Greater Mekong Subregion
Medical Journal

Author Guidelines

Manuscript Types

1. Special Article

These articles are invited by Editor-in-Chief, written in English, and structured as follows: Introduction, Main text, Conclusion and References.

2. Original Article

Original article reveals the research results regarding of basic and advanced clinical research in medicine and related health sciences, as well as medical education.

3. Community Medicine Article

Community medicine is topic related to community in the countries of Greater Mekong Sub-region and also the health issues of people along the border of Thailand.

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Review article aggregates acknowledge from the journals or books.

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Short report may be a preliminary study, short communication, case report or new emerging diseases.

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This is for a communication between scholars or readers to the authors who published their papers in this journal.

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English language manuscript should provide concise title which should not exceed 50 letters.

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English keywords. Each language does not exceed 5 words, are put at the end of the abstract for the reason of doing subject index. Key words should be in Medical Subject Headings (MeSH) terms of U.S National Library of Medicine.

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Includes Introduction, Methodology which should detail materials or participants, ethical approval, clinical trial registration number (if any), methods, and statistical and data analysis, results, review contents, discussion and criticism, conclusion, acknowledgements (if any) and references. Total length of the body from abstract to conclusion does not exceed 4,000 words for original and review article and do not exceed 2,000 words for others.

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Contents

Correlation of Hypertension and Hypertensive Heart Disease in Mae Fah Luang University Medical Center Hospital

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Abstract:

Background: Ambulatory blood pressure (ABPM) can monitor blood pressure by obtaining multiple readings over the 24-hours, capturing the blood pressure variability, and an important predictor of cardiovascular outcomes in a hypertensive population.

Objective: To determine the correlation of hypertension and hypertensive heart disease by using ABPM.

Material and Methods: The present study was a cross-sectional study. 30 participants were assigned for detected left ventricular hypertrophy (LVH) using echocardiography and detected hypertension using ABPM.

Result: Participants who were diagnosed with hypertensive heart disease (HHD) by echocardiography found 26 samples (86.67%) and diagnosed with hypertension by ABPM found 20 samples (66.67%). The proportion of silent hypertension and HHD was found to be statistically correlated (p< 0.002). SBP significant correlation with LVH (r = 0.53, p-value = 0.001). Systolic blood pressure (SBP) was positively correlated with age (r = 0.40, p-value = 0.014), triglyceride (r = 0.32, p-value = 0.042), and low density lipoprotein (LDL) levels (r = 0.31, p-value 0.050).

Conclusion: This study found a high proportion of silent hypertension as measured by ABPM in participants who were diagnosed with HHD. Silent hypertension is also correlated with LVH. Moreover, age had been an important factor that correlated with increased systolic blood pressure and HHD.

Keywords: Incidence, Hypertension, Hypertensive heart disease

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Introduction

Hypertensive heart disease (HHD) refers to a group of changes in the left ventricle, left atrium, and coronary arteries caused by chronically high blood pressure.[1] Hypertension, also known as high blood pressure (BP), is diagnosed when systolic blood pressure is higher than 120 mmHg or diastolic blood is more than 80 mmHg.[2] The fiscal year in Thailand was from 2015 to 2017, new cases of hypertension of 50,000 to 70,000 are diagnosed each month.[3] Hypertension is a silent disease and is known as a "silent killer" because most people with high blood pressure do not know it. Most of the time, the symptoms are minimal or absent in their early stage.[4] Uncontrolled high blood pressure increases the workload on the heart, causing structural and functional changes in the myocardium. These changes include left ventricular hypertrophy (LVH) or LV systolic and diastolic dysfunction, which can lead to heart failure. In addition, hypertensive heart disease also causes cardiac arrhythmias, and sudden cardiac death.[5]

According to World Health Organization (WHO) statistics in 2020, cardiovascular disease is the leading cause of death worldwide, with an estimated 17.9 million deaths from the disease.[6] In 2018, cardiovascular disease was one of the top three causes of mortality among Thai people. According to the survey, the death rate from stroke and ischemic heart disease is on the rise. The mortality rates were 47.1 and 31.8 deaths per 100,000 people, respectively.[7] In Thailand, 45% of people with hypertension either never knew of it or knew but were not aware of it. Although they may have previously had their blood pressure measured because there are frequently no symptoms, a lack of trust in the system, and the accuracy of blood pressure measurement.[8]

Electrocardiography (ECG) and echocardiography are the primary tools used by cardiologists to diagnose hypertensive heart disease. ECG is the recommended test for the initial evaluation of hypertensive heart disease due to its high specificity but low sensitivity. The echocardiogram is an investigation to confirm HHD.[9] Ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) are the primary methods for measuring out-of-clinic BP to diagnose hypertension. HBPM is less expensive than ABPM. However, HBPM does not measure BP during routine daily activities and sleep. Thus, HBPM may have the potential for measurement error and incorrect classification of BP status, especially in people having high nocturnal BP.[10] ABPM is more useful than HBPM in monitoring BP by obtaining multiple readings over the 24-hours, capturing the blood pressure variability, and an important predictor of cardiovascular outcomes in a hypertensive population.[11,12]

Despite this recommendation, there is published data about people with silent hypertension and HHD. This study is to determine correlation of hypertension and hypertension heart disease by ABPM at the Mae Fah Luang University (MFU) Medical Center Hospital.

Materials and Methods
Participants

The present cross-sectional study was conducted between October 1, 2020, and January 30, 2021. The population in this study were all person who came to the clinic for a normal health checkup at the MFU Medical Center Hospital, Chiang Rai, Thailand. The author enrolled participants who were aged more than 18 years, had never been diagnosed with hypertension, followed a health check-up protocol with ECG, and were willing to participate in the study. The

exclusion criteria were participants who had been diagnosed with valvular heart disease equal to or higher than level 3, had not received ECG in the health check-up protocol, and had been diagnosed with hypertension.

The sample size was calculated using the infinite population proportion formula, considering the 15% prevalence of patients who receive health check-ups at MFU Medical Center Hospital, a total of 1138 cases were found to have been examined. There were 291 echocardiograms, 44 of which were diagnosed with left ventricle hypertrophy, with a 99% confidence interval (CI), and a 20% precision error. The study required 22 participants based on the calculations. To avoid missing data, the author increased the number of participants. As a result, the samples of 30 participants were gathered using a consecutive sampling technique.

Instrument and procedure

The Mae Fah Luang ethics committee on human research provided its approval (COA no. 202/2020) before the study began. Participants went through a normal health checkup routine after enrolling, following which patient information was collected from hospital records, and a direct patient interview was conducted. The findings of the sample group's ECG were read by the cardiologist. All participants had echocardiography to verify the LVH. The author employed an ABPM to collect blood pressure measurements for 24 hours, for a total of 30 samples. After removing the apparatus, the cardiologist read the results.

All analyses were performed at MFU Medical Center Hospital, Chiang Rai, Thailand. ECG was measured using the GE Healthcare MAC 800 version. Echocardiography was measured using the echocardiogram Epiq7c version. Blood pressure was measured using the ABPM GE tonoport version. This laboratory was regularly audited for international standard quality controls.

LVH was defined by LV concentric geometry greater than 0.43.[13] According to the 2017 American Cardiology Association/American Heart Association recommendations, hypertension is defined as systolic blood pressure higher than 120 mmHg or diastolic blood pressure of more than 80 mm Hg.[2] HHD was defined as having LVH and a systolic blood pressure of more than 130 mmHg.[1,14]

Statistical analysis

The data was analyzed using the IBM SPSS statistics, version 26. The general characteristic data were analyzed using descriptive statistics as frequency, percentage, mean and standard deviation. Univariate analysis was performed to demonstrate various possible associated factors among patients by using Pearson's correlation coefficient, Spearman rank correlation coefficient, and the Chi-square test. The p-value of less than 0.05 was considered statistically significant.

Results

A total of 30 participants participated in this study. Most of them were female (56.67%), over 60 years old (56.67%), and overweight (63.33%), with dyslipidemia as the underlying disease (33.33%). None of the participants had ever smoked before. Twenty percent of the individuals drank alcohol, and 56.67% took an NSAID. The result of the participants' laboratory. The most of them were FBS< 100mg/dL (76.67%) (mean ± SD = 97.87 ± 20.32), Cholesterol level < 200 mg/dL (70.00%) (Mean ± SD = 189.93±51.30),triglyceride level<150mg/dL (63.33%) (mean ± SD = 162.20 ± 121.94), high HDL level (53.33%) (mean ± SD = 53.6 ± 14.4), low LDL level (63.30%) (mean ± SD = 105.03 ± 43.24).

The results of the clinical data analysis found six samples were detected in LVH from ECG (20.00%). Participants who were diagnosed with HHD by echocardiography found 26 samples (86.67%). However, those who were diagnosed with hypertension by ABPM found 20 samples (66.67%), as shown in table 1.

Table 1 The characteristics of clinical data (n = 30)

Characteristics	N	%
ECG result		
Yes (LVH)	6	20.00
No	24	80.00
Echocardiographic result		
HHD	26	86.67
Normal	4	13.33
ABPM result		
HT	20	66.67
Normal	10	33.33

Hypertension (HT) among HHD patients were found to be significantly higher than normal blood pressure (p-value = 0.002). Participants who were diagnosed with HHD had a statistically significantly higher proportion of HT as measured by ABPM than participants who were not diagnosed with HHD, as shown in table 2

Table 2 Comparison of blood pressure among HHD patients (n=30)

Diagnosis	ABPM result		p-value
	HT (N, %)	Normal (N, %)	
HHD	20 (76.89)	6 (23.11)	0.002
Normal	0 (0)	4 (100)	

Table 3 shows the correlation between HT as measured by ABPM and LVH. Systolic blood pressure (SBP) revealed a direct and positive correlation with LVH (r = 0.53, p-value = 0.001). As a result, high SBP than normal range (>130 mmHg) was correlated with LVH.

Table 3 The correlation between silent hypertension and blood pressure as measured by ABPM and LVH (n = 30)

HT measured by ABPM	Mean	SD	LVH	
			Correlation coefficient	P-value
SBP	139.93	15.10	0.53	0.001*
DBP	78.46	9.06	0.13	0.251

*p-value < 0.05

Table 4 shows the correlation between variables and SBP as measured by ABPM. SBP was positively correlated with age, triglyceride, and LDL levels (r = 0.40, 0.32, and 0.31, p-value 0.05, respectively).

Tabel 4 The correlation between variables and SBP as measured by ABPM (n = 30)

variables	Mean	SD	SBP (mmHg)	
			Correlation coefficient	P-value
Age	61.73	12.91	0.40	0.014*
BMI	23.93	3.04	0.03	0.436
FBS	97.86	20.32	-0.06	0.386
Cholesterol level	189.93	51.30	0.27	0.075
Triglyceride level	162.20	121.93	0.32	0.042*
HDL level	53.60	14.40	-0.23	0.110
LDL level	105.03	43.25	0.31	0.050*

*p-value < 0.05

Table 5 shows the comparison between the characteristics of patients with and without HHD. It was found that age was significantly different between the two groups. Most patients with HHD were around 40-60 years old. On the contrary, BMI, FBS, cholesterol level, triglyceride level, HDL level, and LDL level found no difference between HHD and normal patients.

Table 5 Comparison between characteristics of patients with and without of HHD (n = 30)

Variables	Diagnosis		p-value
	HHD (N, %)	Normal (N, %)	
Sex			
Female	15 (57.69)	2 (50.00)	0.773
Male	11 (42.31)	2 (50.00)	
Age (year)			
≤ 40	0 (0.00)	1 (25.00)	0.005*
40 – 60	9 (34.62)	3 (75.00)	
≥ 60	17 (65.38)	0 (0.00)	
BMI			
< 18.5	2 (7.69)	0 (0.00)	0.800
18.5 – 22.9	8 (30.76)	1 (25.00)	
23.0 – 24.9	16 (61.55)	3 (75.00)	
Fasting blood sugar (FBS)			
< 100	20 (76.92)	3 (75.00)	0.778
101 – 125	4 (15.39)	1 (25.00)	
> 126	2 (7.69)	0 (0.00)	
Cholesterol level			
< 200	17 (65.38)	4 (100.00)	0.160
≥ 200	9 (34.62)	0 (0.00)	
Triglyceride level			
< 150	15 (57.69)	4 (100.00)	0.102
≥ 150	11 (42.31)	0 (0.00)	
HDL level			
Low level	12 (46.15)	2 (50.00)	0.886
High level	14 (53.85)	2 (50.00)	
LDL level			
Low level	16 (61.5)	3 (75.00)	0.603
High level	10 (38.5)	1 (25.00)	

* p-value < 0.05

Discussion

The current study found that most ECG results were not found to be LVH in participants. Several ECG criteria have previously been proposed to diagnose LVH in the past.[15] However, criteria for the diagnosis of LVH had relatively low sensitivity, and high specificity.[16] ECG indices and subsequent poor diagnostic performance of these indices in the elderly.[17,18] Similar to the results in this study, most participants with HHD were found in the age groups 40-60 and over 60. Most likely, the age-related counterclockwise turn of the frontal QRS axis is primarily responsible for the reduced magnitude of LVH.[19] Therefore, echocardiography should be considered a screening device for the detection of LVH in the elderly. Hypertension is regarded as the most important trigger of LVH development that adversely affects the left ventricular structure.[20] Many early hypertensive patients have no symptoms and are unaware of their condition. As a result, early detection of hypertension remains a challenge, especially in the subclinical population. In this study, ABPM was used as a reference standard to assess blood pressure, avoid possible false readings, and predict cardiovascular outcomes in a hypertensive population.[2,13]

According to the findings of the present study, participants with HHD reported a statistically significantly larger proportion of HT as determined by ABPM than those who were not diagnosed with HHD. Age was a variable that showed significant correlation with SBP by using ABPM. Moreover, age was significantly different between patients with and without HHD. An explanation for this finding, that aging is associated with ventricular remodeling, is likely related to the coupling of ventricular and vascular stiffening processes that can occur over a lifetime.[21,22]

In vasculature studies, in elderly subjects without atherosclerosis, arterial wall media thickens, smooth muscle cell hypertrophy, extracellular matrix accumulation, and calcium deposition were found. Intimal-medial thickness (IMT) was nearly three times greater than that of those aged 20 and 90 with normal blood pressure. This factor affects the increase in blood pressure in older people.[23,24] A study of myocardial thickening. In younger adults, the heart is composed of approximately 25% cardiomyocytes and a complex structure of connective tissue, unlike in the elderly; with aging, there is a decrease in the total number of cardiomyocytes, likely due to apoptosis, as well as an increase in their size. The cardiac MRI study shows age-related declines in both LV diastolic and systolic volumes and an increased LV mass/volume ratio in both sexes.[23]

Study limitations

The small number of participants in this study constituted a limitation. Further research involving a greater number of healthy persons will contribute to the identification of risk factors that potentially predict HHD.

Conclusion

This study found a high proportion of HT as measured by ABPM in participants who were diagnosed with HHD. HT in the participants who had never been diagnosed with hypertension before was also correlated with LVH. Moreover, age has been an important factor that is correlated with increasing SBP and HHD.

What is already known on this topic?

Among people with HHD, this study discovered a significant incidence of silent hypertension as evaluated by ABPM. Echocardiography should be considered a screening device for the detection of LVH in the elderly.

What this study adds?

Echocardiography should be regarded as a screening tool for detecting LVH in the elderly. Furthermore, many people with high blood pressure have no abnormal symptoms. By utilizing a more sensitive tool to do a health check-up, early detection of hypertension can help to prevent consequences from high blood pressure.

Conflicts of interest

There are no conflicts of interest for the authors to disclose.

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Comparison of Suction Drain and Corrugated Drain after Hydrocele Surgery

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Abstract:

Background: Corrugated drain is conventionally used after hydrocele surgery to prevent hematoma formation. However, it may not prevent hematoma, may result in retrograde infection and requires frequent change of dressings.

Objective: To prove the hypothesis that close system suction drain will avoid these problems.

Patients and methods: Fifty patients with 60 hydroceles (10 patients had bilateral hydroceles) were operated by Jaboulay procedure. They were randomized into study group (suction drain; n = 31) and control group (corrugated drain; n = 29 patients). Outcome measures included hematoma, seroma, surgical site infection, frequency of change of dressings and Visual Analogue Score for pain.

Results: Incidence of hematoma, seroma, surgical site infection and Visual Analogue Score was similar in both groups. However; dressing change was not required in the study group.

Conclusion: Suction and corrugated drains are equally effective following hydrocele surgery, but suction drain has the advantage of no dressing change.

Keywords: Hydrocele, Surgery, Complications, Corrugated drain, Suction drain

Introduction

Surgery is the treatment of choice for primary hydrocele, which is estimated to affect 1% of adult men.[1] Hydrocele surgery is often associated with complications such as infection, hematoma or seroma. The most common complication after hydrocele surgery is scrotal hematoma which occurs in about 9% of cases.[2,3] Complications after surgery for hydrocele may lead to prolonged hospitalization and additional morbidity for the patient. A corrugated drain is conventionally put in at the most dependent

part of scrotum to reduce the chance of post-operative hematoma. But it may be associated with more pain and retrograde infection and requires frequent change of dressings. Therefore, we hypothesized that using close suction drain will avoid/minimize these problems and studied its efficacy to prevent complications after hydrocele surgery.

Material and methods

This prospective interventional study was conducted in a tertiary hospital in Central India over a period of 1 year (January 2021-December 2021). Local ethics committee approval and written/informed consent from patients were taken.

Based on our own experience and literature review,[3,4] we assumed that 25% of the subjects in the corrugated group would experience complication. As there was no report on closed suction drain, we hypothesized that 1% of subjects in this group would experience complications. After applying continuity correction, a sample size of 30 in each arm was calculated *a priori* to achieve a power of 80% and a level of significance of 5%.

Fifty patients (60 primary hydroceles) with age ranged from 17-80 years (mean 43.72 years) were included. Patients with small hydrocele, secondary hydrocele, congenital hydrocele, recurrent hydrocele, pyocele, filarial scrotum and patients not willing to participate in the study were excluded.

Sizes of the hydroceles were graded as suggested by Capuano et al.[5]

• *Stage I*: The size of the scrotum is less than that of a tennis ball.

• *Stage II*: The size of the scrotum is greater than that of a tennis ball.

• *Stage III*: The lower pole of the scrotum goes down to mid-thigh.

• *Stage IV*: The lower pole of the scrotum reaches the area between the upper edge of the patella.

• *Stage V*: The lower pole of the scrotum reaches the area between the lower edge of the knee and mid-leg.

• *Stage VI*: The lower pole of the scrotum reaches the area between mid-leg and the ankle.

All patients were operated using Jaboulay procedure and at the end of surgery study group patients had suction drain (Romovac, Johnson & Johnson Pvt. Ltd. 501 Arena Space, Jogeshwari (E) Mumbai India 400060) (study group) and control group patients had corrugated drain (Johnson & Johnson Pvt. Ltd. 501 Arena Space, Jogeshwari (E) Mumbai India 400060) [Figure 1]. Alternate patients were drained by suction and corrugated drains, and in cases of bilateral hydroceles one side was drained by suction and the other by corrugated drain. Scrotal support dressing was applied at the end of the procedure.

Outcome measures included hematoma (defined as post-operative swelling of scrotum with skin discoloration and oozing of blood through the incision site), seroma (serous collection), surgical site infection (sero-purulent discharge from the incision site with edema, redness and tenderness), frequency of change of dressings and Visual Analogue Score (VAS) for pain. Drains were removed when drainage stopped, usually on the 2nd or 3rd postoperative day. All patients were advised scrotal support for 6 weeks at the time of discharge.

Results

Total 78 hydrocele patients underwent surgery during the study period, 18/78 were Capuano Grade I size and underwent Lord's operation without drainage and were excluded from the study.[6]

Figure 1 Showing the two types of drain, suction drain on the left and corrugated drain on the right side

Table 1 Comparison between two types of drain in hydrocele

Parameters	Study group (Suction drain, n = 3)	Control group (Corrugated drain, n = 2)	P value
Hematoma	1	2	0.60
Seroma	3	2	1.00
Surgical site infection	2	1	1.00
VAS score (Mean ± SD)	3.0 ± 2.44	3.8 ± 2.04	2.88
Change of dressing	No dressing required	Average 3 dressings needed	

Twenty-two patients had right, 18 had left and 10 had bilateral hydrocele. These underwent Jaboulay procedure and constituted material for our study. 31 patients had suction drain (study group; stage II 4 cases and stage III 27 cases) and 29 patients had corrugated drain (control group; stage II 5 cases and stage III 24 cases). Volume of drainage in the suction group ranged from 30-50 mL (mean volume 45 mL). Incidence of hematoma, seroma, surgical site infection and VAS score was similar (statistically insignificant) in both the groups (Table 1). Hospital stay for both groups of patients was same (3 days). Patients in the suction drain group required no change of dressing and the dressing applied in operation theatre was removed on the 3rd postoperative day while in corrugated drain group postoperatively average 3 dressings were required for all the patients.

Discussion

Hematoma formation is common after hydrocele surgery as there is little tamponade capability and even capillary oozing can result in a hematoma.[7] In addition to an increased risk for infection a hematoma can lead to prolonged convalescence with marked discomfort.

Various types of preventive pressure dressings have been devised to prevent hematoma.[8-11] However, none of these dressings provide effective constant compression to prevent hematoma formation, do not produce scrotal elevation, are cumbersome and often get dislodged. The primary source of bleeding in scrotal surgery is either the Dartos fascia or the cut edge of the hydrocele sac; and even with meticulous hemostasis, formation of hematoma is common. A drain is recommended when the hydrocele sac that has been excised is large (greater than 15 cm. in diameter).[7] Lord's operation, done for small hydroceles with its minimal dissection, can avoid a drain. However, most of the hydroceles in developing countries are fairly large, and therefore need Jaboulay procedure with partial excision of sac and drainage as the operation of choice and a drain.

In this study we compared the suction drain with corrugated drain after hydrocele surgery. Both groups had similar scrotal dressing after the surgery to remove this variable from equation. The incidence of hematoma, seroma, surgical site infection and pain was similar in both groups. Similar results were seen in a study comparing corrugated and suction drains after simple mastectomy.[12] Decreased incidence of hematoma, seroma, surgical site infection and a lower VAS was expected in the study group but the difference did not reach significance, perhaps because of small number of cases in our study.

Patients with suction drain required no dressing change about 45 mL of post-operative drainage (as measured in the study group) leaking in the dressings caused discomfort and required an average 3 changes of dressings. The other advantages of suction drain include reliable measurement of effluent, minimal tissue trauma, and no skin excoriation. However; there is chance of blockage of drain and regular activation of suction reservoir is required.[13]

To our knowledge, this is the first study to compare the corrugated and suction drains after hydrocele surgery. The limitations of our study include small number of cases, so it might be impossible to show the difference in the outcome; and lack of cost comparison of the two drainage methods. However; it is obvious that patients with corrugated drains require more dressing changes and caused more work for the nursing staff. It stands to logic that patients would prefer suction drains.[12]

Conclusions

Suction drain is not inferior to corrugated drain following hydrocele surgery and has the advantage of no dressing change.

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Perspectives and Confidence of Medical Students toward Telemedicine in Disruptive Era

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Abstract:

Background: COVID-19 pandemic disrupts the current form of patient care such as lock down and fear of disease at hospital. Convenience and modern care of patient emerged such as telemedicine and Metaverse. Preparation medical students for modern care is important. This research assesses the perspectives and confidence of medical students in Telemedicine.

Methods: This study focused on medical cadets of Phramongkutklao College of Medicine. The questionnaire of this study is quantitative data included three parts: general characteristics, perspectives and confidence toward telemedicine. Data were collected by using a five-point Likert-scale in an electronic standardized questionnaire edited in Google platform covering perspectives toward telemedicine (case management, medical teaching, patient convenience, physical convenience) and confidence toward telemedicine (history taking, physical exam, case management, case evaluation). One-way ANOVA was used to compare all perspectives and confidence with independent t-test for comparing perspectives and confidence between groups. Data were analysed using SPSS 26.0.

Results: Ninety-four students enrolled. Most of them were in pre-clinical year (73.4%). There was significant different in perspectives toward telemedicine (F = 4.05, p = 0.008). Perspectives toward case management was lower than use of telemedicine for medical teaching (Mean difference = 0.33, p = 0.013) and patient convenience (Mean difference = 0.29, p = 0.033). Regarding confidence, there was no significant difference in all aspects of case management. All aspect of confidence had generally low mean score.

Conclusion: The perspective of medical students toward the telemedicine is positive attitude except for case management. However, the confident for using telemedicine is rather low as a cause of medical school not prepare or practice medical students for using telemedicine. As a result, medical school is still lack of adaptation for disruptive era as it should be.

Keywords: Telemedicine, Medical students, Perspectives, Confidence

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Introduction

Presently, access to adequate medical care is still a major problem worldwide especially in those developing countries. Thailand has also faced this problem with equality of health workforce distribution. The health workforce has been density in the central region which contributes to disparities in health outcomes especially in rural area.[1]

COVID-19 pandemic has caused significant impact on the accessibility of resources in the healthcare centres, lockdown measurements, physical distancing and limited traveling. Telemedicine is the key to provide equal access of healthcare to the users and minimizing the risk of COVID-19 infection and contributes positively to the realisation of the right to health and the attainment of the United Nations Universal Health Coverage (UHC) Agenda under the Sustainable Development Goals (SDGs) which specifically aims to improve access to health care services for all by ensuring that people can receive health care services whenever the need arises.[2]

However, the use of telemedicine technology is affected by many factors. Human related factors such as physicians' knowledge and their perspective towards the technology are essential factors to be considered before initiating the system.[3,4] A lack of accurate knowledge and necessary skills such as technical expertise among physicians remains a barrier to the efficient use of telemedicine.[5]

The objective of this study was to explore perspectives and confidence toward telemedicine of medical students from Phramongkutklao College of Medicine (PCM) since the preparedness is the key to the success in implementing telemedicine in developing countries.

Materials and Methods

Study population and setting

This study focused on medical students of Phramongkutklao College of Medicine (PCM). The potential participants included medical cadets in pre-clinical years and another in clinical years. The study was conducted during 2021.

Study design

This study used cross-sectional study. This included perspective and confidence toward telemedicine of medical cadet students in PCM.

Questionnaire and data collection

The questionnaire of this study used quantitative data included three parts; general characteristics (gender, year, age and GPAX) perspectives and confidence toward telemedicine which was 5-Likert scale. The perspectives toward telemedicine included 4 aspects: 1) case management: develop healthcare promotion/primary prevention (CM), 2) medical teaching: tele-education (MT), 3) patient convenience (PaC) and 4) physical convenience (PhC). The confidence toward telemedicine included 4 aspects 1) history taking (HT), 2) physical exam (PE), 3) case management (MC) and 4) case evaluation (CE).

The questionnaire was made online on Google form and distributed via messaging applications to participants. Responses from participants were stored on Google sheet which could be downloaded for statistical analysis.

Statistical analysis

SPSS 26.0 (Armonk, New York) was used for statistical analysis. General characteristics were calculated using descriptive statistics. Comparison between perspectives was conducted using one-way ANOVA with post-hoc tests by Bonferroni test. Comparison between internship years and genders were assessed using independent t-test. Significant differences between comparisons were counted at p-value < 0.05.

Results

A total of 94 students responded to the questionnaire. From these, 73.40% were in pre-clinical year. There were 52.13% males and 47.87% females. Most students (57.45%) had GPAX of 3.50 to 4.00, followed by 3.01-3.49 (32.98%). Demographic data were displayed in Table 1.

Table 1 Demographic data of participants

Characteristics	N (%)
Gender	
Male	49 (52.13)
Female	45 (47.87)
Year	
Pre-clinic	69 (73.40)
Clinic	25 (26.60)
GPAX	
2.99 and below	9 (9.57)
3.00-3.49	31 (32.98)
3.50 and above	54 (57.45)

Perspectives toward telemedicine

There was significant difference in perspectives toward telemedicine (F = 4.05, $p = 0.008$). Mean score of patient convenience, physician convenience, medical teaching and case management were 3.99 ± 0.68, 3.84 ± 0.73, 4.02 ± 0.79 and 3.70 ± 0.68, respectively. Perspectives toward case management was lower than use of telemedicine for medical teaching (Mean difference = 0.33, $p = 0.013$) and patient convenience (Mean difference = 0.29, $p = 0.033$). The data were shown in Table 2.

Table 2 Comparison of perspectives of participants toward telemedicine

Mean score				One-way ANOVA				Pair comparison		
PaC	PhC	MT	CM	Leveve's statistic	p	F	p	Pair comparison	Mean difference	p
3.99	3.84	4.02	3.70	15.32	<0.0001	4.05	0.008	CM<PhC	0.15	1.000
±0.68	±0.73	±0.79	±0.68					CM<PaC	0.29	0.033
								CM<MT	0.33	0.013
								PhC<PaC	0.15	0.953
								PhC<MT	0.18	0.524
								PaC<MT	0.03	1.000

Confidence toward telemedicine

It was found that there was not different in confidence in telemedicine among medical students (F = 2.35, $p = 0.072$). Mean score of history taking, physical examination, case evaluation and case management were 3.05 ± 0.88, 2.88 ± 0.85, 2.93 ± 0.86 and 3.18 ± 0.78, respectively. The data were shown in Table 3.

Discussion

This study addressed the perspectives and confidence toward telemedicine of medical student. These two parameters are important indicators for assessing readiness of medical students for future era of health care.

It was found that medical students at PCM viewed telemedicine positively, except for case management. On the contrary, they still lacked confidence in using telemedicine for clinical practice. It can be implied that younger physicians and medical students acknowledged telemedicine as an alternative, or even revolutionary, trend of healthcare, however, due to drastic change in health care delivery amidst COVID-19 pandemic, knowledge and familiarity for telemedicine among them were not well prepared, resulting in low confidence. These findings were parallel to previous study in France where medical students stated that most medical students were not familiar and not well-trained for telemedicine. A study in

Table 3 Comparison of confidence of participants toward telemedicine

Mean score				One-way ANOVA				Pair comparison		
HT	**PE**	**CE**	**MC**	**Leveve's statistic**	**p**	**F**	**p**	**Pair comparison**	**Mean difference**	**p**
3.05	2.88	2.93	3.18	18.91	<0.001	2.35	0.072	PE<CE	0.05	1.000
±0.88	±0.85	±0.86	±0.78					PE<HT	0.17	1.000
								PE<MC	0.30	0.096
								CE<HT	0.12	1.000
								CE<MC	0.25	0.258
								HT<MC	0.13	1.000

China indicated that most medical professions and medical students were familiar with the concept of a "virtual visit", but only a few ever engaged in such visits. A previous study in Sri Lanka stated that even though medical students were familiar with e-health concept, there was an extremely limited practice in this field. As a result, this might reflect the positive attitudes toward telemedicine, but low in confidence and engagement to this type of healthcare.

This study found that perspectives of medical students toward case management were significantly lower than other aspects of

perspectives. This concern could be centered around the quality of healthcare when physical meeting between physicians and patients was omitted. The scope and extent of telemedicine used among physicians, especially specialists who required thorough physical examination was still obscure. Physicians also believed that only objective data could be truly consulted from the distance, whereas relying on remote interpretation of subjective data was inappropriate. To counter this problem, education and training medical students to utilize telemedicine would improve their

understanding and encourage the use of telemedicine, as well as better perceived advantages of telemedicine.

Telemedicine is the state of the art. Medical students should be trained in several aspects, for instance, how to communicate with the patients through video- or voice-call, how to led the patients explain their health problems in distance as similar to physical meetings, how to use instruments, such as phone camera, camera flashlight and messaging applications, to perform basic physical examination, how to give diagnosis with distance and thorough physical examinations and to know the extent of using telemedicine consultation without doing harm to patients.

Further studies should focus on training of the mentioned aspects for medical students. Another study field should explore knowledge, attitude and confidence as well as problems of telemedicine encountered in real practice among intern physicians who had completed the telemedicine training.

Conclusion

Telemedicine is revolutionary trend in health care system. Medical students perceived it with good attitudes, however, confidence is still low in using telemedicine among them. To increase their familiarity and confidence in using telemedicine, training and education to medical students are crucial.

Acknowledgement

Disclosure of interest

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A 61-Year-Old Woman Presented with Gastric Outlet Obstruction

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Abstract:

We reported a case of acute myeloid leukemia (AML), presented with gastric outlet obstruction from granulocytic sarcoma (GS) at duodenum at the same time of AML diagnosis. She also had possible extramedullary involvement at right breast and right presacral area. She achieved remission after induction chemotherapy (cytarabine and doxorubicin). Three months later after the 3rd consolidation, she developed relapsed disease at multiple sites and also in bone marrow. Because of unusual presentation, the physician in-charge should be aware of this disease. With retrospective review, complete blood count and peripheral blood smear examination by hematologist is the key for early diagnosis.

Keywords: Acute myeloid leukemia, Granulocytic sarcoma, Gastric outlet obstruction

Introduction

Granulocytic sarcoma (GS) or myeloid sarcoma, also called chloroma and myelo-blastoma is unusual presentation of AML. GS can present before, at the same time or after diagnosis of AML. Some cases may present GS at the time of relapse. The common sites of GS are bone, periosteum, soft tissues, and lymph nodes, and less commonly the orbit, intestine, mediastinum, epidural region, uterus, and ovary.[1,2] When occurred at skin and subcutaneous tissue, many experts will rename this condition as leukemic cutis (LC).[3] One of the large series from single institution reported 346 AML cases.[4] The incidence of extramedullary involvement (EMI) was 11% (38 patients). The involved sites were: skin (66%), central nervous system (CNS) (23%), pleura (7%), lymph nodes (5%), peritoneum (2%), spleen (2%), pancreas (2%), breasts (2%) and bones (2%). Most patients (91%) had only one EMI site, while 9% had multiple sites affected at the same time. Twenty-four (63%) patients showed signs of EMI at presentation, while extramedullary relapse occurred in 10 patients (26%); 4 patients had EMI both at presentation and relapse. After induction therapy, complete remission (CR) rate was 22%, with a median DFS of 7.4 months. The median OS of all 27 EMI patients was 11.6 months (range 2–79); this resulted significantly longer for the 8 EMI patients who undergone allogeneic hemato-poietic stem cell transplantation (allo-HSCT) than those (19 patients) who did not receive this procedure (16.7 vs 8.2 months respectively, p = 0.02). The authors concluded that

AML with EMI patients had poor prognosis. Allo-HSCT, applicable however only in some cases, seems to have a crucial role in these condition and association with a better prognosis.

Case Presentation

A 61-year-old housewife with underlying hypertension, DM type 2 and dyslipidemia, living in Chiang Rai presented with one-month history of epigastrium discomfort. She also had nausea and vomiting of food and drink almost after every meal with no hematemesis. This made her anorexia, weight loss of 10 kg in 1 month. She had lesser amount of stool but no hematochezia. She had no dysphagia or odynophagia. After receiving supportive treatment at private hospital without improvement, she was suggested esophagogastroduodenoscopy (EGD). Then she went to Medical Center Hospital, Mae Fah Luang University for further investigation and management in September 2021. At the triage, physical examination revealed an old woman, looked fatigue and mild anemia without jaundice or palpable lymph nodes. She had marked abdominal distention, soft, no tenderness, no palpable mass but having positive succession (gastric) splash. Bedside Ultrasound revealed markedly dilated stomach with large amount of food content. Nasogastric suction was immediately done and showed blue-green liquid content about 1.5 L with continuous

drainage. Initial diagnosis was severe gastric outlet obstruction with unknown etiology. CT scan whole abdomen showed 4.2 x 7.6 x 7.1 cm circumferential mass at 2nd and 3rd part duodenum, extension causing 1st part duodenum-gastric dilatation, common bile duct (CBD), intrahepatic duct (IHD) and pancreatic duct dilatation, with perilesional fat stranding, focal thickened peritoneum and minimal ascites, possibly carcinoma of duodenum (Figure 1). Few enlarged hepatoduodenal and aortocaval nodes, possibly nodal metastasis. Fatty liver or liver parenchymal disease. A 2.5 x 2.9 cm lobulated mass at right breast (Figure 2A). A 2.8 x 3.9 cm soft tissue mass at right presacral region, uncertain nature (Figure 2B and 2C). Few enlarged hepatoduodenal and aortocaval nodes, possibly nodal metastasis. She was consulted surgeon on that day and was planned for EGD on the following day after fluid resuscitation. EGD showed large amount of bile about 1 L in the whole part of stomach. The second part of duodenum had abnormal mucosal swelling with could not be passed through. Lymphoma or malignancy of duodenum was suspected and biopsy was done at the lesion. During wait for pathology result, she subsequently underwent gastroje-junostomy for gastric decompression. After bypass surgery, she was unfortunately developed aspiration pneumonia from bile and required intubation with respiration support in the intensive care unit (ICU).
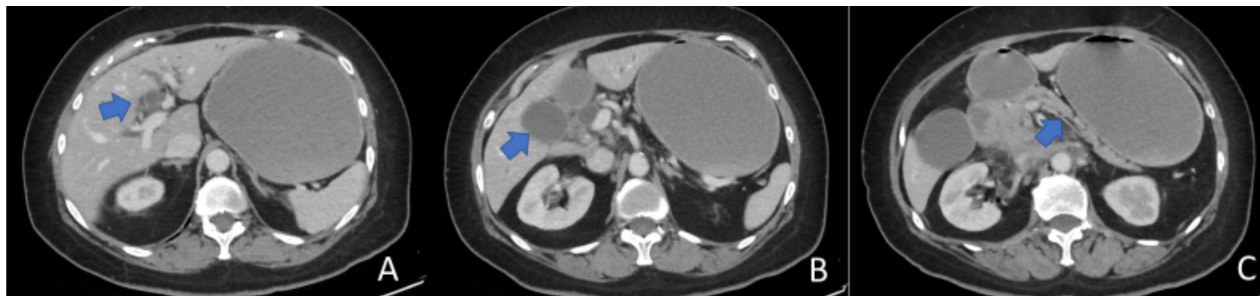
Figure 1 CT scan of abdomen shows mass at duodenum causing marked gastric dilatation, dilatation of intrahepatic duct (A), gall bladder (B) and pancreatic duct (C).
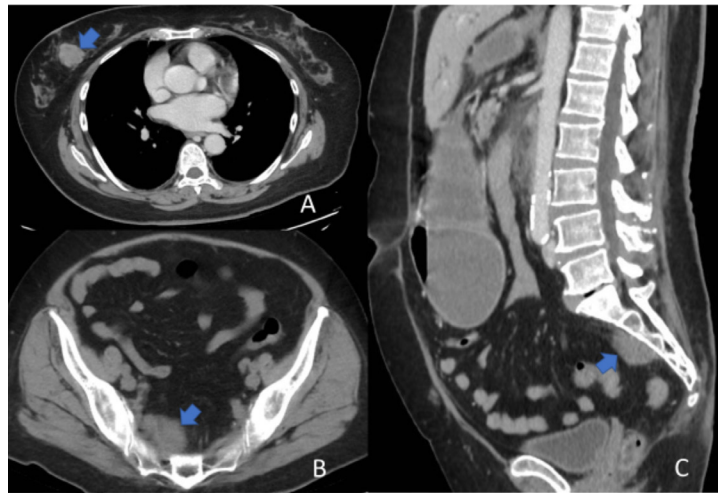
Figure 2 CT scan of abdomen shows right breast mass (A) and right presacral mass (B) and (C).

Duodenum biopsy showed dense lymphoid infiltration in lamina propria. Immunohistochemistry of atypical lymphoid infiltrate results as follows: CD3 (-), CD 5 (-), CD 10 (-), CD 20 (-), CD 23 (-), BCL6 (-), Cyclin D1 (-), PAX5 (+) (weak nuclear staining), CD43 (+) (diffuse and strong), BCL2 (+), Ki67 (80-90%), CD21: No follicular dendritic cell meshwork highlighted, Kappa and lambda: No light chain restriction demonstrated. The initial immunohisto-

chemical (IHC) findings were suggestive of involvement by hematolymphoid neoplasm. Additional immunohistochemistry of atypical mononuclear cell infiltrate results as follows: CD34 (+), MPO (+), TdT (-), Lysozyme (-), CD79a (-), OCT2 (-), BOB1 (-), CD2 (-), CD30 (-), ALK-1 (-). Final diagnosis: Duodenum, biopsy: Leukemic infiltrate, immunophenotypically consistent with myeloblasts.
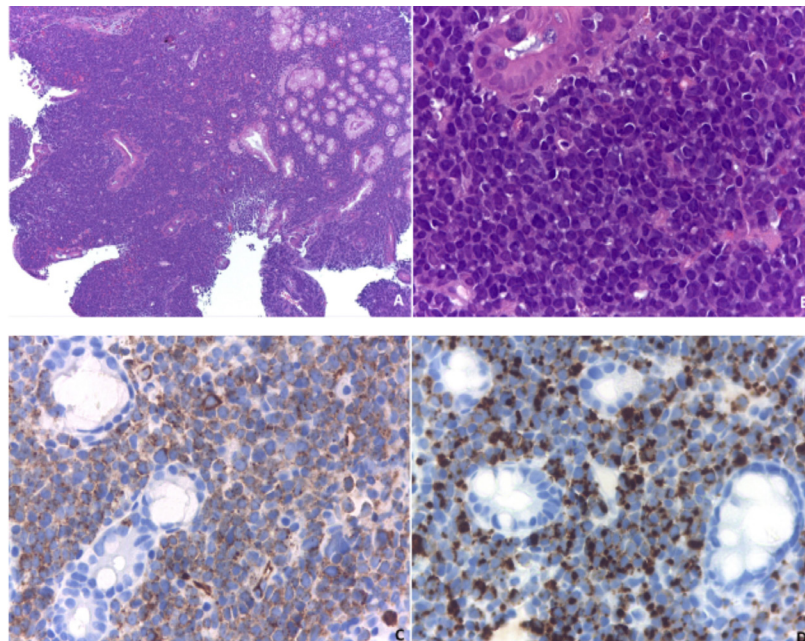
Figure 3 Low-power view of gastric biopsy demonstrates dense infiltrate by round blue cells (A). At high-power view (B), the neoplastic cells are uniform medium-sized nuclei, fine chromatin, inconspicuous nucleoli and small amount of cytoplasm. The neoplastic cells are positive for CD34 (C) and MPO (D).
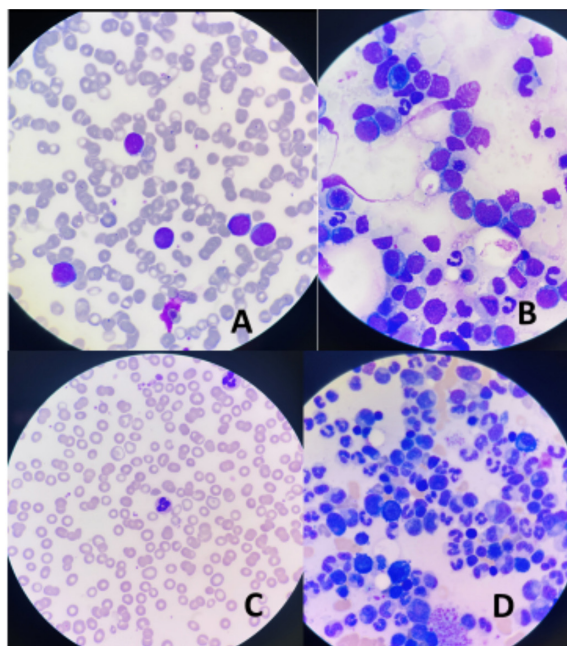
Figure 4 Peripheral blood smear (A) and bone marrow aspiration smear (B) at diagnosis show numerous myeloblasts. After induction chemotherapy is in complete remission (C) and (D).

After definite final diagnosis, the patient was consulted hematology service. CBC showed Hct 28.5%, Hb 8.9 g/dL, WBC 7.44 x 10^9/L, PMN 49%, L 15%, M 32%, E 2%, platelet 220 x 10^9/L, MCV 77 fL, Peripheral blood smear revealed size 2-3 times the size of small lymphocytes, immature nuclear chromatin with blue cytoplasm possible myeloblasts. Bone marrow aspiration: immature mononuclear cells 60% of total nucleated cells size 2-3 times the size of small lymphocyte and bone marrow biopsy: Acute myeloid leukemia [CD34 (+), CD117 (+), MPO (+), CD68 (-), lysozyme (-), CD3 (-), PAX5 (-)]. Bone marrow cytogenetics revealed 46, XX, der (9) del (9) (p22p24) del (9) (q32q33) [20].
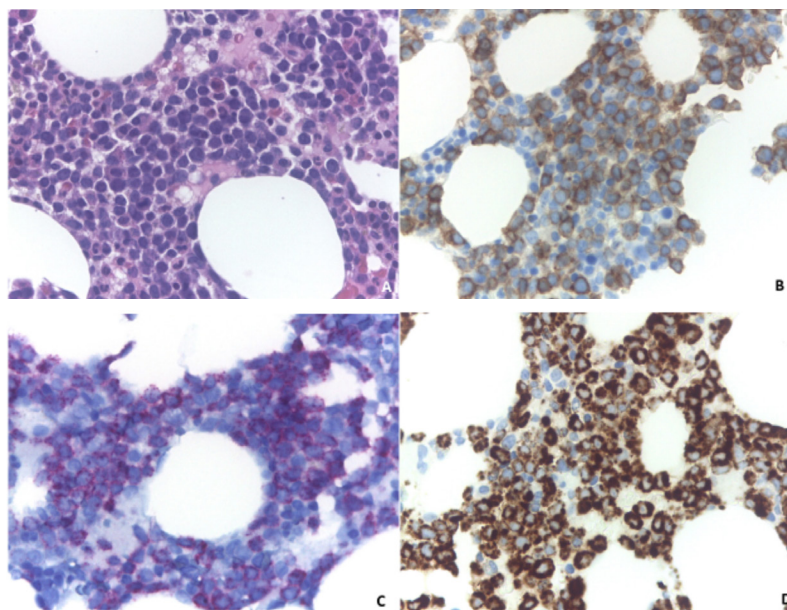
Figure 5 Bone marrow biopsy demonstrates hypercellularity with dense monomorphic blastoid cell infiltrate (A). The neoplastic cells are positive for CD34 (B), CD117 (C) and MPO (D).

The 10-colored flow cytometric analysis of bone marrow revealed an increased abnormal population in dimCD45/low SSC region which comprised approximately 28.90% of all nucleated cells and expressed CD13 and CD33/MPO/CD34/CD117. CD19/CD20/cytoplasmic CD3 /cytoplasmic CD79a/CD10/CD14/CD64/TT were negative. Aberrant expression of CD7 was found. Findings were diagnostic of acute myeloid leukemia.

Final diagnosis: AML with granulocytic sarcoma at duodenum presented with gastric outlet obstruction with possible GS at breast and presacral area. After resolution of aspiration pneumonia and was without respiration support, the patient developed cholestatic jaundice. Liver function test (LFT) showed AST 44 U/L, ALT 56 U/L, ALP 261 U/L, TB 3.4 mg/dL, DB 2.9 mg/dL Leukemic infiltration in the liver or granulocytic mass compression was suspected. She initially received induction chemotherapy with cytarabine 100 mg/d for 5 days and doxorubicin 25 mg/d for 2 days with granulocyte-colony stimulating factor (G-CSF) support. After the first induction chemotherapy, LFT and CBC returned to normal, also bone marrow achieved CR with normal cytogenetics. She subsequently received three cycles of consolidation with same regimen of induction chemotherapy. However, three months later after the 3rd consolidation, she unfortunately developed relapsed disease at right breast, multiple subcutaneous sites at back (Figure 6), left flank, suprapubic area, both thighs and bone marrow. Then, she received radiation treatment at back and subsequently was put on modified intermediate-dose cytarabine in August 2022. We hope to get the good result which might not be as good as the first diagnosis because of extensive extramedullary involvement.

Discussion

This patient presented with gastric outlet obstruction and was proved to be granulocytic sarcoma (GS) of duodenum with morphology and IHC. She also had acute myeloid leukemia at the time of GS. Although CBC at diagnosis, showed anemia with normal platelet count, peripheral blood smear had numerous abnormal cells, falsely counted as monocytes but morphology consistent with myeloblast and bone marrow showed numerous myeloblasts with IHC proved. So, we recommend the physician in-charge review blood smear whenever facing cases with abnormal CBC.
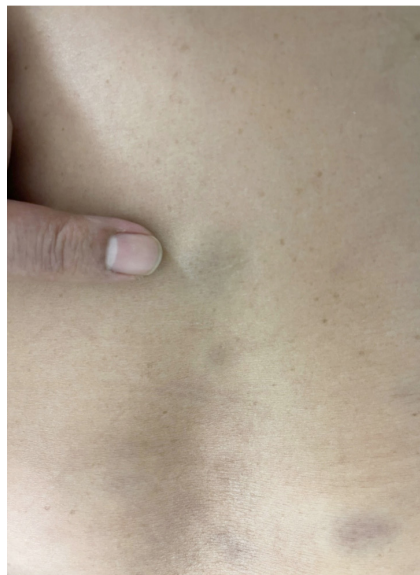
Figure 6 Subcutaneous nodules on back

She also had possible GS at breast and presacral area. Bone marrow also showed cytogenetics involving abnormalities of chromosome 9 [der (9), del (9p), del (9q)]. GS can occur at any extramedullary organs such as skin, soft tissue, brain, breast, GI tract and so on. Tissue biopsy and IHC should be done in order to get definite diagnosis. Fine needle aspiration is not adequate for diagnosis.[5] Lymphoma, non-RE malignancy are differential diagnosis of GS[6] and have different treatment.[7,8] This patient had good response to suboptimal dose of cytarabine and doxorubicin. She also received G-CSF after completion of induction chemotherapy and could achieve CR only after 1st cycle of induction. She also received 3 cycles of consolidation. Unfortunately, she achieved only short remission duration and developed relapse at multiple sites included bone marrow.

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Computational Analysis of Active Phytochemicals Came from GC-MS Chromatogram of *Rhynchanthus longiflorus* Hook.f. against Thymidine Phosphorylase Enzyme

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Abstract:

Background: A previous study reported fifteen identified compounds that were obtained from an essential oil extract from *Rhynchanthus longiflorus* Hook.f., carried out by using the GC-MS technique, which revealed possible potential candidates for further drug development in cancer chemotherapy.

Objective: This study aimed to determine and predict the most effective compound obtained from the GC-MS chromatogram of the essential oil extract from *Rhynchanthus longiflorus* Hook.f., active against the human thymidine phosphorylase enzyme, again carried out using computational analysis.

Materials and methods: All compounds identified by GC-MS analysis were three-dimensionally optimized and docked with a well-prepared crystal structure of the human thymidine phosphorylase enzyme. Additionally, the *in silico* pharmacokinetic properties, bioactive activities, and toxicity profiles prediction were determined.

Results: Amongst these identified compounds, beta-eudesmol showed the highest binding affinity against thymidine phosphorylase, with a binding energy of -7.44 kcal/mol, showing better values than that of the reference compound (5-iodouracil). The pharmacokinetic properties, bioactive activities, and toxicity profiles of all compounds met the acceptance criteria.

Conclusion: This study suggests that an active phytochemical, revealed by the GC-MS chromatogram, may be a most promising candidate drug, acting on the thymidine phosphorylase enzyme, and so should be studied further.

Keywords: In silico analysis, *Rhynchanthus longiflorus* Hook.f., Thymidine phosphorylase

Introduction

Thymidine phosphorylase (TP) is the nucleoside metabolism enzyme that mainly catalyzes thymidine to thymine and 2-deoxy-alpha-D-ribose-1-phosphate (dRib-1-P).[1]

TP is an attractive target for the treatment of cancer, due to evidence from many studies, indicating that TP is correlated to malignant phenotypes of cancer cells.[2] The mechanism

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postulated is that a dephosphorylated product of dRib-1-P, called 2-deoxy-alpha-D-ribose (dRib), promotes angiogenesis and anti-apoptotic activity in cancer cells.[3] In an attempt to develop new substances for cancer chemotherapy, TP inhibition is an interesting concept for the inhibition of angiogenesis in many types of cancer.[1]

The plant studied has long been used to alleviate illness or diseases. Many plants from the family Zingiberaceae have been used in traditional for many purposes.[4] *Rhynchanthus longiflorus* Hook.f. (RL), one of the species in this family, is a rare and endangered epiphytic, perennial rhizomatous plant mainly found in Myanmar and India.[5] The decoction of the plant's rhizomes is being used for the treatment of hypertension and convulsions as folk remedies in some Akha villages.[6] In a previous study by our group, the chemical constituents of the RL rhizome was determined, using the GC-MS technique. This found twelve monoterpenes, two sesquiterpenes, and a phenylpropene identified from the essential oil.[7] Unfortunately, scientific data about the biological activities of RL is limited because of consideration of conservation of the scant plant material. However, the GC-MS chromatogram is valuable, not only for understanding of the chemical constituents of this plant, but also as a guide for compu-tational screening of various drug targets for the treatment of many diseases. Thus, it is necessary to evaluate the TP inhibition of all of the phytochemicals, identified by GC-MS analysis, from the essential oil extract of R. longiflorus (RLO), by using computational analysis, to predict the role of these terpenoids and phenylpropanoid compounds.

Methodology
1. Preparation of phytochemical structures obtained from chromatogram of RLO
A detailed explanation of the RLO

preparation and GC-MS analysis of active phytochemical constituents has already been reported in our previous paper.[7] All known structures that have been identified, from the main EI MS library of NIST/EPA/NIH Mass Spectral Library 2005 (NIST05), were constructed and the energy of freely rotatable bonds of all active constituents was determined, by using Chem3D Professional 10.0 (CambridgeSoft Inc., Cambridge, USA).

2. Structure preparation of human thymidine phosphorylase
A Crystal structure of human thymidine phosphorylase and another of 5-iodouracil (PDB ID: 2WK6),[8] were prepared, by removing all water molecules, any solvent, and the ligand (5-iodouracil as reference molecule), using the ViewerLite program (Accelrys, San Diego, USA).

3. Computational prediction of pharmacokinetic properties, bioactive activities, and toxicity profiles of compounds obtained from RLO
Canonical SMILES format of all known structures that have been identified from GC-MS chromatograms were retrieved from the PubChem compound database[9] and then entered into SwissADME (http://www.swissadme.ch/index.php), to compute their physicochemical and pharmacokinetic properties.[10] *In silico* bioactivity prediction of these compounds in SMILES format was evaluated using PASSonline software, which selected potential activity as a phosphorylase inhibitor, angiogenesis stimulant, as well as antineoplastic activity.[11] Computational toxicity analysis of all phytochemical compounds from RLO in SMILES format was performed by using a ProTox-II web-based tool.[12]

4. Molecular docking of compounds obtained from GC-MS of RLO against TP
The predicted binding free energy of compounds from RLO following docking

was analyzed by using AutoDock 4.2.6 software.[13] Each energy-minimized compound from RLO was mated to the well-prepared targets with default parameters of docking procedures. The molecular docking protocol was obtained from the active site of the human TP, with a molecular grid set at 0.375 Å grid spacing. The location of the grid was located at x = 15.497, y = 17.393, and z = 47.496 Å. Docking results of all compounds were evaluated using the best predicted binding free energy (BE, kcal/mol), along with the inhibitory constant from all clusters of each conformational structure. Virtual analysis of the best results was then viewed and analyzed using UCSF Chimera.[14]

Results and discussion.

The challenge of drug discovery and development for antineoplastic agents is to reduce development times and effectively screen out unfavorable compounds.[15] Computational analysis is one of the approaches that can be used to search for more effective drug candidates with potentially fewer side effects.[15] Free accessible computer aided web-based tools for drug screening are versatile, user-friendly, and fairly efficient, being based on bioinformatics, cheminformatics, chemical biology, and molecular modeling.[10-12]

In our study, we selected SwissADME, PASSonline, and ProTox-II online tools to predict and estimate the potential pharmacokinetic properties, bioactive activities, and toxicity profiles, respectively. All compounds from RLO fell within Lipinski's rule of five, with no effect on any pharmacokinetic parameters. The logP parameter (octanol/water partition coefficient) is a physiochemical descriptor for lipophilicity which affects drug absorption, distribution, drug-receptor interactions, and drug metabolism.[16] The predicted logP values of known phytochemical compounds from RLO were within the acceptable range (range of 2.58 to 4.37), and so were expected to display good bioavailability (Table 1).

Table 1 Physiochemical properties and molecular docking analysis of compounds identified by GC-MS analysis from RLO toward TP

Compound number	Phytochemical name	Predicted binding energy (kcal/mol)[a]	Predicted inhibitory constant (μM)[a]	MW[b]	HBA[c]	HBD[c]	cLogP[c]
1	α-pinene	-5.44	102.31	136.23	0	0	3.44
2	(+)-sabinene	-5.29	132.63	136.23	0	0	3.25
3	(-)-β-pinene	-5.45	101.68	136.23	0	0	3.42
4	β-myrcene	-4.88	265.31	136.23	0	0	3.43
5	(+)-3-carene	-5.34	121.47	136.23	0	0	3.42
6	Eucalyptol	-5.41	109.16	154.25	1	0	2.67
7	*trans*-β-ocimene	-5.15	168.35	136.23	0	0	3.4
8	γ-terpinene	-4.87	269.91	136.23	0	0	3.35
9	Linalool	-5.21	150.49	154.25	1	1	2.66
10	Unknown	-	-	-	-	-	-
11	4-carromenthenol	-5.92	45.75	154.25	1	1	2.6
12	(-)-α-terpineol	-5.71	65.56	154.25	1	1	2.58

Compound number	Phytochemical name	Predicted binding energy (kcal/mol)[a]	Predicted inhibitory constant (µM)[a]	MW[b]	HBA[c]	HBD[c]	cLogP[c]
13	2-carene	-5.37	116.16	136.23	0	0	3.12
14	Methyl eugenol	-5.78	57.76	178.23	2	0	2.58
15	(+)-9-aristolene	-6.32	23.23	204.35	0	0	4.37
16	β-eudesmol	-7.44	3.51	222.37	1	1	3.61
Ref[d]	5-iodouracil	-5.95	43.20	237.98	2	2	0.59

[a] Results were obtained from AutoDock 4.2.6 software.
[b] Calculated using ChemBioDraw Ultra16.0. MW: molecular weight
[c] Calculated using SwissADME. HBA: number of hydrogen acceptors; HBD: number of hydrogen donors; RB: number of rotatable bonds; tPSA: total polar surface area; cLog P: log octanol/water partition coefficient.
[d] Reference compound: 5-iodouracil

The prediction of potential bioactive activities of identified compounds were then analyzed, using the PASS Online web-based tool. The output result of potential activity, both as a phosphorylase inhibitor and antineoplastic agent, is given in Table 2, where "Pa" represents the probability to be active in the sub-class of bioactivities.[11] In this study all compounds from RLO showed antineoplastic activity in a variety of cancers. Compound 2, 7-12, and 16 displayed phosphorylase inhibition, which indicated their potential use as an inhibitor of the TP.

Table 2 In silico bioactivity prediction of compounds identified by GC-MS from RLO

Compound	1	2	3	4	5	6	7	8	9	11	12	13	14	15	16
Phosphorylase inhibitor	0	0.15	0	0	0	0	0.17	0.13	0.17	0.14	0.14	0	0	0	0.14
Angiogenesis stimulant	0	0	0	0.24	0	0	0.51	0.19	0.31	0	0	0	0.26	0	0
Antineoplastic (bladder CA)	0	0.17	0.16	0	0.17	0	0	0.15	0	0	0	0.19	0.16	0	0
Antineoplastic (bone CA)	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0.19
Antineoplastic (brain CA)	0	0	0	0.30	0.26	0	0.30	0	0.26	0	0	0.28	0.22	0	0
Antineoplastic (breast CA)	0	0.15	0.16	0.89	0	0.16	0.76	0	0.26	0	0	0	0.40	0	0.17
Antineoplastic (carcinoma)	0	0	0.12	0.56	0.11	0	0.46	0	0.23	0	0	0	0.16	0	0.18
Antineoplastic (cervical CA)	0	0	0	0.14	0	0.178	0.24	0	0	0	0	0	0.32	0	0
Antineoplastic (colon CA)	0	0	0	0.18	0	0.75	0.22	0	0	0	0	0	0.20	0	0
Antineoplastic (colorectal CA)	0	0	0	0.18	0	0.76	0.28	0	0	0	0	0	0.21	0	0
Antineoplastic (endocrine CA)	0	0.19	0.20	0	0	0	0	0	0	0	0	0	0.17	0	0.29
Antineoplastic (gastric CA)	0	0	0	0	0	0	0	0	0	0	0	0	0.13	0	0
Antineoplastic (glioma)	0	0	0	0.22	0	0	0.3	0	0	0	0	0	0	0	0
Antineoplastic (liver CA)	0	0.38	0.35	0.35	0	0	0.30	0.15	0.26	0	0	0	0.24	0	0.30
Antineoplastic (lung CA)	0	0.41	0.49	0.68	0.19	0.78	0.64	0	0.37	0	0	0.16	0.24	0	0.41
Antineoplastic (lymphoma)	0	0	0	0	0	0	0	0	0.15	0	0	0	0.18	0	0
Antineoplastic (melanoma)	0	0.30	0.38	0.36	0.16	0	0.48	0	0	0	0	0	0.21	0	0.19
Antineoplastic (MM)	0	0	0	0	0	0	0	0.37	0	0	0	0	0	0	0
Antineoplastic (NHL)	0	0	0	0	0	0.34	0	0	0	0	0	0.3	0	0	0
Antineoplastic (NSCLC)	0	0	0	0	0	0	0.17	0	0	0	0	0	0.30	0	0
Antineoplastic (ovarian CA)	0.12	0.13	0.20	0.30	0.11	0.36	0.35	0	0	0.15	0	0	0.18	0	0.15
Antineoplastic (pancreatic CA)	0.22	0.49	0.44	0.25	0.25	0	0.28	0.25	0.29	0.33	0.34	0	0.26	0	0.40
Antineoplastic (renal CA)	0	0.19	0.19	0.50	0.14	0	0.50	0	0.17	0.18	0	0.18	0.19	0	0.14
Antineoplastic (SCLC)	0	0	0	0	0	0	0	0	0	0.21	0	0	0.26	0	0
Antineoplastic (solid tumors)	0	0	0	0	0	0	0.26	0.25	0	0	0	0	0.28	0	0
Antineoplastic (SCC)	0	0.13	0.16	0.29	0.16	0	0.35	0	0.10	0	0.09	0.09	0.16	0	0.21
Antineoplastic (thyroid CA)	0.18	0.24	0.26	0.15	0.19	0	0.17	0	0	0	0	0.20	0.19	0.21	0.30
Antineoplastic (uterine CA)	0	0	0	0	0	0	0	0	0	0	0	0	0.13	0	0

[a] Pa value is probability "to be active", by using PASSonline software; CA: cancer, SCLC: Small cell lung cancer; SCC: Squamous cell carcinoma; NSCLC: Non-small cell lung cancer; NHL: Non-Hodgkin lymphoma; MM: Multiple myeloma;

In addition, the toxicity prediction of 15 compounds identified by GC-MS analysis from RLO were also evaluated using ProTox-II. Almost compounds showed prediction for low toxicity except for β-myrcene (4), methyl eugenol (14), and (+)-9-aristolene (15). Beta-myrcene (4) has classified toxicity *via* nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE) and heat shock factor response element (HSE)

mechanisms. Methyl eugenol (14) was predicted to be carcinogenic and have anti-aromatase activity. (+)-9-aristolene (15) was predicted to exhibit immunotoxicity. For predicted toxicity class and toxic dose (LD50) values of compounds from RLO, almost compounds fell under toxicity class III except *trans*-β-ocimene (7) which fell in toxicity class III with the lowest LD50 as displayed in Table 3.

Table 3 Toxicity profiles of compounds identified by GC–MS from RLO

Compound number	Predicted LD50 (mg/kg)	Predicted toxicity class	Classification
1	3,700	5	Inactive
2	5,000	5	Inactive
3	4,700	5	Inactive
4	5,000	5	Nuclear factor (erythroid-derived 2)-like 2, Heat shock factor response element (HSE)
5	4,800	5	Inactive
6	2,480	5	Inactive
7	113	3	Inactive
8	2,500	5	Inactive
9	2,200	5	Inactive
10	-	-	-
11	1,016	4	Inactive
12	2,830	5	Inactive
13	4,800	5	Inactive
14	810	4	Carcinogenicity, Aromatase
15	4,800	5	Immunotoxicity
16	2,000	4	Inactive

[a] LD50: The median lethal dose, is the dose of a compound that is caused death for 50% of the animals in a dose group.

All compounds from RLO were docked with the human TP in the region of the receptor-protein binding interface. The binding energy of the reference compound, 5-iodouracil was -5.95 kcal/mol, with an

estimated inhibition constant (Ki) of 43.20 μM. The compounds that exerted binding free energy greater than that of the reference compounds towards TP were (+)-9-aristolene (15) and β-eudesmol (16) which provided

binding energies of -6.32 and -7.44 kcal/mol, respectively (Table 1).

This finding indicated that there are promising compounds exerting thymidine phosphorylase inhibition. In this study, we selected only β-eudesmol (16) for binding mode analysis. The interaction of β-eudesmol against TP is by H-bonding interaction with Ser117 residues, with bond distances of 2.98 Å, and also by hydrophobic interaction with the hydrocarbon chain of His116, Thr118, Gly119, Gly120, Asp123, Gly145, Arg146, Leu148, Thr151, Gly152, Gly153, Thr154, Tyr199, Ser217, Ile218, and Lys221 (Figure 1). This compound binds with an enzyme in a good conformational position, with proximity to the catalytic site of TP, including Arg202, Ser217, and Lys221.[17]
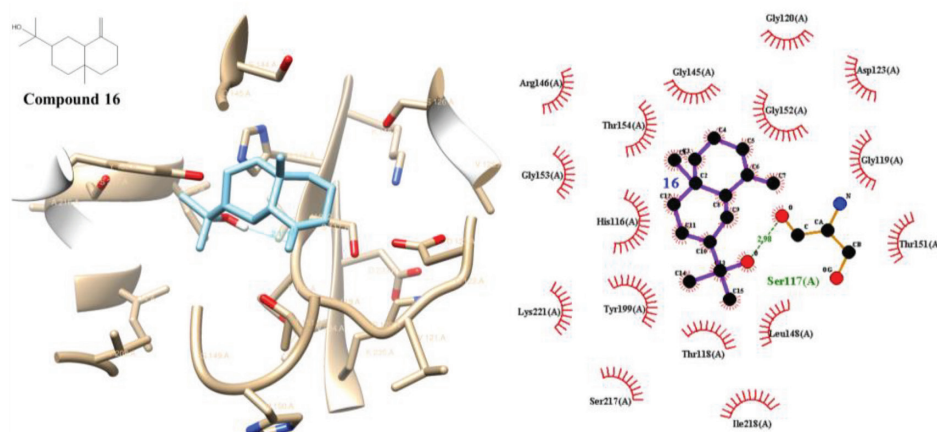
Figure 1 Binding mode of compound 16 toward human TP (2WK6)

The essential oils, which contain the most terpenoid compounds may play a role in pharmaceutical, food, and cosmetic applications. The biological effects of certain terpenes have been reported in a broad range of therapeutic areas, including anticancer chemotherapy, anti-inflammatory, antimicrobial chemotherapy, antioxidant, and anti-parasitic activities. This has led to widespread drug research and development.[18] Beta-eudesmol, a sesquiterpene from RLO. seems to be a promising compound, that binds effectively to the TP enzyme. This enzyme might have a possible role in the pathogenesis of cancer. There have been several previous reports about the beneficial roles of β-eudesmol in anticancer chemotherapy. For example, it had *in vitro* and in *vivo* activities against a wide range of cancers, including lung cancer, colon cancer, liver cancer, bile duct cancer/cholangiocarcinoma (CCA), gastric cancer, melanoma, and leukemia.[19] The mechanism of action of β-eudesmol against cancer cells was reported in cholangiocarcinoma cell lines *via* inhibition of STAT1/3 phosphorylation, heme oxygenase (HO)-1 activation, and NF-kB expression.[20] Therefore, the mechanisms of action of β-eudesmol *via* TP inhibition require further exploration.

In this particular study, even though the plant RL is rare and endangered, all compounds identified by GC-MS analysis from this plant are commercially available as pure chemical reagents which can be obtained without invasion of this plant's resources. This study paves the way for further drug development from active compounds of RLO, as a new class of cancer chemotherapy. It demonstrates that this rationale of *in silico* prediction is an approach that can be used to screen and design drug candidates, which is less time-consuming and provides essential information to prioritize drug discovery and ongoing development processes.

Conclusion

This computational analysis revealed that β-eudesmol, selected from all of the compounds identified by GC-MS analysis from RLO, showed the best binding affinity towards human TP, so could be the start point of further cancer chemotherapeutic development.

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Conflicts of Interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of Dust Collector for Electric Cast Saw in Reduction of Dust and Noise during Cast Removal Procedure

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Abstract:

Background: Heavy noise and air pollution, both of which are classified as occupational health hazards, were produced during the cast removal procedure.

Objective: The purpose of this article was to design and build a dust collector that could operate with an oscillating saw, to reduce plaster dust and noise during cast removal, protecting healthcare workers and patients from occupational hazards.

Methods: A dust collector was designed and fabricated. The experiment was divided into two groups: five trials for cast saw testing with a vacuum cleaner and five trials for cast saw testing with a vacuum cleaner and a dust collector. Acoustic levels as well as aerosol detection were tested. A dual coil spring could work as a force moderator in this application. When a user applies forces to the cast surface, this spring set returned the cast saw and saw blade to a neutral position, promoting safety.

Results: The traditional cast removal group had higher average acoustic levels in a closed room during every experiment (LAeq), measuring 79.3 dBA, compared with the dust collector group, measuring 77.9 dBA, while the dust collector group had slightly higher 8-hour TWA and LCpeak. Total particle concentration was lower in the dust collector group (-0.0235 mg/m^3) than in the traditional cast removal group (0.005 mg/m^3).

Conclusion: This apparatus may protect patients from overpressure applied to the cast surface. During acoustic tests, the average noise levels differed only slightly between the two groups. In terms of dust containment, a dust collector linked to a vacuum cleaner performed better during the cast removal procedure. In the future, robotic technology and sensor applications may be adapted for this machine.

Keywords: Cast removal; Electric cast saw; Dust collector; Plaster of Paris; Oscillating saw

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Introduction

The human skeleton is made up of living tissues that respond to load and support the rest of the human body's tissues, such as muscles, ligaments, tendons, and so on. However, fractures or injuries to bone tissue can compromise its integrity, necessitating orthopedic surgery and immobilization methods such as intramedullary nails, external fixators, or osteosynthesis plates. There are numerous fixation devices available for fracture immobilization, which can be classified as external or internal fixators, based on their use.[1] Since ancient times, various materials have been used to help immobilize fractures for non-operative management, such as simple wooden splints and rags, plaster of Paris, fiber and soft casts. Plaster of Paris ($2CaSO_4.H_2O$) bandages remain one of the most popular materials, having first been used in the nineteenth century. It is made up of calcium sulphate and water. It is created by partially dehydrating gypsum ($CaSO_4 \cdot 2H_2O$) at 120°C. When mixed with water, it emits heat and hardens to a porous mass in 5 to 15 minutes. The reason for its popularity is that it is inexpensive, non-irritant, and simple to use.[2] The removal of a circumferential shell of casting material after applying a plaster cast is an important skill for physicians. In this step, physicians will also require a cast saw to remove a plaster cast in certain circumstances, such as removing a cast for reassessment, splitting open a tight cast, removing a wet cast, removing a foreign body underneath the cast, removing a cast to rule out an underlying infection, splitting a cast for airline travel, splitting or removing a cast for suspected compartment syndrome, and removing or trimming an incorrectly applied cast.[3]

The oscillating cast saw was designed to attack any rigid object, but it has the potential to occasionally damage soft tissues. Thermal or abrasive (or both) cast saw injuries

may occur during cast removal operations.[4] According to one study, using the safety strip reduced the number of simulated skin touches, when compared to casts removed without the safety strip. Heat transfer was reduced by the safety strips, preventing temperatures at the cast-skin interface from exceeding 50°C. Finally, there was no increase in pressure beneath the casts with the safety strip present after splitting the cast.[5] However, two factors that should be considered when using a cast saw are noise and air pollution. A study found that the mean equivalent continuous noise levels of orthopedic cast clinics were 77.8 dB, the mean noise levels adjusted for an 8-hour day were 76.6 dB, and the mean peak noise levels in adult orthopedic clinics were of the order of 140.0dB. It should be noted that the National Institute of Occupational Safety and Health considers levels above 85 decibels (dB) to be harmful.[6] A study found 2.5-g and 10-g particulate matter (PM2.5 and PM10), also known as coarse particles, with the mean particle concentration in the casting room measured by laser photometer over 5 hours and 50 minutes, being 378.1 g/m^3. When inhaled, this fraction enters the thoracic but not the alveolar parts of the human respiratory system.[7] Exposure to coarse PM was associated with an increase in asthma diagnosis prevalence, hospitalizations, and emergency department visits in children, whereas long-term PM2.5 exposure primarily reduces the vital capacity of lung function in the elderly. Furthermore, PM2.5–10 has a greater negative impact on conductive airway function than PM2.5.[8,9]

As stated above, the purpose of this article was to design and fabricate a dust collector, combined with an oscillating saw, in order to reduce plaster dust and noise during the cast removal procedure, thereby protecting healthcare workers and patients from occupational hazards.

Materials and Methods

The method of design and testing method for a dust collector is shown below.

Machine Design

Normally an electric cast saw is connected to a vacuum cleaner to prevent plaster dust from spreading. However, dust can leak due to a gap between the saw blade and cast. Again, normally nothing is used to absorb noise during the cast removal procedure. Finally, in the absence of a protection mechanism, the control of saw blade depth is solely dependent on the physician's skill, which could result in patient injury. As a result, the authors created a dust collector to aid in improved function of the attached vacuum cleaner. This machine would be designed to be combined with an electric cast saw and a vacuum cleaner without the use of drill holes, screws or bolts. This apparatus's main structure was made of acrylic. To fill the gap between a cast surface and a dust collector, a sheet rubber strip was attached to the lower edge of a dust collector. To protect against mechanical injuries during the cast removal procedure, a dual coil spring was applied. Figure 1 depicts the dust collector drawing.
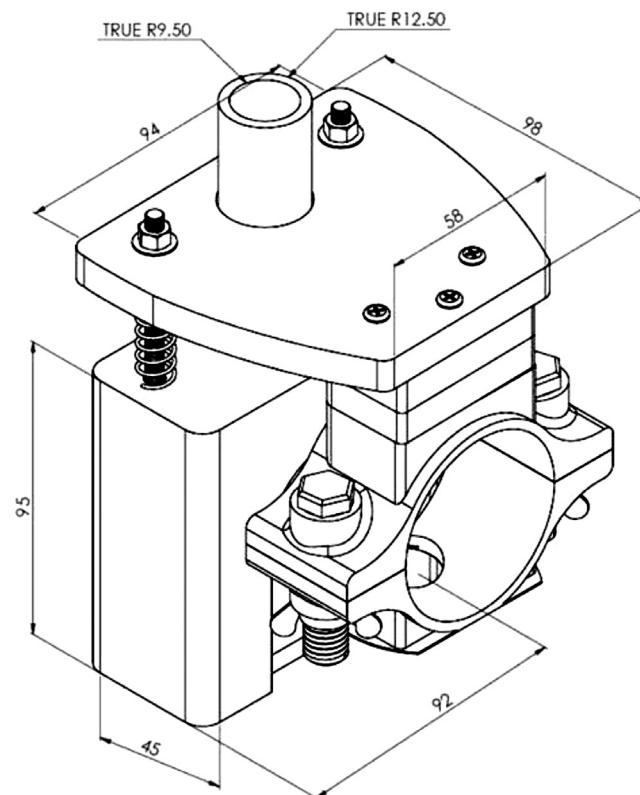
Figure 1 Dust collector's drawing (millimeter)

Experimental Design

The experiment consisted of two groups; five trials for a cast saw with vacuum cleaner testing and five trials for a cast saw with vacuum cleaner and dust collector apparatus. For each experiment, a realistic arm model with plaster cast was placed on the same modified cardboard base within a closed room (Figure 2). The same physician modified all plaster casts, using the same type and amount of undercast padding and plaster of Paris. The same doctor performed all cast cutting operations. Figure 3 illustrates an example of a cast removal operation. There was no cast removal procedure

for at least 5 minutes before, during, and after each experiment. Each group's cast cutting procedure was run continuously, followed by a one-hour wait before beginning the next procedure. Each experiment used the Larson Davis LxT2 Sound Level Meter at the same distance as well as the same electric cast saw. To collect larger dust particles, the Universal PCXR8 air sample pump was placed below the operation site.

For all experiments, an oscillating saw 'OSCIMED ERGO SG-OSC-180' 230V 180W speed 12000 to 21000 /min, noise level 65-78 dB and a vacuum cleaner 'OSCIMED ERGO SG-OSC-206-1' 220-240V 50-60Hz 1000W, noise level 60-70 dB, suction 1800 mm water column (40 Litres/sec) were used.

Figure 2 The position of an arm model with plaster cast

Figure 3 The use of a dust collector amalgamated with an oscillating saw and a vacuum cleaner

Acoustic Test[10]

All acoustic trials were carried out with a Larson Davis LxT2 Sound Level Meter. The sound level meter was placed 95 cm away from the center of the plaster cast in horizontal axis and 35 cm above the center of the plaster cast in vertical axis. The equivalent continuous sound level (LAeq) and the C-weighted peak sound pressure level (LC$_{peak}$) were averaged. The following formula was used to calculate the daily noise dose:

$$D = [C_1/T_1 + C_2/T_2 + C_n T_n] \times 100$$

Where D is the daily dose, C_n is the total time of exposure at a specified noise level, and T_n is the exposure duration for which noise at this level becomes hazardous.

Using the following formula, the daily dose can be converted into an 8-hour TWA (time-weighted average):

$$TWA = 10.0 \times \log(D/100) + 85$$

Aerosol Test[11]

The aerosol particles were detected using a Universal PCXR8 air sample pump during all experiments. The total aerosol mass of all tests was compared before and after particulate testing. A cassette for the sampling filter was placed 95 cm below the center of the plaster cast, while a cassette for the blank filter was placed 65 cm away from the center of the plaster cast on the parallel axis. The following formula was used to calculate the concentration of total particulate in the air volume sampled:

$$C = \frac{(W2 - W1) - (B2 - B1)}{V} \times 10^3$$

Where C is the concentration of total particle (mg/m^3), W1 is the mean tare weight of filter before sampling (mg), W_2 is the mean post-sampling weight of sample-containing filter (mg), B_1 is the mean tare weight of blank filter (mg), and B_2 is the mean post-sampling weight of blank filter (mg).

Results

The same healthcare team carried out all of the experiments. Five plaster casts were cut by the oscillating cast saw with the vacuum cleaner and five by adding the dust collector, making a total of ten. When cutting during the tests, an integrated dual coil spring regulated pressure. When a user applied forces to the cast surface, this spring set then pushed the cast saw and a saw blade back into a neutral position, promoting safety. The following are the sound level and dust particle measurements:

Acoustic Levels

The traditional cast removal group had higher average acoustic levels in a closed room during every experiment, (LAeq), measuring 79.3 dBA, compared with the dust collector group, measuring 77.9 dBA, whereas the dust collector group had slightly higher 8-hour TWA and LCpeak than the traditional cast removal group. Table 1 displays the noise data.

Table 1 The noise exposures during cast cutting in a closed room

Procedure	Average noise levels			
	LAeq (dBA)	8-hr TWA (dBA)	LCpeak (dBC)	Standard Deviation (S.D.)
Traditional cast removal group	79.3	60.9	97.7	18.4
Dust collector group	77.9	61.7	99.0	18.7

Aerosol Levels

Table 2 shows the total aerosol mass of blank filter compared with sampling filter of each group. The dust collector group had a lower total particle concentration (-0.0235 mg/m^3) than the traditional cast removal group (0.005 mg/m^3).

Table 2 The dust concentrations in the dust collector and traditional cast removal groups

		Procedure	
		Traditional cast removal group	Dust collector group
Blank filter	Before	$B_1 = 0.0122$ g	$B_1 = 0.0119$ g
	After	$B_2 = 0.01225$ g	$B_2 = 0.0123$ g
Sample filter	Before	$W_1 = 0.0143$ g	$W_1 = 0.0136$ g
	After	$W_2 = 0.01445$ g	$W_2 = 0.0136$ g
Air volume		20 L	17 L
Concentration of total particle		0.005 mg/m^3	-0.0235 mg/m^3

Discussion

Although oscillating cast saws are widely used for cast removal operations, some problems have arisen, as previously stated. A dust collector was created to aid in the operation of a cast saw linked to a vacuum cleaner. This apparatus could protect the patient from overpressure that may be applied to the cast surface. However, at times human error can occur during this procedure. It should be attached, via a secure plate that is inserted beneath the cast to reduce the rate of error. The average noise levels were only slightly different between the two groups during acoustic tests. As a result, this novel technique may not help during cast removal procedures, in reduction of potentially hazardous sound. However, the noise levels in all trials did not exceed the NIOSH recommended exposure limit (REL) for occupational noise exposure (85 dBA as an 8-hr TWA), as recommended by the National Institute for Occupational Safety & Health (NIOSH)[10]. Therefore, if a researcher needs to improve sound absorption efficiency, acoustic absorbing materials, such as nylon fiber, cotton fiber, polypropylene, and rubber should be amalgamated with the newly designed acrylic structure.[11]

Furthermore, the dust concentration measurement results in this article did not deviate from the primary hypothesis. The traditional method revealed a large gap between the saw blade and cast, resulting in marked air born dust production, whereas the dust collector method could confine the plaster dust to a small area. During the dust collector group's test, however, an unusual occurrence occurred. According to Field blanks definition in Quality Assurance Guidance Document 2 - US EPA. (n.d.); If the weight change between pre- and post-field blank weighing exceeds 30 g, contamination may occur during transportation or at the sampling site.[12] In this experiment, the weight difference between pre- and post-field blank weighing in this experiment was - 0.0235 g. The dust collector group's negative total particle concentration was caused by an increase in dust from the mean post-sampling

weight of the blank filter in both groups. This phenomenon could be caused by dust particle fluctuation within a closed room.

Another obvious result is an increase in the mean post-sampling weight of the sample-containing filter in the traditional cast removal group, whereas the dust collector group was the same before and after the sampling procedure. To summarize, a dust collector could help the vacuum cleaner work better during the cast removal procedure.

A future study should incorporate a water spray within the acrylic box of a dust collector for absolute dust confinement to improve its capability. Robotic technology is another technique that can be used to reduce human error. For the next dust collector model, the manipulator with actuator motors, a modified gearbox, and a servo motor attached to an oscillating saw could be used.[13] To improve patient safety, sensor technology similar to that used in robot navigation applications should be used to detect the thickness of cast and undercast padding.[14]

Conclusion

A novel dust collector was designed and manufactured in response to the health risk posed to patients and healthcare workers during the cast removal procedure. This device demonstrated how to support the operation of a cast saw and a vacuum cleaner. When compared to the traditional cast removal group, the results showed that it could reduce aerosol spreading while having no discernible difference in acoustic level. Other devices, such as a secure plate, acoustic absorbing materials, and water spray, should be added to improve the safety of patients and medical personnel. Robotic technology and sensor applications can be adapted for this machine in the future. Eventually, the authors hope that this apparatus will inspire anyone to improve their environmental safety workplace in order to reduce risks during biomedical procedures.

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Monkeypox: Prevalence, Diagnostics, and Prevention

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Abstract:

Human monkeypox is a viral zoonotic disease that occurs mostly in the rain forests of central and western Africa. However, the disease recently emerged in the United Kingdom resident who had recently traveled to Nigeria. There are now more than 4100 confirmed infections in nearly 46 countries where outbreaks do not usually occur. Monkeypox virus is a double-stranded DNA virus that found to infect tissues ranging from the heart and brain to the ovaries and lymphoid tissue. It has a clinical presentation very similar to that of ordinary forms of smallpox, including flulike symptoms, fever, malaise, back pain, headache, and characteristic rash. Given this clinical spectrum, differential diagnosis to rule out smallpox is very important. There are no definitive therapies for human monkeypox; however, the smallpox vaccine can protect against the disease. Effective prevention relies on isolation of infected patients or animals, contact tracing, limiting the respiratory exposure to infected patients and ring vaccination with smallpox vaccine.

Keywords: Monkeypox virus, Tecovirimat, JYNNEOOS vaccine

Introduction

Monkeypox outbreaks that have started to reappear in the last month caused by the monkeypox virus (MPXV), a member of the genus *Orthopoxvirus* (family Poxviridae, subfamily Chordopoxvirinae).[1] Human monkeypox is a zoonotic disease, similar to variola virus (which causes smallpox), vaccinia virus (the virus used in the smallpox vaccine), cowpox virus, ectromelia, and camelpox.[1-5] Human monkeypox is clinically almost identical to ordinary smallpox, and therefore, since the global eradication of smallpox in 1977, much attention has been paid to monkeypox as a smallpox-like disease.[2,3] Additional attention was brought to Monkeypox recently when, in May 2022, it reemerged in western countries, causing a cluster.[2] According to the World Health Organization (WHO) nearly 4100 cases have been identified outside the virus's usual areas of circulation.[4,5] However, only a handful of articles in the medical literature have described the continuing occurrence of human monkeypox. Therefore, here we will review the current state of knowledge about human monkeypox, emphasizing epidemiologic characteristics, clinical features, diagnosis, treatment, and prevention.

Epidemiologic Characteristics

Monkeypox has presumably occurred in sub-Saharan Africa for thousands of years, ever since humans acquired the virus through direct contact with infected animals.[1-5] The reservoir for MPXV is still unknown, although there is data to suggest that monkeys are, like humans, incidental hosts and that the reservoir is likely to be one or more species of rodents or squirrels of secondary forest in central Africa.[1,6] Monkeypox was not recognized as a distinct disease until 1970, when the elimination of smallpox from Democratic Republic of the Congo (DRC) revealed the continued occurrence of a small-pox-like illness in rural area.[1]

Initial epidemiologic studies conducted from 1970-1979 detected a total of 47 cases of human monkeypox near sub-Saharan African rainforests, of which 38 occurred in the DRC and the remainder in Cameroon, the Central African Republic, Gabon, Cote d' Ivoire, Liberia, Nigeria, and Sierra Leone.[1,7] All cases in the DRC occurred in areas bordering tropical rainforests and appeared to be associated with animal contact. Seven were fatal and secondary transmission was determined to be the most likely cause of infection in 4 cases, with secondary attack rates of 7.5% among household family members and 3.3% among all susceptible contacts.[8]

WHO conducted an active surveillance program in the DRC, where 338 of the 404 recognized African cases occurred from 1970-1986.[8,9] An animal source of infection was suspected in 245 of the 338 cases, and secondary transmission from a human source was presumed in the remaining 93 cases. The majority of cases occurred in children, with a mean age of 4.4 years. These increases in secondary transmission rate (3 times the 9% rate for cases in the 1970s) and the age distribution were thought to reflect waning immunity since the discontinuation of vaccination. The longest documented chain of infection consisted of only 4 generations of person-to-person transmission, indicating that MPXV had little potential for epidemic spread.[10] Serological surveys from this period involving vaccine-naive children found that 12%–15% of participating children had antibodies against MPVX, but most did not have a history of compatible illness, suggesting that subclinical infection also occurred.[8,10-12]

From 1986-1992, only 13 cases were reported and none were reported from 1993-1995.[3,6,10-12] However, in 1996-1997, more than 500 suspected cases of monkeypox were reported in Kasai-Oriental province, DRC.[13] The percentage of secondary cases was much higher (78%) and the fatality rate much lower (1%–5%). Between 1 January

1998 and 31 December 2002, a total of 1265 suspected cases were reported to the DRC Ministry of Health, with 88 were due to MPXV based on PCR and culture.[1] Of the laboratory-confirmed cases, patient age ranged from 10 months to 38 years, with a mean age of 16.5 years and a median of 15.5 years. 26% of patients were <10 years of age, and 73.2% were <25 years of age.

In 2003, United State reported the first occurrence of MPXV disease cluster in outside Africa. Of 72 reported cases, 37 human cases were laboratory confirmed during an outbreak.[1] Native prairie dogs (*Cynomys* sp.) housed with rodents imported from Ghana in western Africa to US were thought to be the primary source of outbreak, as most of the infected people became sick after contact with pet prairie dogs.[1,14-16] Although viral transmission appeared to be by direct contact with an infected prairie dog, two of the patients provided direct care to their infected children.[14] Unlike African patients, most patients from the US outbreak had a mild, self-limited febrile rash illness; 18 were hospitalized, although some were hospitalized for isolation precautions only and there were no deaths associated with the outbreak.[17,18] Two child patients had serious clinical illness. The first developed severe encephalitis a very rare complication of monkeypox and required intensive care unit hospitalization.[14,17,18] The second child was hospitalized with profound painful cervical, tonsillar lymphadenopathy and diffuse pox lesions, including lesions throughout the oropharynx.[14,17,18] Interestingly, only one child patient had a generalized rash similar to that seen in previous African patients, whereas many patients developed only localized lesions on the hands and fingers associated with direct contact with infected animals.[14,17,18] In 2018 and 2019 United Kingdom (UK) and Singapore reported first cases of monkeypox infections and later 2021 UK alone reported three additional domestic cases.[19,20]

Currently, there is an ongoing monkeypox outbreak of west African clade MPXV in predominantly Europe, with cases also in the Americas, Asia, Africa, and Australia.[2,4,5] The outbreak was initially reported in May 2022 in a United Kingdom resident who had recently traveled to Nigeria.[2,4,5] As of April 2022, 33 countries have confirmed cases, totaling to 1489 cases with 45 suspected in over 10 other countries.[4,5] The 2022 outbreak is exhibiting a different transmission pattern compared to other outbreaks outside of Africa with an increased frequency of human to human transmission, particularly in prolonged close contact.[2,4,5,21,22] Most of the cases observed so far have been in men, with a significant number being among active homosexual men, suggesting that sexual activity is a likely method of transmission.[2,4,5,21,22] This is possibly due to having close contact with infectious skin lesions during sexual relations.[2,4,5,21,22] It should be noted however, that monkeypox is not considered to be a sexually transmitted disease. The US Centers for Disease Control and Prevention (CDC) reported genomic data showing that there are at least two strains of the monkeypox virus responsible for the outbreaks.[5] This finding suggests that the virus might have been circulating internationally for longer than was thought. No deaths from monkeypox have been reported outside Africa so far this year; however, 4.7% of people who have contracted monkeypox across seven countries in West and Central Africa in 2022 have died.[2,4,5,21,22]

Diagnosis

As the clinical picture of monkeypox is very similar to that of chickenpox and smallpox, definitive diagnosis is key to keeping natural disease under control or in the early detection of outbreaks.[14] The differential clinical diagnosis for patients with monkeypox, chickenpox, or smallpox

are shown in table 1.[1] Although clinical characteristics can be useful in distinguishing poxvirus infections from other causes of vesiculopustular rashes, laboratory confirmation is required for a definitive diagnosis. During active infection, laboratory confirmation can be performed by various diagnostic assays including virus isolation and electron microscopy, PCR, IgM and IgG ELISA, immunofluorescent antibody assay, and histopathologic analysis.[1,14,22-26] However, histologically, the lesions of monkeypox are similar to other viral exanthems due to variola, cowpox, varicella-zoster, and herpes simplex viruses and include ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation.[1] However, immunohistochemistry analysis, including use of either polyclonal or monoclonal antibodies against all orthopoxviruses, can differentiate between a herpes virus and poxvirus infection.[1,2,14,15,21-23,25-27]

Characteristic poxvirus virions showing the typical brick shape with lateral bodies and a central core would be expected to be observed under electron microscopy (Figure1).[4] Virus isolation, growing in mammalian cell culture (propagated in Vero E6 cells or BS-C-1) and characterization by various PCR techniques, followed by restriction fragment length polymorphism analysis or whole genome sequencing are considered to be definitive for the identification of MPXV.[1,2,14,15,21-23,25-27] Additionally, the availability of various real-time PCR assays that use panorthopoxvirus or MPXV-specific targets and DNA oligonucleotide microarray with the TNF receptor gene *crmB* has also been developed as another rapid method for species-specific detection of orthopoxviruses.[1,2,14,15,21-23,25-27]. Given the ease of transmission through direct contact and aerosol particles, specimens such as scab or other cutaneous tissues should be handled with care and collected aseptically with respiratory precautions.

The clinical features of human monkeypox closely resemble those of ordinary smallpox.[1-7,13,21,22,28] It was first reported as a human disease in a 9-month-old Zairean child in 1970.[7,8,29] It is believed that the virus is transmitted to humans during handling of infected animals or by direct contact with the infected animal's body fluids or lesions.[7,8,29,30] Person-to-person spread by large respiratory droplets during prolonged face-to-face contact can occur but is much less efficient than that seen with smallpox.[1-7,13,21,22,28] After a 10-14 day incubation period, prodromal illness with fever, malaise, and swollen lymph nodes is observed in most patients before rash development.[1-7,13,21,22,28] Other signs and symptoms of monkeypox include chills and/or sweats, headache, backache, sore throat, cough, and shortness of breath. Lymphadenopathy, which has been observed in 90% of unvaccinated patients, is not a common feature of smallpox and is therefore considered to be a key distinguishing feature of monkeypox (Figure 2 and 3).[1-7,13,21,22,28] Lymph node enlargement can occur in the submandibular and the cervical or inguinal regions. The prodromal period generally lasts 1–3 days before the occurrence of the typical maculopapular rash.[1-7,13,21,22,28] During the first week of the rash, the patient is considered to be infectious and should be isolated until all scabs separate and throat swab PCR results are negative.[1-7,13,21,22,28] The mean diameter of the skin lesions is 0.5–1 cm, and the clinical progress is very similar to that of ordinary smallpox lesions.[1-7,13,21,22,28] During a 2–4-week period, lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation (Figure 2).[1-7,13,21,22,28] The rash starts mainly on the trunk, but can spread in a peripheral distribution to the palms and soles of the feet. Lesions can be observed on mucous membranes, in the mouth and tongue, and on genitalia.[1-7,13,21,22,28]

In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%–5%), and encephalitis (<1%) can be observed in patients infected with MPXV.[1-7,13,21,22,28] The fatality rate is 10%, and death generally occurs during the second week of the disease.[1-7,13,21,22,28]

Table 1 Differential clinical diagnosis of patients with monkeypox, smallpox, and chickenpox.

Characteristics	Monkeypox	Chickenpox	Smallpox
Recent contact with exotic animal	Yes	No	No
Recent exposure to a patient with vesicular rash	Yes	Yes	Yes
Time period			
Incubation period, days	7–17	7–17	12–14
Prodrome period, days	1–4	2–4	0–2
Rash period (from the appearance of lesions to desquamation), days	14–28	14–28	10–21
Symptom			
Fever, severity	Moderate	Severe	Mild or none
Malaise, severity	Moderate	Moderate	Mild
Headache, severity	Moderate	Severe	Mild
Lymphadenopathy, severity	Moderate	None	None
Lesions			
Depth (diameter in mm)	Superficial to deep (4–6)	Deep (4–6)	Superficial (2–4)
Distribution	Centrifugal (mainly)	Centrifugal	Centripetal
Evaluation	Heterogeneous rash	Heterogeneous rash	Heterogeneous rash
Time to desquamation, days	14–21	14–21	6–14
Frequency of lesions on palms or soles of feet	Common	Common	Rare
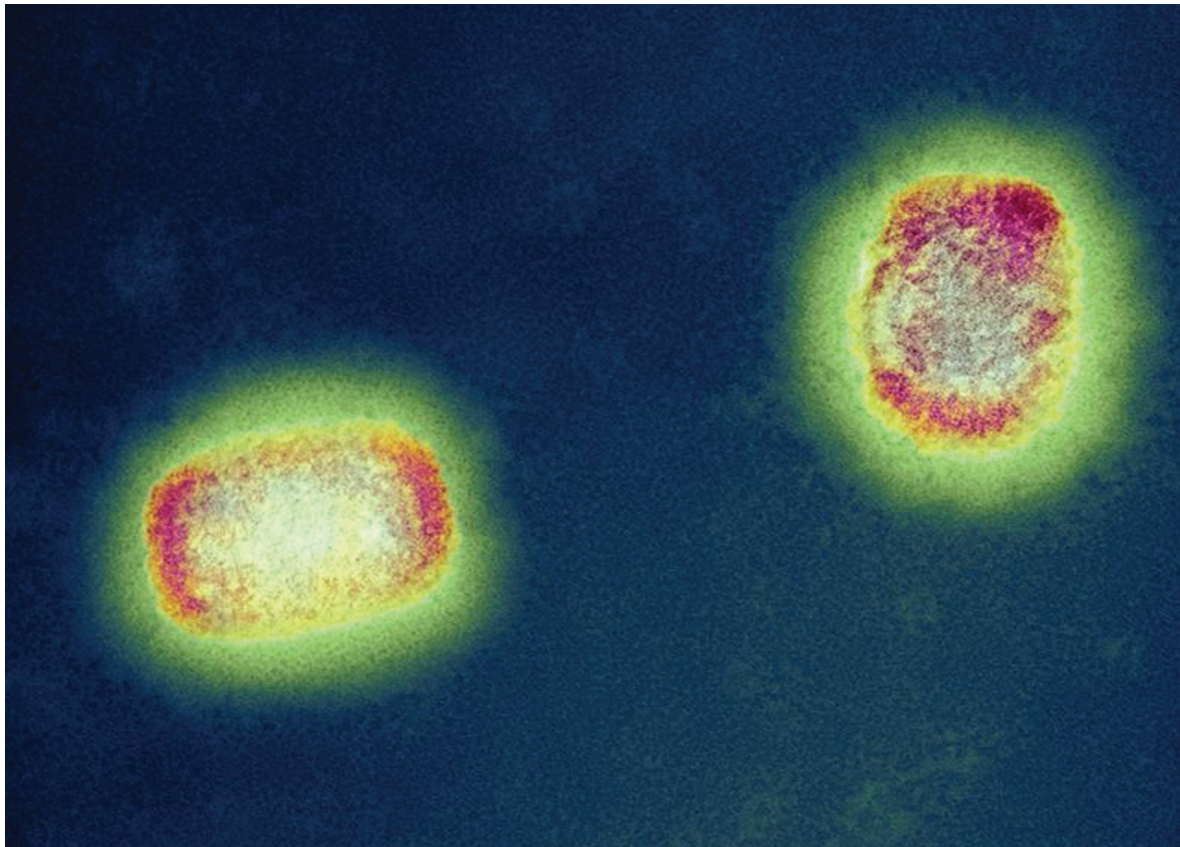
Figure 1 The monkeypox virus, a brick shape with lateral bodies and a central core shown here in a colored electron micrograph[4]

Figure 2 A, A 3-year-old African boy with monkeypox and axillary lymph node enlargement *(arrow)*. B, A 7-year-old African girl with monkeypox and bilateral inguinal lymphadenopathy *(arrows)*. For both patients, lymphadenopathy was the main differential diagnostic criterion that distinguished monkeypox from smallpox. C, A 7-year-old girl from Tokondo village, Kasai-Oriental province, Democratic Republic of Congo, with reported exposure to a dead monkey. Note the characteristic pustules on her back.[1]

Figure 3 Skin and soft tissue manifestations of monkeypox; the early skin lesions are vesicles, which form into pustules that typically have an umbilicated centre. Their size can be variable. These skin lesions ulcerate and heal with crusting and scabbing.[19,20]

Genomic epidemiology of monkeypox virus

MPXV is a 197 kb linear DNA genome including 190 nonoverlapping ORFs > 180nt in length.[1,7,26,31] The central coding region sequence (CRS) at MPXV nucleotide locations 56000–120000 is highly conserved and flanked by variable ends that include inverted terminal repeats (ITRs), like with other orthopoxviruses (Figure 4).[31] The core region of the MPV genome encodes structural and essential enzymes and is like the variola virus by 96.3%. Despite this, the terminal regions of the MPV genome that

encode virulence and host-range factors differ considerably. Comparing the genomes of MPV and smallpox virus demonstrates that MPV is a distinct species that evolved from an orthopoxvirus ancestor independently of variola virus.[31] The 2022 monkeypox virus is most closely related to viruses associated with the exportation of monkeypox virus from Nigeria to several countries in 2018 and 2019, including the UK, Israel, and Singapore.[31] The outbreak virus differs by a mean of 50 SNPs from the 2018–2019 viruses, which is far more than one would expect given the estimated substitution rate for Orthopoxvi-
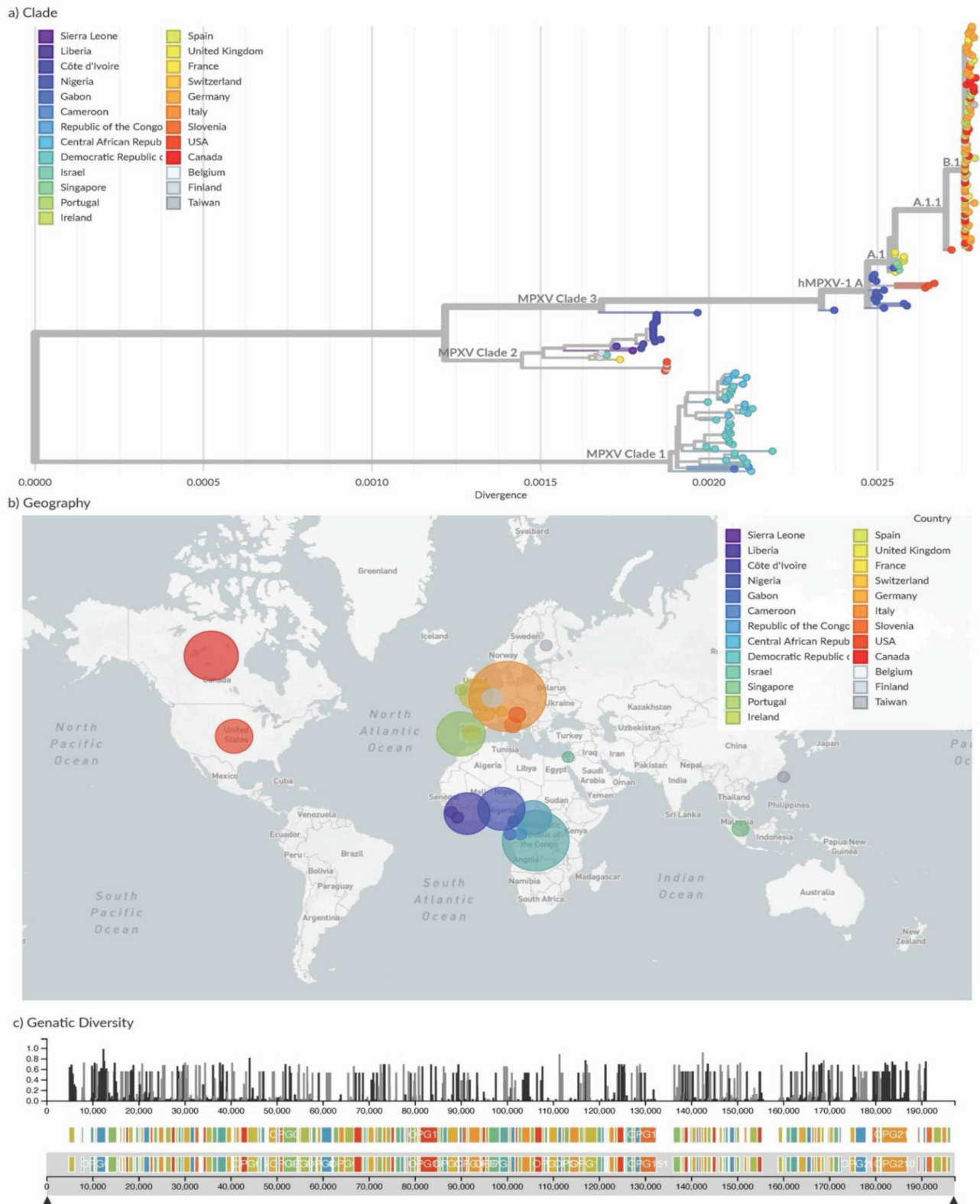
Figure 4 Genomic epidemiology of monkeypox virus, built with nextstrain/monkeypox[31], enabled by data from GenBank. a) Phylogenetic analysis of monkeypox clade, b) geographical distribution of different clades and c) genomic diversity.

ruses. Gene loss events have already been observed in the context of endemic Monkeypox circulation in Central Africa, and they have been linked to human-to-human transmission.[31] The microevolution scenario also implies that genome sequencing may provide sufficient resolution to track virus spread in the context of the current outbreak. There are two clades of monkeypox virus: West African and Congo Basin (Central African). Although infection with the West African monkeypox virus may cause significant sickness, the disease is typically self-limiting. The case-fatality ratio for the West African clade has been estimated to be less than 1%, but it may surpass 10% for the Congo Basin clade.

Prevention and Treatment

Unfortunately, eradication of monkey-pox is not possible because of the existence of an animal reservoir.[1-7,13,21,22,28] However, vaccination with vaccinia virus (smallpox vaccine) is highly protective against infection with MPXV.[1-7,13,21,22,28,32] Researchers in the 1960s showed that monkeys could be successfully immunized against monkeypox by smallpox vaccination.[30] Additionally, not only were reduced numbers of human monkeypox cases observed in Africa among persons who were vaccinated, many of the cases were extremely mild (with very few lesions), and some cases may have been subclinical.[1] Because the virus that causes monkeypox and the virus that causes smallpox are so closely related, smallpox vaccination may also protect against monkeypox. According to African investigations, smallpox vaccination is at least 85% effective in preventing monkeypox. For these reasons, the Centers for Disease Control and Prevention recommends pre-exposure vaccination for research persons, health care workers, anyone who has direct contact with suspected MPXV-infected animals or infected persons, and laboratory workers who handle specimens that may contain MPXV.[2,4,5,21,22] JYN-

NEOS™ (also known as Imvamune or Imvanex) has been approved in the United States for the prevention of monkeypox and smallpox.[2,4,5,21,22] In terms of postexposure treatment, vaccination within 4 days after initial close contact with a confirmed monkeypox case is recommended by the Centers for Disease Control and Prevention; however, vaccination should be considered up to 14 days after exposure.[2,4,5,21,22] It is unknown whether a person with severe MPXV infection will benefit from treatment with immune globulin, and such therapy may be considered as a prophylactic for use in an exposed person with severe immunodeficiency in T cell function for whom smallpox vaccination would be contraindicated.[1,2,4,5,21,22]

There are currently no directly licensed antiviral drugs available for the treatment of MPXV infection.[21] In the 1950s, a number of thiosemicarbazone derivatives were found to inhibit the replication of vaccinia virus. Specifically, methisazone became the first antiviral drug to be introduced into clinical use, but it was fairly toxic when administered systemically and is no longer in use.[1] Cidofovir is a broad-spectrum antiviral drug that has activity against many DNA viruses, including MPXV, and treating cytomegalovirus retinitis in patients with AIDS.[1] Cidofovir has not been used to treat orthopoxvirus infection in humans but has been tested extensively in laboratory animals.[33] The antiviral therapy, tecovirimat (Tpoxx), is approved for smallpox by US FDA and is being studied for monkeypox treatment. Studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses.[19] Clinical trials in people showed the therapy was safe and had only minor side effects.[19] In addition, tecovirimat was given to one patient who had monkeypox.[19] The patient received 600 mg of the therapy twice a day for 2 weeks and experienced a shorter duration of illness and viral shedding.[19]

For the ongoing outbreak, countries are taking a variety of precautions to prevent transmission and contain the outbreak.[2,4,5,21,22] In the United States, post-exposure smallpox vaccination are being performed and alerts are going to the general populace and directed towards homosexual and bisexual men.[2,4,5,21,22] Similarly, the United kingdom has purchased smallpox vaccines and is investigating other related treatments and has issued health advisories as well.[2,4,5,21,22] Some countries, such as Thailand, are taking precautions such as airport screening or travelers from at-risk areas, planning purchase of smallpox vaccines, and screening local monkeys and imported livestock.

Conclusion

Monkeypox occurs mainly in the jungles of central and western Africa. The disease, unlike smallpox, is a typical zoonosis in that most cases occur as a result of direct contact with an infected animal. The symptoms of the disease in humans can be very similar to those of smallpox, chickenpox, or other causes of vesiculopustular rash. As global monkeypox cases continue to rise, smallpox vaccines are thought to be effective against monkeypox infection. Although the vaccines are considered safe and effective for use in people with smallpox infection, they have had limited testing against monkeypox. Therefore, accurate and rapid laboratory diagnostics, contact-tracing, and as well as the ability to quickly vaccinate any high-risk contacts are paramount in controlling an outbreak.

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Potential conflicts of interest

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