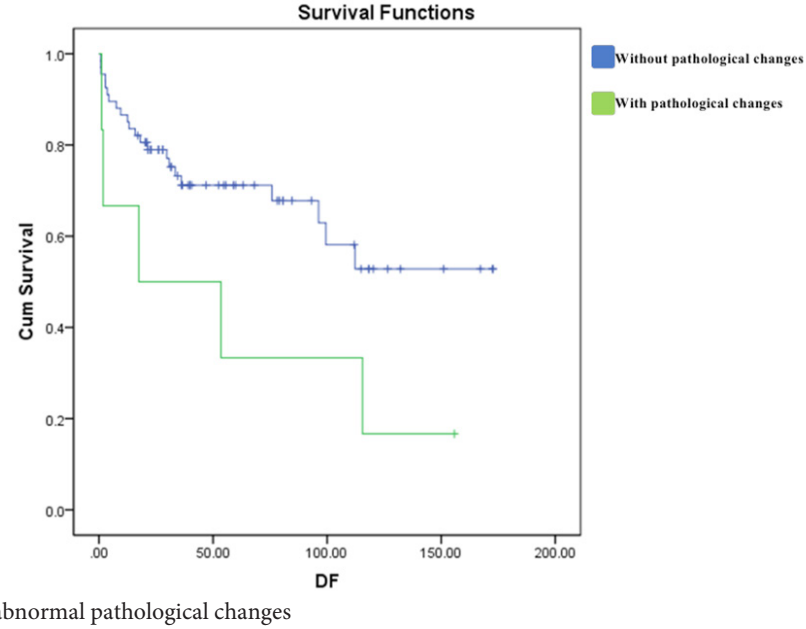

Fig 4. Disease free survival and abnormal pathological changes

DISCUSSION

Factors affecting unfavourable results from SNIP surgeries could be surgical approaches, using microdebrider assisted surgeries, and abnormal pathological changes.

An average age of the patients with unfavourable results was 50.82 years old, which is lower than a mean age of 57.30 years old in the successful group. The patients with unfavourable results of SNIP surgeries were younger than those with good results as other studies[20,36,39], because they might get more risks of exposure with chronic inflammatory conditions, such as chronic infection, smoking, pollution[15,16], which could induce normal tissues developing to SNIPs. However, it might be no clinical significance in surgical decisions between age groups.

The surgical approaches, which depended on surgeons' experience, tumor sites, were selected in each patient. The patients with external surgical approaches had a hazard ratio of 3.88 to get failed results. The groups of using endoscope had better outcomes, as other studies[8,9,18], because endoscope can help surgeons to visualize in all surgical fields, even hidden sites such as an anterior wall of maxillary sinus, a lateral wall of frontal sinus. Therefore, we should use endoscope to assist in SNIP surgeries, especially in high Krouse classification.

The patients operated without using microdebrider assisted surgery had an adjusted hazard ratio of 5.09 to get unfavourable results. The group with using microdebrider, which can cut together with tissue suction, got better results, because surgeon could see clearly operative field and got completely tumor removal.[8,19,22] Unfortunately, the device is a special instrument which is not included in the standard instruments in SNIP surgeries. According to our study, surgeons should use this device to get good outcomes in all cases of SNIP surgeries.

The study by Lisan et al.[2] found that the tumor attachment sites were related to tumor recurrences, especially in the frontal sinus, and in cases with multiple tumor origins. There were not found in our and others study[36,42], because of few patients included in some tumor sites. No relationship was found between Krouse classification, and unfavourable results as other studies[10,12-13,17,38-39], because of also few patients in T1 and T4.

Long intraoperative time and high intraoperative blood loss might be factors of poor surgical outcomes such as delayed wound healing, incomplete tumor removal, but no relationship between those and unfavourable results were found in our study. Experienced surgeons should be better in surgical outcomes than training surgeons. No difference in curative effects in surgical experience was found, because Siriraj Hospital is a tertiary care and an otolaryngological training center. Even though, patients were in training cases, our staffs had to supervise our training surgeons and completely examine those patients before finishing operations.

In this study, a statistical significance was found between the patients with abnormal pathological changes (tissue dysplasia and malignant transformation) and unfavourable results. The patients with that changes got an adjusted hazard ratio of 3.42 to get unfavourable results as previous studies that found features of atypia, enhanced hyperkeratosis, presence of squamous hyperplasia[12,42] may predispose to recurrence. Thus, we should pay more attention to those and frequently postoperative surveillance with the changes that could be a factor of tumor recurrences.

EBV was not detected in all patients as same as other studies[15] and could not be a factor of unfavorable results. One patient with an unfavourable result was positive for HPV type 6 by *in situ hybridization*. Our study is the first study of HPV in nasal tumors in Thailand, so there is no study in that for comparison. The HPV studies, which were found low HPV detection, in head neck tumors in Thailand[25-29], might be used as comparison. HPV was low detected in our study, which contrasted with previous studies[21-24] because HPV might rarely be found in these regions in Thailand, and Ventana Inform HPV Family® cannot detect all HPV types. Our negative results could be true negative, because Ventana Inform HPV Family® can be usually used in paraffin-embbed tissues as other studies and *in situ hybridization* can detect HPV as same as other molecular techniques.[30-35] The study by Holte et al.[36] found a decreasing ratio of HPV-positive SNIPs with advanced tumor stages as T3,4 of Krouse classification. The positive case in our study was in T2 of Krouse classification and other negative results were usually found in T3 of Krouse classification. Accordingly, HPV infection may not be a risk factor of unfavourable results in SINP surgeries in Thailand.

The unsuccessful treatment rate of 36.99%, in our study, was nearly the recurrent rate of 30.51% in the past study by Jareoncharsri et al.[37] and 37% in the other study in Thailand by Fooanant et al.[18] The recently meta-analysis study by Peng et al.[9] found the recurrence rate was 12.8%. In our study, the unsuccessful treatment rate was higher than that study, because our study included residual and recurrent tumors, was long terms postsurgical surveillance, and microdebrides were not used in all surgical cases. SNIPs in our country may tend to recur. The 115 months of 50 % finding postoperative tumor were suggested postoperative surveillance should be at least 10 years.

Malignant transformation (4.11%) was lower than other studies of 5 to 15 % of malignant transformation.[11-12,38] This finding may indicate that SNIPs in Thailand are non-violent, but frequently recurrent.

The drawback of this study is not included some factors, which might be factors of unfavourable results, such as smoking, pollution, revision surgery, sending an intraoperative tumor margin and few patients in some Krouse classification.

The prominence of this study is a retrospective study, which is no bias in surgical outcomes, and long postsurgical surveillance. From our and other studies in Thailand[18,37], SNIPs may tend to recur, low malignant changes and need long postsurgical surveillance. The future study should include a medical genetic study in patients with SNIPs and malignant changes, and a benefit of using microdebrider assisted surgery.

CONCLUSION

Non-endoscopic nasal surgery, non-using microdebrider assisted surgery, and abnormal pathological changes were possible risk factors of unfavourable results in SNIP surgeries. Because of the patients, with using nasal endoscopes and microdebriders assisted SNIP surgeries, gotten better surgical results, both devices should be the standard equipments in SNIP surgeries. The patients with abnormal pathological changes should be frequently surveilled, because they had a risk of postoperative recurrences. Long postsurgical surveillance should be done, because of 36.99% of patients received unfavourable results from SNIP surgeries.

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Long-Term Vipassana Meditation Enhances Executive Function in Adult Meditators

Thawatchai Lukseng, Vorasith Siripornpanich, Nuanchan Chutabhakdikul, Ph.D.

Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Nakornpathom 73170, Thailand.

ABSTRACT

Objective: Vipassana meditation (VM) is a traditional Buddhist meditation practice that focuses on monitoring of clear awareness of oneself exactly what is happening as it happens, without judging. Executive functions (EF) are the high-level cognitive processes that facilitate goal-directed behaviors. It is well known that VM has significant effects on various affective states of the mind, such as relaxation, reduce stress and anxiety; however, less is known about the effect of VM on the executive function. This study aims to examine the effects of VM practice on the performance of the executive function in the adult meditators.

Methods: Forty adult participants, age range between 25-50 year-olds, were recruited to this study. They were divided into three groups; the control group (N=20, mean age = 40.5 ± 5.8 years), Short-term VM group (N=6, mean age = 38.0±9.1 years), and Long-term VM group (N=14, mean age = 37.7±7.3 years). All participants were examined by 1) State-trait anxiety inventory (STAI); 2) Philadelphia mindfulness scale (PHLMS); 3) Digit span task of WAIS-IV, 4) Tower of Hanoi (ToH), and 5) Wisconsin Card Sorting Test (WCST-CV4). The mean scores of all task performance were statistically analyzed and compared between groups. Alpha values of .05 were considered significant throughout.

Results: Both short-term and long-term VM has common benefits to decreased anxiety and increased mindfulness score as compared with the non-meditator group. Although short-term VM shows some benefits to the performance of several EF tasks, the discrepancy was not significant when compared with the control group. In contrast, long-term VM had a significant benefit to the performance of working memory, planning, and shift/cognitive flexibility, when compared with the non-meditator group. Our results indicated that long-term VM practice not only reduces anxiety and improves mindfulness, but the benefit also extends to improve the performance of the executive function in adult practitioners.

Conclusion: In conclusion, our results suggest that continued practice of VM is highly effective for enhancing EF in healthy individuals. Long-term VM practice not only reduce stress and improve mindfulness but also enhance the performance of EF tasks of the practitioners.

Keywords: Vipassana meditation; executive function; Philadelphia Mindfulness Scale; Wisconsin Card Sorting Test; Digit Span; Tower of Hanoi (Siriraj Med J 2020; 72: 352-360)

INTRODUCTION

Meditation is the method of body and mind training for promoting relaxation, improving focus attention, and concentration.[1,2] Previous studies demonstrate various benefits of meditation practice on body and mind, such as; reduced anxiety and stress,[3-5] improve emotional stability,[6] improve concentration and enhance personal well-being,[7] and produce long-term increases

Corresponding author: Nuanchan Chutabhakdikul
E-mail: nuanchan.chu@mahidol.edu
Received 23 July 2019 Revised 5 January 2020 Accepted 18 February 2020
ORCID ID: http://orcid.org/0000-0001-7338-4824
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in efficiency of the attentional network.[8] Moreover, the clinical effectiveness of meditation has been reported for the treatment of various physical and mental illnesses.[9-11]

Buddhist meditation can be classified into two main methods according to the mental skills that exercise during meditation practice as follows; 1) Focused Attention (FA) in which the practitioner requires to attend or focus onto the selected object, such as breathing or candlelight, and to avoid mind wandering for a period of practice,[12,13] and 2) Open Monitoring (OM)in which the practitioner requires to maintain awareness of their mental, interoceptive, and exteroceptive experiences, and without any object to focusing on.[14-16] These two types of meditation have been reported to affect brain function differently. For example, FA improves sustained attention associated with increased activity in the dorsolateral PFC (DLPFC).[17] In contrast, OM improves sustaining internalized attention associated with increased activity in the posterior insular cortex.[18] The previous study reported that one of the OM-like meditation called Mindfulness-based stress reduction (MBSR), not only has a significant benefit on emotional well-being but also improved cognitive inhibition in the school-aged students as examined by various cognitive tasks.[19] Importantly, a study in the healthy individuals shows that MBSR increased brain activity in the insular cortex (the brain area involved with self-awareness and interoceptive awareness) but no significant effect on the DLPFC activity.[20] In contrast, FA that focuses on the concentration training alone might have less benefit on cognitive abilities since the previous study reported that FA meditators perform various cognitive tasks as equal to the non-meditator group.[19]

Another type of Buddhist meditation that combines both FA and OM together is the so-called Vipassana meditation or VM. VM is the meditation practice that focuses on the monitoring of clear awareness of oneself exactly what is happening as it happens.[15,16] Usually, the VM starts by focusing attention (FA) on to the selected object (such as the breath) and then broadens the focus to the sensory or mental stimuli (OM). Therefore, VM practice uses both FA and OM in order to stay in the monitoring state to any experiences that may arise without selecting, judging, or avoiding the affective responses to that stimuli. In this way, the VM practice could enhance concentration, bare attention, and cultivate a non-reactive form of sensory awareness.

Executive function (EF) is an umbrella term representing higher cognitive processes that are essential for goal-directed behaviors.[21-24] There are 3 main components of EF which compose of; 1) working memory-the ability to updating and monitoring information; 2) Inhibitory control-the ability to inhibit the pre-potent responses and inhibit at the level of attention or inhibit distraction; and 3) Shift/cognitive flexibility-ability to shifting of mental set and flexible thinking.[23] EF gradually develops from early childhood to adulthood, correlate with the maturation of the neural networks that linking the prefrontal cortex with other brain regions.[25] In healthy adults, EF serves as a predictor of everyday functioning since intact is required for daily functions including; setting goals, planning, and prioritizing the complex tasks, initiating, sustaining attention despite distraction. People with proper EF skills show better in managing their life and work performance in the challenge situations, as compared to the one with poor EF.[21]

Although many studies consistently reported the common benefit of meditation on body and mind,[3,5,26,27] however, differential effects of short-term and long-term VM on the performance of EF tasks have yet to be fully elucidated. Interestingly, a recent study showed that amygdala activity response differently in the short-term or long term meditators in response to the negative emotional stimuli.[28] The present study employed various neuropsychological tests to investigate the effects of short-term and long-term VM on executive function in adult practitioners. We hypothesized that long-term VM practice associated with higher mindfulness scale and lower anxiety level that could enhance the performance of EF as compared to the non-meditator group.

MATERIALS AND METHODS

Participants

Participants are healthy adults, aged between 25-50 years, n=40. Vipassana meditators were recruited from the meditation centers in Bangkok metropolitan areas, whereas the control subjects were recruited from the communities in the same area. A demographic questionnaire was completed before any measurements, which included information about age, sex, general health information, and years of education. Participants were asked for information about their meditation background such as; duration, frequency, and average hours of lifetime VM practice, then, they were divided into three groups; 1) Control group, is the participants who had no prior experience of any meditation practice (n =20; mean age = 40.5±5.8 years), 2) Short-term VM group, is the beginner who had average VM practice around 3.5 years (n=6; mean age 38.0±9.1 years), and 3) Long-term VM group is the meditator who had average VM practice for 10 years (n=14; mean age=37.7±7.3 years). There were no significant differences in the mean ages and average years of education of the participants from all

groups (Table 1). The meditation background of the participant in the short-term and long-term VM group was shown in Table 2. Informed consents were obtained from all participants before any measurements, and the experimental protocol was strictly followed the ethical standards outlined of the Declaration of Helsinki in 1975 and has been approved by the Institutional Review Board (COA.No. 2014/146.2011). All participants had no history of neurological illness.

Measures

The State-Trait Anxiety Inventory (STAI-Adult)

The State-Anxiety scale (S-Anxiety) consists of twenty statements that evaluate how participants feel right now or at this moment.[29] The S-anxiety scale represents the feelings of apprehension, tension, nervousness, and worry of the participant at that time. Whereas the Trait-Anxiety scale (T-Anxiety) consists of twenty statements that assess how participants generally feel. The T-anxiety scale has been used for identifying persons with high levels of anxiety. The total questions are 40 items; each item was weighted score from 1 to 4. The raw scores were converted into the standard scores and the percentile rank. The higher means score indicated more anxiety in that section.

Philadelphia Mindfulness Scale (PHLMS-Thai)

Philadelphia Mindfulness Scale (Thai version) from the Department of Mental Health, Ministry of Public Health, Thailand, was used to assess the mindfulness level of the participants.[30,31] The PHLMS has high reliability, and high validity with Pearson's correlation for the awareness and acceptance scale is 0.88 and 0.89, respectively; and the Cronbach's alpha coefficient of the awareness and acceptance scale are 0.87 and 0.88, respectively.[30] It contains 20 items for measurement of awareness and acceptance level of the participants. The awareness and acceptance subscales were obtained from the sum of scores in all odd or even-numbered items, respectively. The score ranged from 10-50 points in each subscale or 20-100 points in the total score. The higher PHLMS score indicates more mindful than lower PHLMS scores.

TABLE 1. Demographic characteristics of the participants. Data represents means±SD.

Participants background	Non-meditation	Short-term VM	Long-term VM
Age (years)	40.5 ± 5.8	38.0±9.1	37.7±7.3
Gender (M:F)	18:2	4:2	11:3
N	20	6	14
Years of Education	15.6 ± 2.5	15.6±1.9	16.8±1.0

TABLE 2. Meditation background of the participants of the Vipassana meditation (VM) group. Data represents means±SD.

Meditation background	Short-term VM			Long-term VM		
	Average	Max	Min	Average	Max	Min
Years of practice	3.6±1.1	5.0	2.0	10.0±6.6	18.0	5.0
Duration of practice (hours/day)	0.5±0.1	0.5	0.3	1.2±0.6	3.0	0.5
Frequency of practice (days/week)	4.3±2.1	7.0	2.0	6.1±1.5	7.0	4.0
Total hours of practice	366±198	650	89	3,462±2,654	8,736	728

Working Memory Scale (WAIS-IV)

The working memory part of the Wechsler Adult Intelligence Scale (WAIS-IV) was used to evaluating the working memory (WM) capacity of the participants.[32] Two categories of WM tasks were used; the digit span forward and the digit span backward. In the forward session, the researcher read a series of number sequences to the subject, and then subjects had to repeat them immediately in the same order. After finish the forward session, the examiner began the digit span backward session by reading a series of number sequences, and subjects had to repeat the number sequences in the reversed order. There are eight blocks of digit span forward, and seven blocks of digit span backward. Each block contains two sets of questions. In both tasks, the length of the most extended number lists that the subject could recall was recorded. The scaled score by the age- and gender-matched was used to compare between the two groups.

Tower of Hanoi (ToH)

The Tower of Hanoi was used for evaluating a higher level of EF, especially the planning process (http://www.coolmath-games.com/0-tower-of-hanoi). It composes of 3 pieces of the rod with several discs. The discs are different in their size and can be moved among the rods. Subjects are required to move the disc from the start point until they reach the goal position. There were three to five discs that represent levels of task difficulties. The numbers of moves and the total time to complete the task were recorded. Lower numbers of moves and shorter response times indicate the better performance of the ToH task.

Wisconsin Card Sorting Test (WCST-CV4)

The Wisconsin Card Sorting Test®: Computer Version 4 (WCST:CV4) (PAR, Inc.) was used for measurement of various EF domains, including; mental shifting, planning, and working memory.[33] For the task, the stimulus cards were presented on the monitor, and the participants were asked to match the stimulus cards with one of the four category cards by trial and error. Subjects were given by the feedback on the screen ("right" or "wrong") immediately after each sorted. The following data were used for analysis: (1) trials administered, (2) total correct, (3) total errors, (4) perseverative responses, (5) perseverative errors, (6) non-perseverative errors, (7) % conceptual level responses, (8) number of Categories Completed, (9) trials to complete the 1st Category, and (10) failure to maintain set.

Data and statistical analysis

Data were analyzed using the SPSS software version 18.0, and the values were reported as mean ± SD. Group differences in the demographic variables were examined with non-parametric chi-square or independent samples t-tests. The normality of standardized residuals for the dependent variables was tested using the Kolmogorov-Smirnov (K-S) test. The data form all groups were found to be normally distributed with all variables demonstrating skewness and kurtosis within standard limits. To investigate the difference among the short-term-, long-term meditators and the control group, the statistical analysis for the mean scores of the state-trait anxiety inventory (STAI), tower of Hanoi (ToH), and the Philadelphia mindfulness scale (PHLMS); scale scores of the WAIS working memory index, and the standard scores of the Wisconsin card sorting test (WCST), were performed using the one-way analysis of variance (ANOVA) and following up a significant result with Tukey's multiple comparisons test. Pearson's correlation examined the correlation between the acceptance scale of PHLMS and the time to complete the 3-discs ToH task. The statistical significance was set at a p-value of less than 0.05.

RESULTS

State-Trait Anxiety Inventory (STAI)

The mean scores of S-Anxiety and T-Anxiety were compared between the three groups. Short-term VM had a significant lower in the mean score of the S-Anxiety as compared to the control group ($p<.05$) (Table 3). Long-term VM had a significant lower in the mean score of both the S- and T-Anxiety as compared to the control group ($p<.05$). Regarding the experience of VM practice, our results indicated that both short-term and long-term VM generally lead to a decrease in stress and anxiety as compared to the non-meditator control group.

Philadelphia Mindfulness Scale (PHLMS)

The mean score of the PHLMS awareness and acceptance subscale were compared between the three groups. Both short-term and long-term VM had a significantly higher mean score of the total mindfulness score of the PHLMS ($p<.01$ and $p<.001$, respectively). For the mean scores of each subscale, short-term VM had a significantly higher in the mean score of the awareness subscale ($p<.001$) as compared to the control group. While long-term VM had a significantly higher in the mean score of both awareness ($p<.001$) and acceptance subscale ($p<.01$), as compared to the control group (Table 3). Results indicate that both short-term and

long-term VM practices had a similar benefit on the mindfulness scale as compared to the non-meditator control group.

Digit Span

Raw scores of the total digit span (digit forward plus digit backward) were converted into the standard score. The standard scores were then compared between the three groups. The result demonstrated that only the long-term VM group had a significantly higher mean standard score of the total digit span as compared to the control group ($p<.001$) (Table 4). Although the short-term VM group show a small increase in the mean, standard score of the total digit span, however, the discrepancy was not significant when compared with the non-meditator control group. Results indicated that long-term VM had a significantly better performance on working memory tasks as compared to the non-meditator group.

Tower of Hanoi

For the ToH 3-Discs level, only long-term VM group significantly use less number of moves as compared to the control group ($p<.05$). For the times to complete the task, both short-term and long-term VM groups significantly perform faster when compared with the control group ($p<.05$ and $p<.01$, respectively) (Table 5). Results indicated that long-term and short-term VM had a significantly better performance on the plan/organize domain of EF than the non-meditator control group.

Wisconsin Card Sorting Test – Computer Version 4 (WCST-CV4)

Although there is no significant difference between the three groups in the Total correct of WCST test, long-term VM had a significantly higher standard score, which means better performance in overall WCST performance, as compared to the control (Table 6). For examples, long-term VM had a significant lower in total error ($p<.001$), perseverative responses ($p<.05$), perseverative errors ($p<.01$), and non-perseverative errors ($p<.001$), and a significant higher in % conceptual level response ($p<.001$), as compared to the control. Long-term VM also had a significant lower in the number of trials administered ($p<.001$), number of trials to completed the 1st Category ($p<.05$), and a significantly higher in number of categories completed ($p<.05$), as compared to the control. For the short-term VM, although they show a trend of better in the overall performance of WCST, however, most of the discrepancy was not significant when compared with the non-meditator or the long-term VM group. Short-term VM had a significantly lower only in the non-perseverative errors ($p<.05$), and a significantly higher in % conceptual level response ($p<.05$), as compared with the control. Our results indicated that long-term VM practice had a better performance on WCST that focuses on the set-shifting domain of EF, especially cognitive flexibility, as compared to the non-meditator group.

Correlation between PHLMS acceptance scale and the time to complete ToH task

Pearson's correlation analysis found the negative correlation between the acceptance scale of the PHLMS and the time to complete the ToH task (3-Discs) within the subjects of the VM group (both short-term and long-term) with $r = -0.52$, $p<0.05$ (Fig 1). The results indicated that the meditator who has a higher PHLMS acceptance score tends to use less time to complete the 3-Discs of ToH task (better performance) than the meditator who has a lower PHLMS acceptance score.

TABLE 3. Table compares the mean standard scores of the STAI and the PHLMS scale scores between the control, short-term, and long-term VM groups. Data represents means±SD.

Tasks	Control	Short-term VM	Long-term VM
State-trait anxiety inventory (STAI)			
State-anxiety	50.1 ± 6.3	43.0±6.5*	44.8±4.5*
Trait-anxiety	54.9 ± 7.6	50.8±8.5	47.2±7.9*
Philadelphia mindfulness scale (PHLMS)			
Awareness	33.8 ± 3.0	40.1±4.1**	42.2±4.4***
Acceptance	29.0 ± 6.2	34.0±5.1	37.2±7.9**
Total scores	62.9 ± 6.1	75.1±7.5**	77.4±9.7***

*$p<.05$, **$p<.01$ and ***$p<.001$, as compared to the control group.

TABLE 4. Table compares the mean standard scores of the digit span total between the control, short-term, and long-term VM groups. Data represents means±SD.

Working memory task	Control	Short-term VM	Long-term VM
Digit span total	9.5±1.9	12.2±1.7	15±3.7***

***p<.001, as compared to the control group.

TABLE 5. Table compares the performance of Tower of Hanoi (ToH) between the control, short-term, and long-term Vipassana group. Data represents means±SD.

Tower of Hanoi (3 discs)	Control group	Short-term VM	Long-term VM
Number of moves	10.0±4.4	7.0±0.0	7.0±0.0*
Moving time (sec)	41.8±29.9	16.6±6.9*	15.0±4.0**

*p<.05 and **p<.01, as compared to the control group.

TABLE 6. The performance of WCST-CV4 compared between the control group, short-term and long-term VM group. Data represents means±SD.

WCST-CV4	Control group	Short-term VM	Long-term VM
WCST-CV4 Standard scores			
Total Errors	82.5±16.5	96.2±11.1	99.6±4.9***
Perseverative Responses	86.3±23.8	95.0±10.9	97.1±4.9*
Perseverative Errors	85.8±23.3	94.0±11.2	97.1±4.7**
Non-perseverative Errors	85.2±23.0	97.2±11.2*	99.8±5.7***
% Conceptual Level Responses	82.5±16.1	97.3±12.8*	100.0±6.0***
WCST-CV4 Raw scores			
Trials Administered	108.1±21.7	92.3±22.7	77.4±7.5***
Trials to Complete 1st Category	30.4±30.3	13.3±5.2	11.6±2.1*
Total Correct	70.1±12.9	73.8±12.3	76.2±4.8
Categories Completed	4.5±2.2	6.0±0.0	6.0±0.0*
Failure to Maintain Set	0.8±1.6	1.0±1.5	0.3±0.4

*p<.05, **p<.01 and ***p<.001, as compared to the control group.

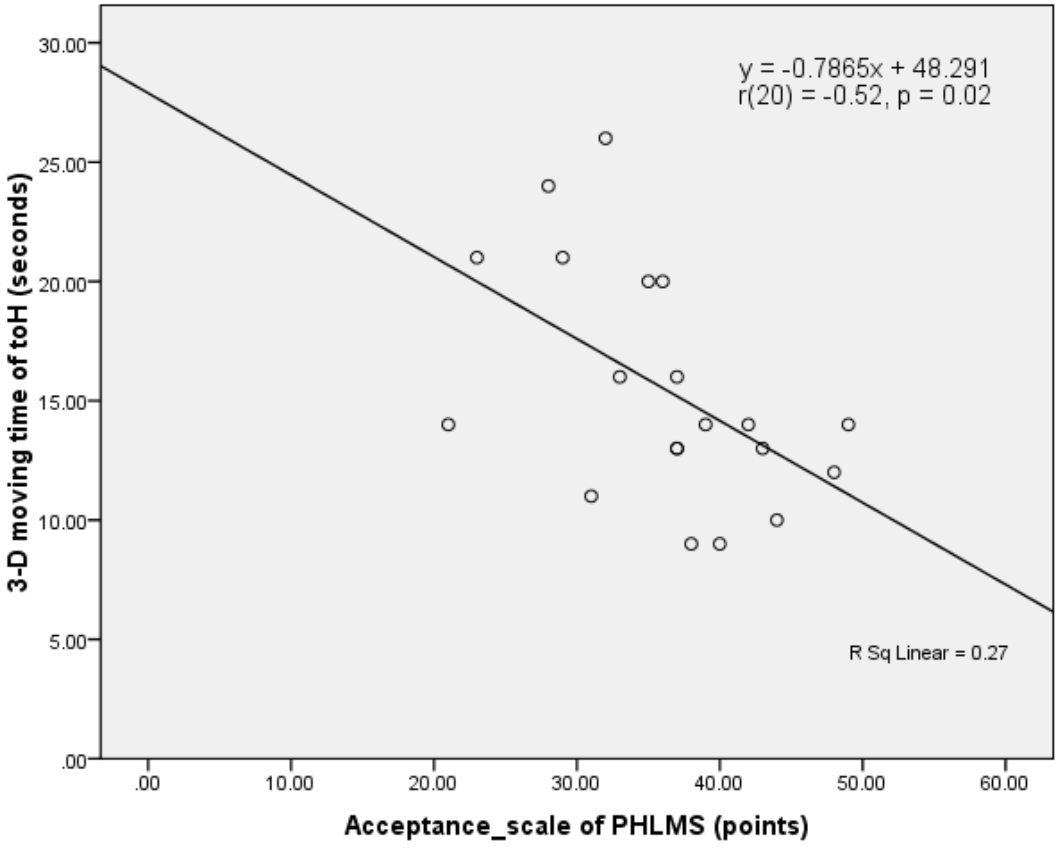

Fig 1. Scatter plot between acceptance scale of Philadelphia mindfulness scale (PHLMS) and 3-D time of tower of Hanoi (toH).

DISCUSSION

This study examined the long-term effects of Vipassana meditation on executive function in adult practitioners. The main findings are; 1) Both short-term and long-term VM groups had a significantly higher PHLMS mindfulness score and a significantly lower state- anxiety score as compared to the non-meditator group. 2) Although short-term VM shows a trend of improving performance on various EF tasks; however, the discrepancy was not significant when compared with the non-meditator group. 3) Only long-term VM shows significantly better performance on various EF tasks that require working memory, shift/ cognitive flexibility and planning, as compared to the non-meditator group. Furthermore, 4) The PHLMS acceptance scale significantly correlates with the performance on the EF task (ToH-3 discs).

Traditional Vipassana meditation combines both FA and OM together. VM usually begins with focus attention (FA) and followed by an open monitoring (OM) session. After practicing of VM for many years, the meditator could gradually cultivate both the narrow or focus attention (during FA) and the broader attention skill (during OM).[16] The previous study found that VM practice could enhance attention and reduce the distracting thoughts and behaviors, indicated that systematic attention training through VM practice has a benefit on the brain plasticity underlying a better cognitive inhibition or focus attention.[27,34] In opposite ways, the neural circuit for cognitive inhibition is required when the meditators monitoring own emotions or inhibit inappropriate behaviors. Importantly, cognitive inhibition is a fundamental requirement for executive function and self-regulation.[19,35]

In this study, we found that both short- and long-term VM group had significantly better performance on planning, as examined by the Tower of Hanoi (ToH) task, than the non-meditator group. Besides, the performance on ToH correlates with the PHLMS acceptance scale. The previous study revealed that during the ToH task, there is an increased activity in the dorsolateral PFC (DLPFC)[36] which is the brain area associated with planning and prediction of the sequence of actions, as well as sustaining focus and monitoring of attention.[37,38] Therefore, the VM practice could enhance the planning domain of EF via increased activity in the DLPFC, especially during the FA session.

Although short-term VM shows a trend of better in the overall performance of WCST, however, most of the discrepancy was not significant when compared with the non-meditator or the long-term VM group. In contrast, long term VM practice significantly improves performance in various executive function tasks. It is possible that during each VM practice, it requires the inhibitory control aspect of EF, either during FA or OM sessions. The inhibitory control composed of; 1) Response inhibition -which means the behavioral inhibition or self-control and 2) Interference control- or the inhibition of the wandering thought at the level of attention (similarly to inhibit distraction).[21] The inhibitory control (includes both response inhibition and interference control) could enhance attentional control, which in turn supports the working memory performance as well. Therefore, the interaction among these factors could explain how long term VM practice could enhance the executive function of the practitioners.

Results from the present study indicated that long term VM practice could improve the overall performance of various EF tasks, which required working memory, plan/organize, and cognitive flexibility. Moreover, the strong correlation between the mindfulness acceptance scale and the performance of EF tasks indicate the benefit of VM on the mindfulness acceptance that might support a better performance of EF tasks as well.

In conclusion, our results suggest that continued practice of VM is highly effective for enhancing EF in healthy individuals. Long-term VM practice not only reduce stress and improve mindfulness but also enhance the performance of EF tasks of the practitioners. Our results suggest that the benefit of VM practice on the performance of EF might need several hours of lifetime practice, therefore, the application of meditation to improve EF in patients with physical and mental problems, should consider both the types of meditation and the duration of practice. Long-term VM practice extends the benefit beyond stress reduction to improve higher cognitive executive function.

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Non-Infectious Scleritis and Systemic Collagen Vascular Disease Association

Sutasinee Boonsopon, M.D.*, Pitipol Choopong, M.D.*, Wisakorn Wongwijitsook, M.D., Wanchana Sopitviriyaporn, M.D.*, Nattaporn Tesavibul, M.D.***

**Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, **Debaratana Nakhon Ratchasima Hospital, Nakhon Ratchasima 30280, Thailand.*

ABSTRACT

Objective: To evaluate the differences between scleritis in association with a systemic collagen vascular disease and idiopathic scleritis and to describe the clinical characteristics of patients presenting with non-infectious scleritis.

Methods: A retrospective cohort study of 95 patients who presented with non-infectious scleritis was conducted. A comparison of the clinical differences between patients who had an associated systemic collagen vascular disease and idiopathic scleritis was performed.

Results: Of the 95 patients (123 eyes), 72.6% was female with mean age of 47 years. Diffuse anterior scleritis was the most predominant type (57.9%). The first and the second most frequent complications were anterior uveitis and scleral thinning. Almost twenty percent of the patients had a systemic collagen vascular disease involvement; rheumatoid arthritis and non-specific anti-neutrophil cytoplasmic antibodies-related scleritis were the two most common (4.2% each). Most of the patients who had a concurrent systemic collagen vascular disease presented with diffuse anterior scleritis, but it was not statistically significant compared with the idiopathic group. The presence of scleral thinning during follow-up periods showed a statistically significant difference between the groups with and without systemic collagen vascular disease at p value 0.038.

Conclusion: Diffuse anterior scleritis was the most common type of scleritis found. Patients who had collagen vascular disease and scleritis commonly developed scleral thinning during follow up visits. Aggressive treatment for scleritis in immune-mediated systemic collagen vascular disease may be considered to prevent progressive scleral thinning.

Keywords: Scleritis; immune; rheumatology; inflammation (Siriraj Med J 2020; 72: 361-367)

INTRODUCTION

Scleritis is a considerably rare ocular disorder which can be characterized by an inflammation of the sclera. Most scleral inflammation is non-infectious in origin and is commonly associated with a systemic collagen vascular disease.[1,2] Previous studies established that approximately 25% to 50% of scleritis cases were associated with an underlying systemic inflammatory condition, including rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), seronegative spondyloarthropathies, and systemic lupus erythematosus.[2,3] RA and GPA were reported to have the highest associations.[2,4-6] Patients presenting with anterior scleritis typically complain of an eye pain with globe tenderness and progressive ocular redness, whereas patients presenting with posterior scleritis may present with a reduced vision without ocular pain.[4,7]

Corresponding author: Sutasinee Boonsopon
E-mail: sutasinee.boo@mahidol.edu
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ORCID ID: http://orcid.org/0000-0002-6556-0215
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Complications of scleritis can be mild, such as limited adjacent structural inflammation, or serious, such as scleral melting and perforation. The treatment decision between non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunomodulatory therapy (IMT) usually depends on disease severity and patient safety. The incidence of overall scleritis varies; in Northern California, it was reported as 3.4 cases per 100,000 person-years[8]; in a Pacific islander (Hawaiian) population, it was approximately 4.1 cases per 100,000 person-years[9]; and in the general population, it was claimed to be 6 cases per 100,000 person-years.[5] Scleritis occurs most frequently among women and the elderly.[10,11] We conducted this study to evaluate the clinical features of non-infectious scleritis in Thailand and the patterns of association of the scleritis with a systemic collagen vascular disease.

MATERIALS AND METHODS

This study was designed as a descriptive retrospective cohort study. A retrospective chart review of 95 patients with non-infectious scleritis presenting at Siriraj Hospital, Mahidol University, Thailand, between January 2013 and December 2015 was performed. The study was conducted in accordance with the declaration of Helsinki, and approved by the Ethics Committee of Siriraj Hospital, Mahidol University. Scleritis was defined as a presentation of edematous episcleral and scleral tissue with deep episcleral and scleral vessels engorgement. Application of 10% phenylephrine revealed no blanching of deep scleral vascular plexus. Scleritis classification was based on site of anatomical inflammation, which was anterior and posterior scleritis. For anterior scleritis, it could present as diffused scleral inflammation, localized nodular inflammation or necrotizing sclera. For posterior scleritis, fundus examination might reveal edematous optic disc and/or retinal striae or subretinal fluid. B-scan ultrasonography showed positivity of T-sign as a result of posterior scleral inflammation and adjacent swollen tenon. Patients with infectious related scleritis including bacteria, mycobacteria, spirochete, fungus, and parasite were excluded from the study. Mantoux test was done in some selected cases. Only patients who had been exposed to tuberculosis, was considered for the skin test. Treponemal and non-treponemal test was performed in most of the patients to rule out syphilitic infection. We documented the demographic data, the scleritis type (namely, diffuse anterior scleritis, nodular anterior scleritis, necrotizing scleritis with and without inflammation [also known as scleromalacia perforans], and posterior scleritis), and the associated systemic collagen vascular disease. The details documented were the ocular findings of a slit-lamp examination, the best-corrected visual acuity at the baseline visit and subsequent follow-ups, the number of recurrences, and the treatment (including any necessity for immunomodulatory therapy). As to the ocular complications, we collected details on associated peripheral ulcerative keratitis (PUK), anterior uveitis, scleral thinning, secondary ocular hypertension (OHT), vitritis, papillitis, cystoid macular edema (CME), and exudative retinal detachment (ERD). For scleral thinning, we normally documented it when sclera appeared blue on a slit lamp examination. Once non-infectious scleritis was suspected, we routinely perform laboratory investigations to evaluate possibility of systemic immune-related diseases. Not only basic laboratory investigations (complete blood count, liver and renal function test, urinalysis, chest radiogram) but also specific investigations such as rheumatoid factor, anti-citrullinated protein antibody, antinuclear antibodies, anticytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein were performed. Some patients with symptoms specific to autoimmune diseases would be further investigated with some of the following tests: anti-double stranded DNA, anti-Smith, urine protein and urine protein to creatinine ratio, paranasal sinus radiogram, and may be sent for a rheumatologist consultation to evaluate cause of inflammation. For the subgroup analysis, we divided our patients into two groups: an idiopathic group, and a scleritis with associated systemic collagen vascular disease group. Patients with incomplete investigations were excluded from the subgroup analysis. For patients who had bilateral eye involvement, only the right eyes were used for analysis. The clinical features were described as descriptive statistics. Pearson's chi-squared test was used to compare categorical data, and Student's t-test was used to compare continuous data. To determine which variables were associated with systemic collagen vascular disease, a multivariate model was developed using variables significantly associated ($p < 0.1$) with systemic collagen vascular disease from univariate analysis. Variables found not to be significant or variables for which 95% confidence limits crossed the line of unity were excluded by backwards elimination, unless they improved the fit of the model. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Ethical approval for this study was provided by the Ethical Committee of Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 703/2015(EC2). Clinical Trials Registration: TCTR2017318001.

RESULTS

There were 95 non-infectious scleritis patients (123 eyes) during the study period; their mean age was 47 years (range: 12-88 years), and 69 patients were female (69/95,72.6%). Of the cohort, 67 presented with unilateral eye involvement (67/95, 70.5%), and 16 had recurrent inflammation (16/95, 16.8%). The numbers of the patients who had diffuse anterior scleritis, nodular anterior scleritis, posterior scleritis, and combined nodular anterior scleritis with posterior scleritis were 55/95 (57.9%), 29/95 (30.5%), 8/95 (8.4%), and 1/95 (1.1%), respectively. Scleritis type was not documented in 2 patients. None of our patients were diagnosed with necrotizing anterior scleritis. The most common associated finding reported in this study was anterior uveitis (39/95, 41.05%), with the second most common being scleral thinning (21/95, 22.11%). The other associated ocular findings were PUK (13/95, 13.7%); secondary OHT (13/95, 13.7%); papillitis (7, 7.37%); vitritis; CME; and ERD (the last three being found in equal numbers: 3/95, or 3.16% each). Through laboratory investigation, 18 patients had an associated systemic collagen vascular disease (18/95, 19%). RA and nonspecific antineutrophil cytoplasmic antibody (ANCA)-associated scleritis were the two most common systemic diseases (4/95, or 4.2% each), followed by systemic lupus erythematosus (3/95, 3.2%) and GPA (2/95, 2.1%). Unfortunately, 27.4% of our cases lacked thorough laboratory investigations to identify a possible associated systemic collagen vascular disease. From a subgroup analysis, after excluded patients with incomplete investigations, the mean age of the idiopathic group was 45.06 years, whereas it was 48.22 years for the scleritis with associated systemic collagen vascular disease group. Both groups were predominantly female, with 40/51 (78.4%) and 10/18 (55.6%) females, respectively. Interestingly, most of the patients in the scleritis with associated systemic collagen vascular disease group (24/27 eyes [88.9%]) presented with diffuse anterior scleritis; on the other hand, only about half of the patients in the idiopathic group (40/70 eyes [58.8%]) did so, which was statistically significant at p-value 0.054 in univariate analysis. The cause of inflammation of all eleven patients who presented with posterior scleritis was not found; thus, all of them were diagnosed with idiopathic posterior scleritis (16.2% versus 0%, p 0.026). As many as 9/27 eyes (33.3%) in the scleritis with associated systemic collagen vascular disease group had subsequent scleral thinning at their follow-up visits, compared to 8/70 eyes (11.4%) in the idiopathic group (p 0.038). No statistical significance was found for the other factors used to compare the differences between the two groups (namely, the best-corrected visual acuity on patients' first and last visits; laterality; the number of recurrences; scleral thinning on the first visit; and OHT, PUK, anterior uveitis, vitritis, CME, ERD, and papillitis on the first and follow-up visits); these are summarized in Table 1. Almost all of our patients received topical, regional, and/or systemic corticosteroids as their mainstay therapy. Some of them were treated with oral NSAIDs. Fifteen patients (29.4%) in the idiopathic group were treated with systemic IMT, whereas 10/18 patients (55.6%) in the scleritis with associated systemic collagen vascular disease group received IMT (p 0.047). Multivariate linear regression analysis between systemic collagen vascular disease association group and idiopathic group is shown in Table 2.

DISCUSSION

Although scleritis is scarcely seen in general ophthalmology practice, its serious complications and its possible association with a systemic inflammatory disease have captured our attention. A delayed diagnosis of an associated systemic rheumatologic disease might result in lethal complications. From previous reports worldwide, approximately 25% - 50% of non-infectious scleritis is related to systemic collagen vascular disease[2,3]; therefore, screening laboratory tests for rheumatoid factors, antinuclear antibodies, and ANCA have been recommended. In our study, 20% of our patients were diagnosed with scleritis as a presenting feature of systemic collagen vascular diseases. This is consistent with the finding of a report from the Ocular Autoimmune Systemic Inflammatory Infectious Study that scleritis occured in conjunction with a systemic collagen vascular disease might be lower in the Asian population.[6] Some of the 27.4% of our patients who lacked a laboratory investigation might have had an undiagnosed systemic rheumatologic disease, which would have affected the study results. RA has been reported to be by far the most common rheumatologic disease related to scleritis[2,4,6], although some other studies found that GPA was far and away the most prevalence.[5] We believe that ethnicity might play an important role in the differences in these results. Certain systemic diseases related to scleritis were found to have an association with the ocular prognosis; GPA had the worst visual outcomes, whereas RA and relapsing polychondritis had intermediate visual outcomes.[12] The two most common rheumatologic diseases found to be related to scleritis in this study were RA and non-specific ANCA associated disease. Our data demonstrated that diffuse anterior scleritis was the main type of scleral inflammation found with a systemic collagen vascular disease; this form of

TABLE 1. Demographics and characteristics of non-infectious scleritis patients.

Factors	Non-infectious scleritis (N=95 cases, 123 eyes)	Subgroup analysis Idiopathic group (N=51 cases, 70 eyes)	Systemic collagen vascular disease association group (N=18 cases, 27 eyes)	*P*-value
Age (years); (mean+/-SD)	46.60	45.06 (+/-12.1)	48.22 (+/-15.45)	0.379
Female	69 (72.6%)	40 (78.4%)	10 (55.6%)	0.074
Unilateral	67 (70.5%)	33 (47.1%)	9 (33.3%)	0.219
Recurrence	16 (16.8%)	19 (27.1%)	3 (11.1%)	0.085
BCVA (LogMAR) (median, range)				
First visit	0.1 (0-3)	0.1 (0-1)	0.1 (0-3)	0.041
Last visit	0.1 (0-2)	0.1 (0-2)	0.1 (0-2)	0.375
Scleritis type (eyes)				
Diffuse anterior	75 (60.98%)	40 (58.8%)	24 (88.9%)	0.005
Nodular anterior	34 (27.64%)	18 (26.5%)	3 (11.1%)	0.104
Posterior	11 (8.94%)	11 (16.2%)	0	0.026
Associated findings (eyes)				
PUK				
First visit	9 (7.32%)	9 (12.9%)	0 (0.0%)	0.058
Other visits	11 (8.94%)	10 (14.3%)	1 (3.7%)	0.281
Anterior uveitis				
First visit	38 (30.89%)	26 (37.1%)	10 (37%)	0.992
Other visits	14 (11.38)	11 (15.7%)	2 (7.4%)	0.343
Secondary OHT				
First visit	9 (7.32%)	5 (7.1%)	4 (14.8%)	0.259
Other visits	13 (10.57%)	7 (10%)	4 (21.1%)	0.180
Scleral thinning				
First visit	12 (9.76%)	8 (11.4%)	2 (7.4%)	0.722
Other visits	19 (15.48%)	8 (11.4%)	9 (33.3%)	0.017
Vitritis				
First visit	4 (3.25%)	3 (4.3%)	1 (3.7%)	0.815
Other visits	1 (0.81%)	1 (1.4%)	0 (0.0%)	1.0
CME				
First visit	3 (2.44%)	3 (4.3%)	0 (0.0%)	0.447
Other visits	2 (1.63%)	1 (1.4%)	0 (0.0%)	0.674
Exudative RD				
First visit	1 (0.81%)	1 (1.4%)	0 (0.0%)	0.674
Other visits	2 (1.63%)	2 (2.9%)	0 (0.0%)	0.550
Papillitis				
First visit	7 (5.69%)	7 (10%)	0 (0.0%)	0.186
Other visits	3 (2.44%)	3 (4.3%)	0 (0.0%)	0.992
Treatment				
Immunosuppressive therapy	25 (26.32%)	15 (29.4%)	10 (55.6%)	0.047

TABLE 2. Multivariate linear regression analysis between systemic collagen vascular disease association group and idiopathic group.

Parameters	Univariate analysis			Multivariate analysis		
	Odd ratio	CI	*P* value	Odd ratio	CI	*P* value
Female	0.31	0.096 to 0.97	0.044	NS	NS	NS
Age	1.02	0.98 to 1.06	0.36			
Bilateral	1.68	0.57 to 4.98	0.99			
VA (LogMAR)						
First visit	4.0	1.05 to 15.3	0.43			
		0.74 to 5.73				
Last visit	2.06	1.66				
Recurrence	0.37	0.08 to 1.73	0.21			
Associated findings						
PUK						
First visit	0.000001	0.000001 to 0.0000002	0.99			
		0.25 to 20.2				
Other visits	2.27		0.46			
AU						
First visit	0.93	0.31 to 2.8	0.90			
		0.29 to 7.77				
Other visits	1.49		0.64			
IOP > 21						
First visit	0.33	0.04 to 2.5	0.28			
		0.62 to 11.1				
Other visits	2.63		0.19			
Scleral thinning						
First visit	0.87	0.15 to 4.93	0.88			
		1.2 to 17.7				
Other visits	4.6		0.03	4.38	1.1 to 17.6	0.038
Vitritis						
First visit	1.44	0.12 to 16.9	0.77			
		NA				
Other visits	NA		NA			
CME						
First visit	0.0001	0.000001 to 0.000002	0.99			
		0.000001 to 0.00003				
Other visits	0.00001		1.0			
ERD						
First visit	0.0001	0.00001 to 0.00001	1.0			
		0.0001 to 0.002				
Other visits	0.001		0.99			
Papillitis						
First visit	0.001	0.0001 to 0.003	0.99			
		0.00001 to 0.0003				
Other visits	0.0001		0.99			
Scleritis type						
Diffuse	3.79	0.98 to 14.7	0.054	NS	NS	NS
		0.16 to 2.6				
Nodular	0.65	0.00002 to 0.0002	0.55			
Posterior	0.0001		0.99			

scleritis is universally the most common.[13] None of our patients were diagnosed with necrotizing scleritis, but as high as 15.48% of them developed subsequent scleral thinning without scleral melting or perforation. Most of them had a systemic rheumatologic disease association. Necrotizing scleritis was defined by Galor and Thorne as an area of scleral infarction and necrosis with or without typical signs of anterior scleritis (which depend on the type of necrotizing scleritis).[5] Given that definition, none of our patients had necrotizing scleritis even though they had scleral discoloration either in conjunction with, or without, signs of anterior scleritis at any time point. Galor and Thorne also explained that the bluish grey hue following anterior scleritis was not scleral thinning but instead a development of scleral collagen fiber rearrangement after inflammation.[5] The mechanism for the subsequent bluish discoloration of the sclera is unclear since there have been few studies on the scleral structure following an inflammation. A study by Kuroda et al., which described the optical coherence tomography of active anterior scleritis, reported that there was a swelling of the conjunctival stroma and episcleral layer without scleral thickening.[14] In contrast, Watson et al. reported that there was scleral edema with collagen fiber separation and infiltration of the inflammatory cells in the active stage of diffuse anterior scleritis.[15] Neither study reported any structural changes during the quiescence period. Further investigations to evaluate the pathophysiology of the subsequent scleral discoloration during the inactive stage of the scleral inflammation need to be considered in the future. Since there is a possibility of developing scleral thinning following a scleral inflammation and as the association is significantly higher among patients with concurrent systemic collagen vascular disease, we believe that aggressive treatment to halt disease progression is warranted. This is especially the case for patients who have a systemic collagen vascular disease, even if they do not initially present with necrotizing scleritis. A multidisciplinary approach is recommended to ensure the provision of a systematic assessment and sufficient treatments. We found that diffuse anterior scleritis had the highest association with systemic collagen vascular disease, which differs from some other reports that necrotizing scleritis had the highest association.[5,6] Based on our study findings, we urge clinicians to be aware of the high proportion of diffuse anterior scleritis found in patients who had a systemic collagen vascular disease, and of the chance of patients developing scleral thinning in cases of non-necrotizing anterior scleritis.

Limitations

As this was a retrospective study, incomplete data might have distorted its results. A sizeable proportion of our patients had not had a thorough investigation to rule out the possibility of there being an associated systemic inflammatory disease; thus, the percentage of patients who had scleritis in association with a systemic disease was probably underreported. Follow up duration of each patient was not reported and analyzed, which might also interfere with the study result. A further study with a larger number of patients would make the data analysis more reliable.

CONCLUSION

Scleritis can be a presenting sign of some systemic collagen vascular diseases. The pattern of scleral inflammation can be an indicator of the need to investigate for the presence of a more serious systemic disease. From this study, diffuse anterior scleritis was more likely to occur in conjunction with a systemic collagen vascular disease. Scleral thinning was found more frequently among patients who had a related systemic inflammatory disease; thus, an aggressive treatment should be considered in these patients.

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Emergence of Influenza Pandemic in Bangkok in 1918: Historical Review

To the editor:

Influenza pandemic in 1918 was known as the worst pandemic in human history; it is now well documented to be caused by Influenza A, H1N1 virus. The information regarding this pandemic has been mostly published from the Western countries but only a small number of pieces of information published from Asian countries, even though the origin of this pandemic was speculated to be in China.[1] Unfortunately, only one article regarding this pandemic in Thailand was published in Thai language in 1967 by the late Prof. Dr. Samran Wangspa, an ophthalmologist and a member of the Royal Institute (nowadays, Office of the Royal Society), in Siriraj Hospital Gazette,[2] a local medical journal prior to the transformation to international journal standard level as Siriraj Medical Journal. In his article, based on the Interior Ministry announcement on July 14, 1919 by the Minister of Interior Ministry that was published in the Royal Thai Government Gazette on July 27, 1919,[3] the total Thai population was nearly 9 million people (8,478,566 outside Bangkok + 500,000 in Bangkok), approximately 2.5 million people (27.8%) got the infection and 81,370 people died (0.9%).

Regarding the 1918 influenza pandemic in Thailand, the article by Prof. Wangspa mentioned that the pandemic occurred shortly after the end of World War I, presumably the spreading was introduced by the soldiers who returned to their homes. The late Emeritus Prof. Dr. Prasert Thongcharoen, a well-known senior virologist in Thailand, concurred with this speculation as shown in the excerption of his presentation on "a chronological outbreak of influenza in Thailand, 1918-2010" at the panel talk in the 9th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Global Scientific Conference which was held on 7-11 August 2017 in Chiang Mai, Thailand, as follow: "The outbreak of influenza in Thailand was brought by troops after the World War I (WWI) as Thailand sent the Royal Thai Army Forces to join the Allied Forces in France and returned later when the WWI ended. The troops arrived back with the influenza virus, which was spreading over the frontline. In October 1918, influenza was reported to spread from the harbour city in the southern of Thailand. By November 1918, the infection had been spread throughout the whole country and it was afterwards subsided in March 1919."[4] But, upon the historical review, the Thai troops that joined the WWI could not be blamed for the outbreak of influenza pandemic in Thailand because the 2 Thai troops left Thailand and arrived in France on July 30, 1917 and August 6, 1917, respectively.[5] Then, after the end of the WWI, the troops arrived in Bangkok with the "welcome back home" ceremony taken place on May 1, 1919[6] while the influenza pandemic had already swept throughout Bangkok and the whole country in 2 waves, the first one during October and November, 1918 and the second one during January and February, 1919 as documented in the Royal Thai Government Gazette during 1918.

Historical review brought out the interesting event that might be the cause of the emergence of 1918 influenza pandemic in Thailand. On September 12, 1918, The Siam Red Cross posted the donation of 1,554.30 Bahts collected from the tickets (5,181 people attended, if the ticket cost 0.30 Baht) to watch the charity football match between Thai Royal Navy team and British Royal Navy team taken place at the football field at Suankularb College in Bangkok.[7] The football players of the British Royal Navy team were selected from the crew of the HMS Whiting, a C-class destroyer,[8] that visited Bangkok during that very month of September 1918. This football match brought joyfulness to everyone in this event as mentioned in the book entitled "Chaiyo! King Vajiravudh and the development of Thai nationalism" written by Walter F. Vella in 1978 as follow:

The match, held on September 12, was attended by "a huge crowd." The game, after "a hard, ding dong struggle," ended in a tie; the crowd was not displeased, and the match was called "one of the happiest and most successful events in the present naval visit."[9]

Note: Certainly, the huge crowd with elation in this particular football match is worrisome in term of spreading germs because social distancing, an important measure used to contain COVID-19 at present, cannot be applied!

Historical search in the internet also helps to find out the log book of this British Royal warship.[10] She had been atomized by a spray of a 2% solution of zinc sulphate

from May 2 to 4, 1918 at the Royal Navy's shore base, HMS Tamar, in Hong Kong as a preventative measure against influenza pandemic before departure on May 6, 1918 to Singapore. The warship received 60 tons of coal in Saigon on May 10, 1918. When she arrived in Singapore on May 14, 1918, one petty officer was sent to hospital one hour after docking – 7 days after departure from Hong Kong. Then, 12 days later, on May 26, 1918, the log book recorded "One sick rating left for Tanglin Hospital (returned to ship after a 29-day-long admission)," 8 days after that, on June 3, 1918, "Mr. Ellis discharged to hospital (returned to ship after a 9-day-long admission)," another 8 days later, on June 11, 1918, "One AB left for hospital (AB = Able Seaman)." Look like the crew experienced the first wave of Influenza pandemic as described in the literature.[1] Then, on August 7, 1918, the log book recorded "One Stoker left for hospital," 15 days later, on August 22, 1918, "One AB sent to hospital," 4 days later, on August 26, 1918, "One Stoker discharged to hospital," and 1 day later, on August 27, 1918, "Leading Signalman left for hospital," then, 5 days later, on September 1, 1918, the warship left Singapore for Bangkok where she arrived on September 5, 1918. The crew spent time in Bangkok for 10 days before departing on September 15, 1918. The log book, however, did not mention any activity in Bangkok at all. During that period of HMS Whiting warship visiting Bangkok, there was not any report of influenza epidemic in Bangkok even though King Rama VI had been ill for 10 days, possibly influenza with pneumonia at right lower lobe, from July 27, 1918 to August 5, 1918. On August 17, 1918, the King did not have any abnormal lung sign and he was advised to leave Bangkok for a 4 to 5-week-long vacation so that the next day he moved to Bang Pa-in Palace in Ayudhaya Province. According to the Royal Thai Government Gazette regarding the news of death, mostly the royal family members, government services, army officers, and priests, on July 26, 1918, an army officer died of fever. On August 30, 1918, a government service in Nakhon Sri Thammarat in the South died of fever. On September 28 and 30, an army officer and a government service were reported as died of fever, respectively. Since October 6, 1918, 20 cases were reported as died of fever in October and 12 more cases in November, presumably corresponding to the second wave of influenza pandemic reported all over the world.

The HMS Whiting warship returned back to Singapore and arrived there on September 19, 1918 and on that very day, 2 ratings were discharged to hospital (4 days after leaving Bangkok). Then, 11 days later, on September 30, 1918, "One Signal rating discharged to hospital." And the log for October 1918 recorded "Singapore dry dock and in harbor during 'flu epidemic" and it started to record sick list during October 1 (sick list of 5) and November 16 (sick list of 8). The peak of sick list was 19 for 3 days during October 12 and 14. There was a note – presumably "Spanish influenza" – recorded on October 8. Even the commander of the ship was recorded to be sent to the hospital on November 13 and he returned on duty 8 days later. No sick list appeared in the log book during November 17 and December 31, 1918 but on January 1, 1919, another sick list of 4 appeared for the very last time and no more! HMS Whiting warship resumed her duty on January 13, 1919. In this log book, no record of death among the crew members is found at all.

However, based on the search of "Royal Navy Service Records" from "The National Archives" website[11] for more than 2,000 records, one ordinary seaman year II, aged 25, on service of the HMS Whiting warship, was recorded as "DD October 4, 1918; influenza and bronchial pneumonia. (Note: DD = died of disease)" Nevertheless, the log book of the warship on this particular date recorded only "One AB discharged to hospital." about the illness of the crew members. But, on October 7, the log book recorded "Medical inspection of seven men who were sick." while the sick list was 6.

At this point, based on the above historical review, it is possible that the emergence of influenza pandemic in Bangkok in 1918 was the result of this charity football match between the Thai Royal Navy team and the British Royal Navy team on September 12, 1918. Due to the limitation of time, even after the scrutiny of more than 2,000 records of the "Royal Navy Service Records" from "The National Archives" website above (time spent on 1 entry, approximately 1 minute), another death record (like the one above on HMS Whiting) cannot be retrieved to show whether at least one of the 60 officers and men on this warship had died of influenza prior to their visit to Bangkok. Certainly, there are approximately 35,748 more records during the year 1918 awaiting further scrutiny.

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Sanya Sukpanichnant, M.D., FRCPath (Thailand)

Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Corresponding author: Sanya Sukpanichnant
E-mail: sanya.suk@mahidol.ac.th
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