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# Lower Plasma Selenium Level in Primary Malignant Bone Tumors: A Survey Research

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## ABSTRACT

**Objective:** To compare plasma selenium levels in primary bone tumor patients with clinically healthy Thai subjects.

**Materials and Methods:** A cross-sectional study on plasma selenium of primary bone tumor patients aged above 12 years old was obtained at Siriraj Hospital. The plasma samples were used for selenium assay by Electrothermal Atomic Absorption spectrometry method. The plasma selenium levels were compared with the clinically healthy Thai subjects or within primary bone tumor groups (age: below or above 30 years, gender: male or female, benign or malignant tumor, metastasis or non-metastasis).

**Results:** One hundred and nine primary bone tumor patients were included in this study. Plasma selenium level in clinically healthy Thai subjects aged more than 30 years old was significantly higher than a primary bone tumor group (121.71 ± 19.96 µg/L vs 111.88 ± 23.62 µg/L, mean difference -9.83, p-value = 0.017). The plasma selenium levels within the primary bone tumor patients did not exhibit significant differences when compared across genders, age groups below and above 30 years old, benign and malignant tumors, or between metastatic and non-metastatic tumor cases.

**Conclusion:** A patient with a history of malignant bone tumors tends to have a lower level of plasma selenium than normal people. However, the study of selenium supplementation for those who have a higher risk of developing malignant bone tumors is needed in the future.

**Keywords:** Selenium; Primary bone tumors; malignancy; metastasis; malignant bone tumor (Siriraj Med J 2024; 76: 333-338)

## INTRODUCTION

Selenium (Se) is a nonmetallic element that has chemical and physical activities like Sulfur and Tellurium. Selenium is distributed in several human tissues; approximately 27.5% is localized in skeletal muscle, 16% in the bone, and 10% in blood.[1] Since selenium is an element, it cannot be synthesized in the human body. Therefore, plasma selenium level is dependent on dietary intake. Selenium is found predominantly as selenomethionine and selenocysteine in foods such as bread, cereals, nuts, meat, fish, and other seafood, but the amount and the type of selenium in foods varies greatly and depends on the soil selenium content and composition.[2,3]

Selenium is an integral component of several selenoproteins. The first true selenoprotein identified was glutathione peroxidases (GPXs) which is one of the most important antioxidant enzymes.[4,5] GPXs protect cells against oxidative damage by reducing hydrogen

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peroxide to water and a wide range of organic peroxides with reduced glutathione, preventing lipid peroxidation and cellular damage from reactive oxygen species (ROS), reactive nitrogen species (RNS) and protecting immune cells from oxidative stress.[4-8]

For the time being, the morbidity and mortality rates of primary bone tumors in Thailand are still high due to late detection, delayed referral, and no tumor marker for the screening of bone tumors. Previous studies demonstrate the differences between plasma selenium and several types of cancer such as prostate cancer, bladder cancer[9], and lung cancer.[10] Also, a higher serum selenium level has been shown potential for cancer risk reduction. Therefore, the primary objective of this study is to compare the plasma Selenium level of the patient who was diagnosed with a primary bone tumor with clinically healthy Thai subjects. The secondary objective is to compare the plasma selenium level of patients with younger age (<30 years) and older age (>30 years) groups, type of tumor (benign or malignant) and with and without a history of tumor metastasis.

## MATERIALS AND METHODS

### Study population

After the ethical committee of Siriraj Hospital approved (COA no. Si 560/2016) the research protocol for this study, primary bone tumor patients aged more than 12 years who had a visit at bone and soft tissue tumor clinic, Siriraj Hospital (as their regular follow-up visit) between September 2016 and August 2017 were informed and consent for this cross-sectional study (the inform and consent were made for with both subjects and at least one of their parent if the subject age lower than 18 years old). The clinically healthy Thai subjects were defined as such based on physical examinations, laboratory tests, and responses to historical questionnaires. Their blood specimens were obtained during a routine check-up program at the National Cancer Institute in Bangkok, Thailand, as previously described.[11] For the primary bone tumor patients, blood samples were collected during their regular follow-up visits after surgical treatment. The diagnosis of a primary bone tumor was confirmed by a histopathological report. We include osteoma, osteoid osteoma, osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, synovial chondromatosis, giant cell tumor, fibrous dysplasia, osteofibrous dysplasia, osteosarcoma, chondrosarcoma, fibrosarcoma, and chordoma in this study. The exclusion criterion was a subject with a history of selenium supplementation within 1 year before blood samples were taken.

### Sample size calculation

Using the average selenium level from our pilot study and the value for clinically healthy Thai subjects from Attatippaholkun W, et al.[11] alpha = 0.05, and beta = 0.2, 76 patients was calculated to be the minimum number of primary bone tumor patients needed for this study.

### Plasma selenium assessment

Plasma selenium assay has been reported elsewhere,[12] briefly, blood samples were collected after a 12-hour-fasting period. Heparinized plasma samples were used for selenium assay by the method of Electrothermal Atomic Absorption spectrometry (ETAAS) with Zeeman background correction with a GTA 110 graphite furnace and PSD-100 autosampler (Varian Australia Pty Ltd., Australia). The instrument parameters were 196.0 nm wavelength, 1.0 nm slit width, co-injection mode, and peak height in measurement mode. All the glassware and plasticware were washed with 5% (V/V) nitric acid, rinsed with ultrapure water, and finally dried at 60°C in a hot air oven. High-quality water, obtained using a Mill-Q system (Millipore), was used exclusively. All the chemicals used were of the highest purity available. All the plasma samples were stored in selenium-free plastic tubes and kept at -20°C until analyzed. Each plasma sample (5ml) was added with a matrix modifier containing 1% (v/v) $NiNO_3$ and 2% (v/v) Triton-X-100, to reach the final concentration of 1,000 mg Ni/ml and 0.1% (v/v) Triton-X-100. Samples were measured in triplicate. Appropriate blank measurements were obtained by repeating the procedure in the absence of the selenium standard solution.

### Statistical analysis

Plasma selenium level and demographic data were analyzed by Descriptive statistics in means, standard deviation, 95% CI for mean, number, and percent. Comparison of plasma selenium between primary bone tumor patients and healthy Thai subjects from the previous study.[11] The Shapiro-Wilk test was used for the normality test. For the comparison of the mean, the Student's t-test was used in normally distributed data and the Mann-Whitney U test in non-normally distributed data. All statistical analysis was performed using SPSS version 18 (Chicago: SPSS Inc).

## RESULTS

The average plasma selenium level of 109 primary bone tumor patients was 111.59 ± 22.57 µg/L while the

clinically healthy people were 116.94 ± 30.51 µg/L. There was no significant difference in the plasma selenium level between these 2 groups (mean difference = -5.35, p-value = 0.105). when stratified into younger (< 30 years old) and older (≥ 30 years old) age groups, no statistical difference was observed in the younger age group while in the older age group, a significantly lower plasma selenium was observed (121.71 ± 19.96 µg/L vs 111.88 ± 23.62 µg/L, mean difference = -9.83, p-value = 0.017) (Table 1). Regrettably, with the exception of age and gender, no additional demographic data was collected from the subjects. Consequently, this study was unable to compare and present the baseline characteristics of the clinically healthy individuals and the primary bone tumor patients. Among the primary bone tumor patients, no statistically significant differences in plasma selenium levels were observed when comparing between genders (male 115.32 ± 23.33 µg/L, and female 108.76 ± 21.73 µg/L, mean difference = -6.56, p-value = 0.134) (Table 1), age groups (< 30 years 111.08 ± 20.89 µg/L and ≥ 30 years 111.88 ± 23.62 µg/L mean difference = 0.80, p-value = 0.859), benign versus malignant bone tumors (112.35 ± 22.87 µg/L and 110.28 ± 22.26 µg/L, mean difference = -2.07, p-value = 0.647) or the presence versus absence of metastasis (101.92 ± 14.47 µg/L and 112.90 ± 23.19 µg/L mean difference = 10.98, p-value = 0.100) (Table 2).

There was also no statistically significant difference in plasma selenium levels among clinically healthy Thai subjects (116.94 ± 30.51 µg/L)[11] compared to either the benign primary bone tumor group (112.35 ± 22.87 µg/L, mean difference = -4.59, p-value = 0.250) or the malignant primary bone tumor group (110.28  22.26 µg/L, mean difference = -6.66, p-value = 0.189). However, within the primary bone tumor group, the plasma selenium level

**TABLE 1.** Plasma selenium level of clinically healthy subjects compared to primary bone tumor patients among ages and genders.

| Age | Gender | Plasma selenium level (µg/L)[a] | | p-value[c] |
|---|---|---|---|---|
| | | Clinically healthy subjects[b] | Primary bone tumor patients | |
| < 30 years | Male | 110.20±22.60 (n = 82) | 113.88±22.31 (n = 17) | 0.542 |
| | Female | 105.14±18.03 (n = 90) | 109.00±20.04 (n = 23) | 0.372 |
| | p-value[d] | 0.105 | 0.473 | |
| | Total | 106.95±19.84 (n = 172) | 111.08±24.22 (n = 40) | 0.242 |
| ≥ 30 years | Male | 168.52±46.60 (n = 15) | 116.13±24.22 (n = 30) | <0.001 |
| | Female | 118.52±17.47 (n = 37) | 108.62±22.03 (n = 39) | 0.539 |
| | p-value[d] | <0.001 | 0.193 | |
| | Total | 121.71±19.96 (n = 52) | 111.88±23.62 (n = 69) | 0.017 |
| All | Male | 125.22±39.60 (n = 97) | 115.32±23.33 (n = 47) | 0.115 |
| | Female | 112.74±23.76 (n = 127) | 108.76±21.73 (n = 62) | 0.268 |
| | p-value[d] | 0.004 | 0.134 | |
| | Total | 116.94±30.51 (N = 224) | 111.59±22.57 (N = 109) | 0.105 |

[a] Mean ± Standard Deviation
[b] Data from Attatippaholkun W, et al.[11]
[c] Comparison between clinically healthy subjects and primary bone tumor patients
[d] Comparison between male and female

**TABLE 2.** Demographic data of primary bone tumor patients and their plasma selenium level.

| | n (%) | Plasma selenium level (µg/L)[a] | p-value |
|---|---|---|---|
| Age group | | | |
| < 30 years | 40 (36.7) | 111.08 ± 20.89 | 0.859 |
| ≥ 30 years | 69 (63.3) | 111.88 ± 23.62 | |
| Benign/Malignant | | | |
| Benign | 69 (63.3) | 112.35 ± 22.87 | 0.647 |
| Malignant | 40 (36.7) | 110.28 ± 22.26 | |
| Metastasis | | | |
| Metastasis | 13 (11.9) | 101.92 ± 14.47 | 0.100 |
| Non-metastasis | 96 (88.1) | 112.90 ± 23.19 | |

[a] Mean ± Standard Deviation

of the malignant bone tumor was significantly lower than clinically healthy subjects (121.71 ± 19.96 µg/L)[11] in the older age group (>30 years) (109.88 ± 22.41 µg/L, mean difference = -11.83, p-value 0.020), especially chondrosarcoma (107.75 ± 22.24 µg/L, mean difference = -13.96, p-value 0.020). There is also a trend to lower plasma selenium levels in osteosarcoma in the advanced age group (102.25 ± 14.43 µg/L, mean difference = -19.46, p-value 0.06) as shown in Table 3.

## DISCUSSION

According to the study result, plasma selenium in primary bone tumor patients was not different from the normal average of plasma selenium in the normal Thai population. At the patient age under 30 years old, plasma selenium may not relate to the occurrence of primary bone tumor. However, a patient above 30 years old who was diagnosed with chondrosarcoma, shows lower plasma selenium levels than in the clinically healthy

**TABLE 3.** Comparison of plasma selenium level between the type of primary bone tumor and clinically healthy Thai subjects in the lower and older age group

| | Age < 30 years | | | Age ≥ 30 years | | |
|---|---|---|---|---|---|---|
| | n | Plasma selenium level (µg/L) | p-value[a] | n | Plasma selenium level (µg/L) | p-value[a] |
| Healthy Thai subject[c] | 172 | 106.95 ± 19.84 | | 52 | 121.71 ± 19.96 | |
| Benign tumor | | | | | | |
| Giant cell tumor | 11 | 111.09 ± 21.79 | 0.510 | 28 | 113.75 ± 25.95 | 0.130 |
| Fibrous dysplasia | 3 | 106.67 ± 16.62 | 0.981 | 9 | 113.78 ± 26.55 | 0.299 |
| All benign tumor | 26 | 111.12 ± 20.27 | 0.320 | 43 | 113.09 ± 24.51 | 0.062 |
| Malignant | | | | | | |
| Osteosarcoma | 13 | 109.46 ± 22.96 | 0.664 | 4 | 102.25 ± 14.43 | 0.062 |
| Chondrosarcoma | 1 | 131.00 | N/A | 16 | 107.75 ± 22.24 | 0.020 |
| All malignant tumor | 14 | 111.00 ± 22.80 | 0.469 | 26 | 109.88 ± 22.41 | 0.020 |
| All primary bone tumor | 40 | 111.08 ± 20.89 | 0.242 | 69 | 111.88 ± 23.62 | 0.017 |

[a] Comparison between clinically healthy subjects and primary bone tumor patients
[b] A value of clinically healthy Thai subject from Attatippaholkun W, et.al.[11]

Thai subjects (p-value < 0.05). This finding aligns with an earlier study[11] that in osteosarcoma plasma selenium level is lower than in the normal population.

Although many pieces of research showed lower levels of plasma selenium in relation to the occurrence of many types of cancer[9,10] and increased risk of cancer mortality.[13] Our cross-sectional study shows that only chondrosarcoma in a patient aged more than 30 years old shows a significantly lower level of selenium compared with the normal population. For the osteosarcoma patient aged more than 30 years, the average selenium level was 102.25 ± 14.43 µg/L seems to differ from clinically healthy Thai subjects in the same age group (121.71 ± 19.96 µg/L). However, we cannot demonstrate a statistically significant difference (p=0.06), which is probably because of our limited subject number in this study.

Several theories demonstrate the mechanism of selenium for cancer prevention. Selenium shows its antioxidant effects through selenoprotein (as selenocysteine[14] helping cell growth and survival. Also, selenium promotes anti-tumor immunity by modulating the immune system such as activating immune cells (e.g. macrophage, T-cells, neutrophil, and NK cells) to reverse the immunosuppressive environment in the tumor headed for anti-tumor immunity, and stimulating of pro-inflammatory cytokines such as IFNγ and TNFα release.[8]

Supplementation of selenium in patients with high risk for several kinds of cancer may have some benefits but there is still no recommendation to give individual high-dose selenium supplements for cancer prevention.[15] Also, no evidence demonstrates that selenium supplementation results in cancer prevention in the human.[16] Too high level of daily intake of selenium may lead to selenosis especially when selenium intake exceeds the Tolerable Upper Intake Level of 400 micrograms per day.[17] Also, there was a study that demonstrated that appropriate selenium levels of less than 130 µg/L were associated with decreased mortality.[18]

There are some limitations of our study. First, a selenium level of clinically healthy Thai subjects was collected at a different time point compared with the primary bone tumor patient. The average selenium level in clinically healthy Thai subjects probably differed since the development of food logistics and food science and technology. However, the mean selenium level of our population is not that much different from the earlier reported mean serum selenium level from the US population (125.6 µg/L).[18] Second, the information about the dietary intake of all patients was not collected and analyzed. Therefore, selenium levels in malignant bone tumor patients probably differed from the clinically healthy group due to poorer oral intake results from the tumor itself or cancer treatment. Third, additional factors that could influence the varying plasma selenium levels of our subjects, such as socioeconomic status (reflecting the ability to purchase selenium-rich foods), educational level (indicating knowledge regarding dietary choices), and geographic location (impacting soil selenium content), were not captured in our data collection. The plasma selenium levels observed in our study may have differed if these parameters were taken into account for correction.

## CONCLUSION

A group of patients with a history of malignant bone tumors tend to have a lower level of plasma selenium compared with the general Thai population. These could imply that selenium may be needed for the prevention of malignant bone tumors. The study of selenium supplementation for people who have a high risk for malignant bone tumors should be performed. In order to demonstrate the efficacy and the pathophysiology of selenium in malignant bone tumors.

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### Conflict of interest statement

The authors declare that they have no competing interests.

### Author contributions

Chatchawan Sutthipongkiat MD: Conceptualization, methodology, investigation, data curation, formal analysis, writing original draft preparation – review & editing.

Watcharee Attatippaholkun PhD: Conceptualization, methodology, investigation, formal analysis, writing – review & editing.

Sudarat Srisamutnak BNS: Methodology, investigation, writing – review & editing.

Saranatra Waikakul MD: Conceptualization, methodology, investigation, data curation, writing – review & editing.

Pojchong Chotiyarnwong MD, PhD: Conceptualization, project administration methodology, funding acquisition, investigation, formal analysis, supervision, writing – original draft preparation, review and editing, visualization, validation, supervision, corresponding author.

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# Effect of Thermoablation with pH Change on Giant Cell Tumor of Bone: An In Vitro Study

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## ABSTRACT

**Objective:** To evaluate the effect of pH on the apoptosis and necrosis rate of giant cell tumor of bone (GCTB) cells during thermoablation.

**Materials and Methods:** GCTB tissues were collected from 15 patients. Cells were incubated at 25 ºC , 37 ºC, 45 ºC, and 50 ºC, with the variation of the pH at 4.7, 5.6, 6.5, 7.4, 8.3, and 9.2 for 20 minutes (in triplicate for each condition). The effect of thermoablation and pH variation on GCTB cells death was evaluated by staining with Annexin V-FITC and propidium iodide solution after 3 days of incubation. The fluorescence intensity was evaluated by flow cytometry to evaluate the percentage of tumor cells death.

**Results:** Thermoablation alone increased the percentage of tumor cells death. However, when combined with an increase in pH, the percentage of GCTB cells death increased more. Conversely, lowering the pH did not increase the tumor cells death compared with thermoablation treatment alone, while changing the pH alone had only a low effect on increasing the percentage of GCTB cells death.

**Conclusion:** Thermoablation the temperature between 37 ºC and 45 ºC plus a pH level slightly higher than physiologic pH (between 7.4 and 8.3) for 20 minutes increased GCTB cell death. However, determining the optimum condition to kill tumor cells while causing minimal harm to normal cells requires more study.

**Keywords:** Thermoablation; pH; giant cell tumor of bone; in vitro (Siriraj Med J 2024; 76: 339-345)

## INTRODUCTION

Giant cell tumor of bone (GCTB) is a locally aggressive primary intermediate bone tumor, accounting for 6% of all primary bone tumors.[1,2] Extended intralesional curettage, together with bone grafting/cementing, is a mainstay surgical treatment for this condition.[3] However, intralesional curettage alone results in an approximately 15%–25% recurrence rate,[4,5] and thus adjuvant treatment is often recommended.[6] Adjuvant treatment, such as with ethanol,[7] phenol,[8] botulinum toxin,[9] raloxifene,[10] argon beam,[11] warm Ringer's lactate solution,[12] or liquid nitrogen,[13] can reduce tumor recurrence. However, in some situations, such adjuvant treatment is not suitable since it could damage nearby important tissues, such as nerves or arteries.[14] The comparison of adjuvant treatments for GCTB has been reviewed in other publications.[15,16]

A new generation of adjuvants are now becoming available from the successful use of certain drugs in osteoporosis treatment, since the target of antiresorptive drugs (i.e., bisphosphonates[17] and denosumab[18]) in such treatments. Bisphosphonates can reduce the local recurrence of GCTB, especially for patients who have undergone intralesional curettage, but is not recommended for those who have undergone wide resection.[19] Using denosumab for the treatment of GCTB was found to be related with osteonecrosis of the jaw or atypical long

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bone stress reactions during treatment and a rebound in hypercalcemia[20,21] after discontinuing denosumab for the treatment of GCTB. Malignant transformation is also possible during denosumab treatment, probably due to immunosuppression from the inhibition of RANKL.[22] The cost of these new drugs is also problematic for many developing countries. Hence, adjunctive therapy may serve as a viable consideration for patients encountering financial constraints.

Our group reported an alternative adjuvant technique using thermoablation[23,24] for the treatment of GCTB. This adjuvant has the benefits of being cheap and it will not damage nearby structures. In thermoablation, the process is performed after the extended intralesional curettage step has been done, whereby a 45 °C lactate-ringer solution (LRS) is irrigated into the GCTB lesion using a sterile IV set to a free flow rate for 20 minutes, followed by bone grafting or cementing and then augmentation of the bone, and finally wound closure. Unfortunately, not all tumor cells may be eradicated by the thermoablation, and some tumor cells can survive, causing a recurrence in the patient. Therefore, to improve thermoablation adjuvant therapy, we realized that something else would need to be included in the solution to ensure the death of all the tumor cells.

Some previous studies have reported apoptosis induction by changing the cellular pH by several mechanisms.[25] Matsubara et al., for instance, found that additional stress, such as extracellular pH, influenced the invasiveness and survival of osteosarcoma.[26] Therefore, we hypothesized that alteration of the pH of the solution that carries the heat for thermoablation after extended intralesional curettage could boost the tumor cells death rate without affecting normal cells. Consequently, the objective of this study was to examine whether thermoablation with a changed pH of the solution used for thermoablation could increase the percentage of tumor cells death without harming the normal osteocytes and chondrocytes *in vitro*.

## MATERIAL AND METHODS

### *Patients*

The protocol was approved by the Institutional Review Board (COA no. Si 711/2014). Included patients were those with giant cell tumor of bone (GCTB) confirmed by a pathological report from a tissue biopsy, who provided written informed consent the day before surgery, and agreed their left-over tumor tissue could be collected for the study. On the operation day, after the surgeon had performed the curettage and collected enough tissue for the pathological study, the remaining tissue samples were collected using a sterile technique and sent directly to the laboratory for analysis for this study. Cell preparation was conducted individually for each patient, ensuring there was no cross-contamination between patients. The procedure for each specimen was carried out on separate days.

### *Primary culture*

The giant cell tumor tissue samples were washed with sterile PBS and minced by a sterile blade. The tissue was digested in 0.5 mg/mL collagenase in serum-free DMEM supplemented with 100 U/mL penicillin and 100 mg/mL streptomycin at 37 °C for 30 minutes with gentle agitation. The mixture was filtered through a 70 mm cell strainer (Falcon®, Corning, NY, USA) to obtain a single cell suspension that was then washed 3 times with 10% DMEM by centrifugation at 900 g for 5 minutes. The obtained pellets were resuspended in 10% DMEM and the total cells were counted using a hemocytometer.

### *Differential pH and temperature treatment*

Cell suspensions of $1 \times 10^6$ cells/mL were aliquoted into 300 µL medium at different pH levels (pH 4.7, 5.6, 6.5, 7.4 (physiologic pH of blood), 8.3, and 9.2) in 0.5 mL Eppendorf tubes. The cell suspensions were incubated at 25°C (considered as room temperature), 37 °C (considered as body temperature), 45°C, and 50°C for 20 minutes. The cells in each tube were seeded in each well at 300,000 cells/well and incubated in a CO2 incubator at 37 °C for 3 days. The experiment is conducted in triplicate for every condition, except for the chondrocyte and osteocyte conditions, owing to the constrained availability of primary cells.

The temperature in this study was elevated to 45°C and 50°C, drawing upon the principles of hyperthermia-based therapies.[27] Also, temperatures above and below physiological conditions to investigate the potential impact of temperature variations on treatment efficacy. We selected a range of pH values from 4.7 (acidic) to 9.2 (alkaline) to explore the impact of acidity/alkalinity on treatment effectiveness. This range covers the physiological pH of blood (7.4). We include both acidic and alkaline environments to understand the potential impact of pH manipulation on the treatment's ability to kill tumor cells. However, the current understanding of bone cells behavior at extreme pH is limited.

### *Apoptosis analysis*

The Annexin V-FITC Apoptosis Detection Kit (Sigma, St Louis, MO) was used to measure the cytotoxic activity of the giant cells. The cells were resuspended in

500 µL binding buffer. The cell suspension was stained with 5 µL Annexin V-FITC and 10 µL propidium iodide solution. The tube was incubated at room temperature for 10 minutes and protected from light. The fluorescence intensity of the cell suspension was determined using a flow cytometer (FACSCalibur, BD Biosciences).

Thermoablation responder was defined as when the change in temperature resulted in a difference in the percentage of total cells death of more than 50%, while partial responder was a difference of 20%–50%, and non-responder meant less than 20% cell death difference between the different temperatures at pH 7.4. pH responder was defined as when the change in temperature resulted in a difference in the percentage of total cells death of more than 50%, while partial responder was a difference of 20%–50%, and non-responder meant less than 20% cell death difference between the different pH levels at the temperature of 37°C.

*Statistical analysis*

The percentages of cell death were assessed in relation to either a temperature of 37°C (under consistent pH) or pH 7.4 (under consistent temperature), compared with various alternative conditions. For instance, when examining a temperature of 45°C, the percentages of cell death for pH levels of 4.7, 5.6, 6.5, 8.3, and 9.2 were juxtaposed with those for pH 7.4 using a paired T-test. Similarly, when focusing on a pH of 8.3, the percentages of cell death at temperatures of 25°C, 45°C, and 50°C were compared with those at 37°C. A p-value below 0.05 indicated a statistically significant distinction. All statistical analyses and graph generation were conducted using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA). Error bars on the graphs denote the standard error of the mean.

## RESULTS

All the GCTB patient's demographic data enrolled in this study are shown in Table 1. Of the 18 included patients, 3 patients did not have a high enough cell count to undergo the full protocol. Only 15 patients had enough cells to go through all the experiments and be included

**TABLE 1.** Patient demographic data and the response of each patient to thermoablation and pH changes *in vitro*.

| Patient number | Sex | Age at surgery | Final diagnosis | Thermoablation response | pH adjustment response | Recurrent after surgery within 1 year |
|---|---|---|---|---|---|---|
| 1 | F | 32 | Recurrent GCTB of right proximal humerus with lung metastasis | Y | Y | N |
| 2 | M | 35 | GCTB of right distal femur | N | N | N |
| 3 | F | 25 | Recurrent GCTB of right distal femur | N | N | N |
| 4 | F | 56 | Recurrent GCTB of sacrum | Y | N | 7 months |
| 5 | M | 39 | GCTB of right distal radius | Y | N | N |
| 6 | M | 24 | GCTB of right proximal fibular | Y | N | N |
| 7 | F | 42 | GCTB of left acetabulum | Y | N | 1 year |
| 8 | F | 29 | Recurrent GCTB of right distal femur | P | N | N |
| 9 | M | 19 | GCTB of right distal femur | Y | N | 1 year |
| 10 | F | 30 | GCTB of left proximal tibia | Y | N | N |
| 11 | M | 54 | Recurrent GCTB with secondary ABC of right proximal tibia | N | N | N |
| 12 | M | 29 | Recurrent GCTB of right distal femur | Y | N | N |
| 13 | M | 31 | Recurrent GCTB of right distal femur | Y | N | N |
| 14 | F | 70 | GCTB left proximal tibia | Y | N | N |
| 15 | M | 37 | Recurrent GCTB of right distal radius | Y | N | N |

**Abbreviations:** GCTB giant cell tumor of bone, ABC aneurysmal bone cyst, M male, F female, Y yes (more than 50% of total cells death), N no (less than 20% of total cells death), P partially (20-50% of total cells death).

in the data analysis. We could obtain only one osteocyte and chondrocyte control from subject number 13, who had undergone a wide resection operation.

The profiles of the osteocyte and chondrocyte total cell death after treatment with the different temperature and pH solutions for 20 minutes are shown in Fig 1a and b. At temperatures 25 ºC, 37 ºC, and 50 ºC, across all pH levels, there is no discernible disparity in the percentage of cell death observed among osteocytes, chondrocytes, or tumor cells (Fig 3). When examining solely the temperature of 45 ºC, osteocytes exhibit a survival rate of approximately 40% within the pH range of 5.6-8.3, whereas chondrocytes demonstrate survival rates exceeding 50% when the pH falls within the range of 6.5-7.4. However, chondrocyte survival notably diminishes as the pH increases to 8.3, resembling the pattern observed in tumor cells (Fig 3).

There were four response patterns of giant cell tumor cells to various temperature and pH, as shown in Fig 2, and as described in the following. Tumor cells from 1 patient (patient number 1) responded to either thermoablation or the increase in pH (pattern a). Two of the patients (patient numbers 14 and 15) responded only to thermoablation but not to the pH change (pattern b). The majority (patient numbers 4, 5, 6, 7, 8, 9, 10, 12, and 13) of patients showed a response (pattern c) whereby the percentage cell death increased after both the temperature and pH increased. Three patients (patient numbers 2, 3, and 11) did not show a response to both temperature or pH change; however, the total cell death in patients number 3 and 11 was more than 80% for all the temperature and pH levels tested, with the majority of cell death in both patients from the early apoptosis of the cells.

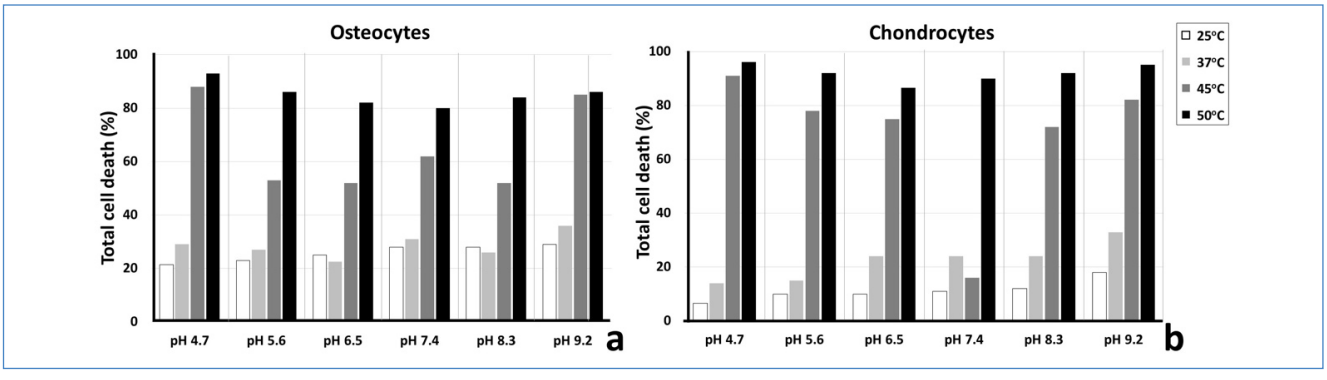


**Fig 1.** Percentage of osteocytes (a) and chondrocytes (b) cell death with various temperature and pH invitro.

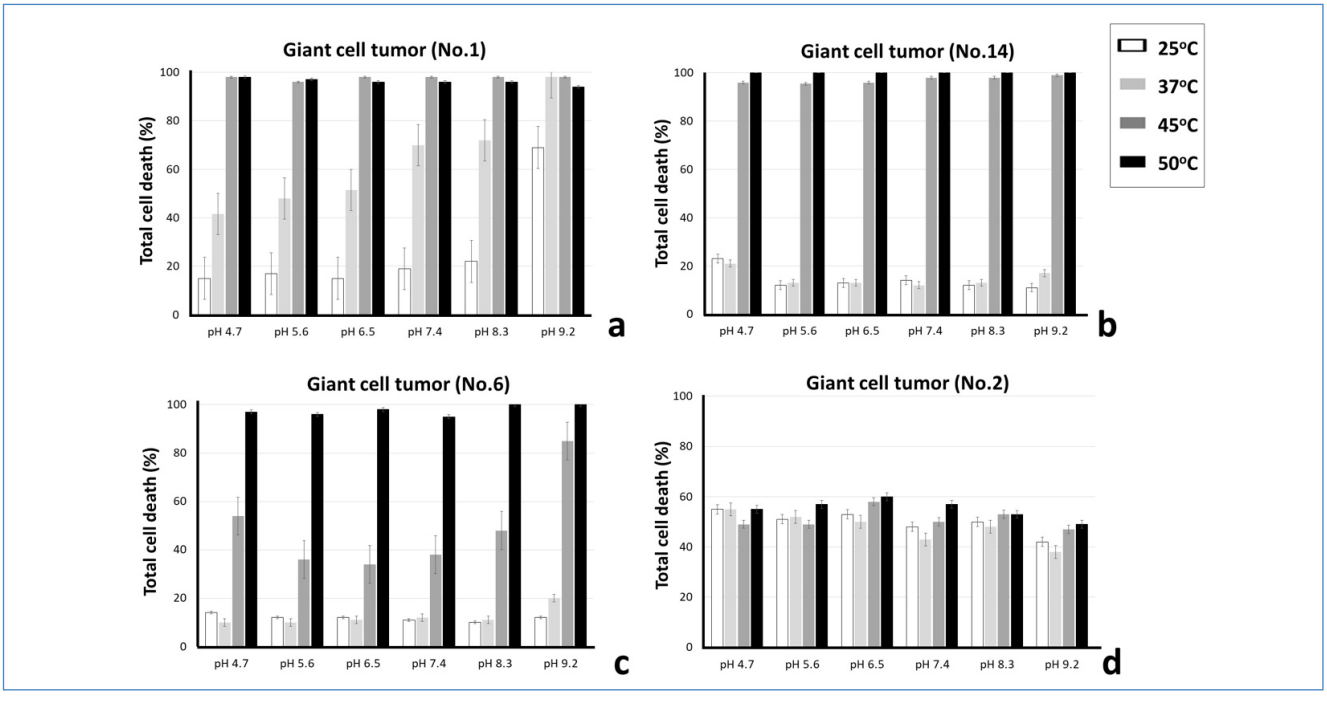


**Fig 2.** Shows 4 different patterns of giant cell tumor response to various temperatures and pH. The percentage of tumor cell death changes in response to both temperature and pH changes (a), only temperature but not pH changes (b), change of pH after temperature changed (c) and no different percentage of cell death after changes in both temperature and pH (d). The error bar represents the standard error of the mean.

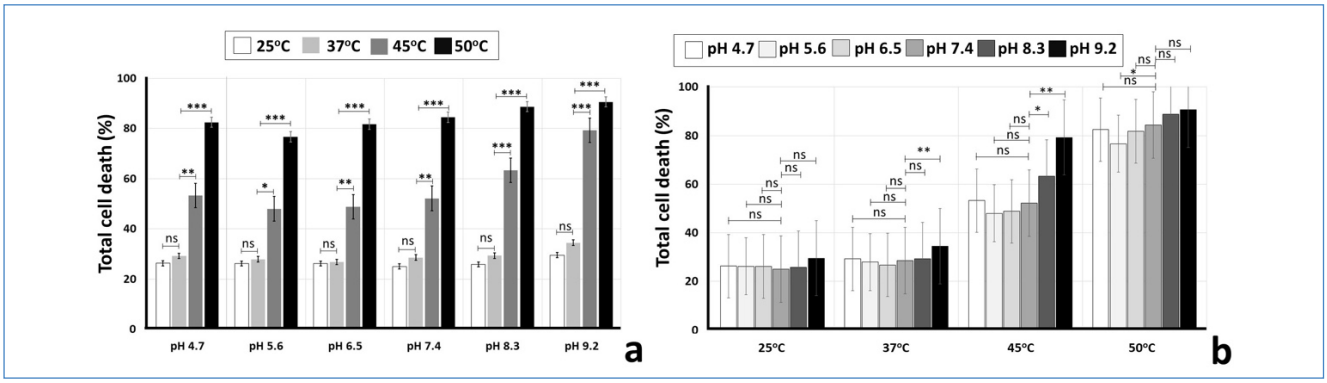


**Fig 3.** Shows the overall percentage of total GCTB cell death after being treated with various temperatures and pH for 20 minutes in vitro. Under consistent pH, the percentages of cell death at temperatures of 25 °C, 45 °C, and 50 °C were compared with those at 37 °C (a). Under consistent temperature, the percentages of cell death for pH 4.7, 5.6, 6.5, 8.3, and 9.2 were compared with those for pH 7.4 (b).
* = p-value < 0.05, ** = p -value < 0.01, *** = p-value < 0.001

The data from the 15 patients were pooled, and the average percentage of total cell death at various temperature and pH levels are shown in Fig 3. Thermoablation seemed to have some potential to increase the percentage of cell death. Changing the pH alone had only a low effect on inducing tumor cell death. However, the combination of increased temperature and pH around the tumor cells environment showed a trend in increasing the percentage overall giant cell tumor cell death.

## DISCUSSION

The standard treatment of choice of GCTB is still extended intralesional curettage with bone grafting/cementing.[3] The use of adjuvant treatment can increase the success rate of the surgery by decreasing the recurrence rate. Thermoablation has also been reported to be an adjuvant for extended intralesional curettage.[23,24] However, to the best of our knowledge, using a pH adjusted medium together with thermoablation has not been tested and reported yet. Consequently, we performed an *in vitro* study of GCTB treatment with thermoablation with a variation of the pH of the solution too. Thermoablation alone still showed promising results as an adjuvant for extended intralesional curettage in GCTB treatment. Increasing the temperature to around 45°C could increase the percentage of tumor cells death, while normal bone and cartilage cells still displayed a high percentage of survival. Increasing the pH of the solution to a basic range would probably be better than an acid range, in that it should provoke a greater percentage of overall tumor cells death. However, changing the pH alone seemed to have no additional effects over thermoablation alone. Both increasing and decreasing the pH of the thermoablation solution showed only slight or no effects on tumor cell death but increased the rate of normal cell death. Therefore, the adjustment of the pH of the thermoablation medium is probably not necessary, since the benefit gained from changing the pH was not much in the current condition involving 20 minutes incubation time.

Our study reveals four distinct patterns of GCTB tumor cell response to variations in pH and temperature (Fig 2). Unfortunately, the relatively small sample size in this study precludes the feasibility of conducting robust statistical analyses to isolate and identify the specific factors contributing to these divergent responses. Nonetheless, we acknowledge the potential importance of further exploring this phenomenon. Therefore, we propose that future genetic investigations may hold promise in elucidating the underlying determinants governing these response patterns, thereby addressing this intriguing aspect of our findings.

Upon scrutiny of the effects of extreme pH levels, particularly at 45°C, it becomes evident that both chondrocytes and osteocytes face challenges in survival under conditions of extreme acidity (pH 4.7) and extreme alkalinity (pH 9.2). However, intriguingly, tumor cells exhibit a potentially higher survival rate in acidic environments, contrary to previous findings.[25] This discrepancy prompts consideration of the intracellular pH dynamics within tumor cells, which notably resemble osteoclast-like multinucleated cells. A comparative analysis reveals that while chondrocytes maintain an estimated intracellular pH range of 6.9-7.2[28] and osteocytes around 5.8-6.2[29], osteoclasts exhibit a lower pH range of 5.5-6.0[30], attributed to their primary function in bone resorption. This distinction in intracellular pH levels leads us to postulate that giant cell tumors of bone (GCTB) possess an enhanced ability to withstand acidic environments relative to other bone cell types due to their inherently lower intracellular pH. Nonetheless, further investigation is warranted to elucidate the underlying mechanisms and

implications of this observed phenomenon, which could yield valuable insights into the behavior and resilience of tumor cells under acidic microenvironments, contributing to our understanding of tumor biology and potentially informing therapeutic strategies targeting pH-associated vulnerabilities in cancer.

Thermoablation also has some limitations in clinical practice. Although *in vitro* studies have shown promising results, in clinical practice, it is not easy to control the temperature of the solution at 45°C for all 20 minutes of irrigation. Also, this procedure prolongs the operation time and can lead to an increase in intra- and post-operative complications,[31] such as inappropriate blood loss or surgical site infection. Future research avenues in the utilization of thermoablation as an adjunctive therapy should prioritize efforts aimed at reducing thermoablation duration. This can be achieved through the implementation of commercially available intravenous (IV) fluid warmers such as the ThermoTouch IV Fluid Warmer (Smiths Medical), Level 1 Fluid Warmer (Meditech), or Warm-It Express IV Fluid Warmer (Parker Laboratories). These devices offer precise control over the temperature of the output fluid, maintaining it within the range of 34 to 42°C. Coupled with the identification of the optimal thermoablation period (up to 20 minutes) to minimize intraoperative time, this approach holds promise for mitigating post-operative complications.

This study has some limitations to note. First, the majority of our subjects were not primary cases of GCTB, since this study required a large amount of tumor cells. However, the majority of first diagnosed lesions of GCTB did not have enough tumor cells for both the pathological study and the *in vitro* study. We therefore needed to include the recurrent GCTB patients who tend to have a larger lesion size, which could give enough cells for the varied conditions in the *in vitro* study. Secondly, our experimentation involving osteocytes and chondrocytes is constrained by the availability of a singular set of experiments due to the limited quantity of cells obtainable from a single subject. Future studies investigating the survival rates of those normal cells, under relevant experimental conditions simulating the proposed treatment modalities may guide surgeons in selecting the most suitable adjuvant therapy for GCTB cases where the tumor is located adjacent to a joint. Thirdly, one of our patient's age was much more than the normal range of GCTB; however, all the patients in our study had a definite pathological study confirming GCTB.

In conclusion, the suggested optimal condition for the use of thermoablation as an adjuvant is a temperature around 45°C and pH between 7.4–8.3 for 20 minutes. Future studies should aim to abbreviate the duration of thermoablation by fine-tuning the temperature to fall within the range of 37 to 45°C and adjusting the pH between 7.4 to 8.3, all while employing a reduced thermoablation timeframe.

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**Disclosure:** The authors have no conflicts of interest to declare.

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# Distribution of Foot Arch Type and Associated Symptoms in Medical Students at Faculty of Medicine, Thammasat University

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## ABSTRACT

**Objective:** To determine the distribution of foot arch type, associated symptoms, and factors associated with moderate to severe pain

**Materials and Methods:** The cross-sectional study was collected data from 5th year medical students, Faculty of Medicine, Thammasat University in academic year 2020. The distribution of foot arch type used the footprint and classified by Harris imprint index (HII), Chippaux-Smirak index (CSI), Staheli index (SI). The associated symptoms were collected into pain and tightness. Pain score was rated by the volunteer using numeric rating scale (NRS) at each foot/leg separately.

**Results:** A total of ninety-eight medical students (196 feet) were recruited and analyzed. The distribution of foot arch type by HII, CSI and SI were 1) bilateral normal arched feet: 42.9%, 67.3%, 54.1% 2) bilateral pes planus: 8.2%, 12.2%, 21.4% 3) bilateral pes cavus: 25.5%, 6.1%, 5.1% 4) unilateral pes planus: 2%, 9.2%,15.3% 5) unilateral pes cavus: 21.4%, 5.1%, 4.1%, respectively. The most commonly associated symptom of pes planus was midfoot pain (17%) while pes cavus and normal arched foot were hindfoot pain (22.4% and 17.3%). The factor associated with moderate to severe pain was BMI ≥ 23 kg/m$^2$ (OR = 3.23, 95%CI 1.63 - 6.41, p-value = 0.001).

**Conclusion:** Bilateral normal arched feet were mostly found. Midfoot pain in pes planus and hindfoot pain in pes cavus and normal arched foot were the greatest symptoms. BMI was a risk factor.

**Keywords:** Prevalence; flatfoot; talipes cavus; students medical; pain (Siriraj Med J 2024; 76: 346-352)

## INTRODUCTION

The difference of foot arch such as pes planus (flatfoot) and pes cavus (high arched foot) cause ankle and foot pain, ankle deformity, walking instability, or frequent fall.[1] Additionally, some symptoms as knee pain, back pain, or leg muscle tightness might be found in patients with abnormal foot arch.[2] Pes planus is defined as a low medial longitudinal arch. The patient's symptoms showed a medial longitudinal arch collapse, prominent talar head along the medial border of the foot, hindfoot valgus, forefoot varus, medial ankle swelling, or too many toes sign. The causes of pes planus are divided into congenital causes such as idiopathic, tarsal coalition, etc., or acquired causes such as posterior tibialis tendon dysfunction, arthritis, and trauma.[1,3] Pes cavus is defined as a high medial longitudinal arch. The patient's symptoms showed an increased calcaneal pitch, hindfoot varus, tight plantar fascia, medial forefoot plantar flexion, metatarsus adductus, or peek a boo sign. The etiologies of pes cavus are 1) congenital as idiopathic cavus foot,

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2) neuromuscular disease such as Charcot-Marie-Tooth disease, poliomyelitis, and 3) trauma. Cavus foot is commonly caused by the idiopathic condition.[3] The abnormality of foot arch might be found in one side or both sides.[4] In Thailand, the prevalence of pes planus in 3rd year medical students at Chiang Mai University was 62%, divided into male 38% and female 24%.[5] The treatments usually use a foot orthosis or to properly choose a type of shoe following the different foot arch type. The foot orthoses as a customized insole, medial arch support, or wedge, were frequently used in the clinic because it helped to reduce pain, decrease foot pressure, and improve balance.[6,7]

Meanwhile, medical students had to study in the clinic level with extended standing or walking per a day. The foot and leg pain commonly found on study days might interfere with their learning. Foot deformity or other factors might cause their pain. Therefore, this study aims to determine the distribution of foot arch type by the footprint evaluation, associated symptoms, and the factors associated with moderate to severe pain in the 5th year medical students at Faculty of Medicine, Thammasat University.

## MATERIALS AND METHODS

This cross-sectional study was approved by the Human Research Ethics Committee of Thammasat University (Medicine), MTU-EC-RM- 2-092/63, on 4 June 2020.

The 5th year medical students of academic year 2020 studied in the orthotic and prosthetic clinic, department of Physical Medicine and Rehabilitation, Thammasat University. Data was collected from ninety-eight 5th year medical students. Inclusion criteria was age ≥ 18 years but history of fracture and/or surgery in ankle and foot were excluded.

After screening and receiving volunteers' informed consent, the demographic data, the associated symptoms, and pain score were collected by the research assistant. The footprints were performed by the Harris mat footprint method. The Harris imprint index (HII), Chippaux-Smirak index (CSI), Staheli index (SI) were used because of ease-of-use, rapidity, and low tech in terms of instruments. Moreover, the accuracy of HII, CSI, and SI was fair in screening of pes planus and pes cavus.[8] The HII, CSI and SI were conducted with computer-assisted program and measured by the rehabilitation physician. 1) The HII is a distance in centimeters (cm) measured between the origin of a horizontal line to its perpendicular contact point of a vertical landmark. The vertical axis (y-axis) halves the foot from the tip of the 2nd toe to the center of heel margin. The horizontal axis (x-axis) is drawn at 90 degree to the vertical axis starting from the most medial side to the most lateral side of the arch. HII score is inferred from the relative distance from the origin of x-axis to the y-axis where the medial side of the y-axis has positive score, and the lateral side of the y-axis has negative score. HII score of -1, 0, 1 is classified as normal arched foot, whereas HII score of -4,-3,-2 and +2, +3, +4 is defined as pes cavus and pes planus respectively.[8] 2) The CSI is the ratio of the arch at its narrowest (line b) to the forefoot at its widest (line a). Line b and line a should be parallel. CSI = b/a x 100. CSI for normal arched foot ranges from 25% to 45%. Pes cavus is defined as CSI ≤ 24% and Pes planus is classified as CSI ≥ 46%.[8] 3) The SI is the ratio of the arch at its narrowest (line b) to the heel at its widest (line c). Line b and line c should be parallel. SI = b/c. SI for normal arched foot ranges from 0.5 to 0.7. SI ≤ 0.4 is defined as pes cavus and SI ≥ 0.8 is classified as pes planus.[8] The associated symptoms divided into pain and tightness, which depended on the area. The areas of pain were forefoot, midfoot, hindfoot, ankle, leg, and back. The areas of tightness were sole, calf, and back. Pain score rated by the volunteer using numeric rating scale (NRS), which ranged from 0 of no pain to 10 of the most severe pain. They had to rate the pain NRS at each foot/leg separately. The pain NRS was classified into 4 groups as no pain (NRS =0), mild pain (NRS 1-3), moderate pain (NRS 4-6), and severe pain (NRS 7-10).[9]

### Sample size calculation

The sample size was calculated from the prevalence of pes planus in a study of 3rd year medical students of Chiang Mai University, Thailand (62%) under 0.05 alpha error and 0.1 maximum tolerated error.[5] Nighty-one was a sample size calculated, but the total number of 5th year medical students in the academic year 2020 was 98.

### Statistical methods

Categorical data is presented as frequency and percentages. Continuous data is presented as mean, median, standard deviation and interquartile range, dependent on nature of data. The factors associated with moderate to severe pain were tested using univariate logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were reported. A P-value of < 0.05 was considered statistically significant. The data was analyzed via STATA version 15.1.

## RESULTS

A total of ninety-eight 5th year medical students of academic year 2020 (196 feet) were recruited and analyzed

in this study. (Fig 1) The average age was 22.9±1.9 years. Female and male were 49% and 51%. Body mass index (BMI) was 22.3±4.6 kg/m$^2$. On studying days, the duration of standing/walking was 8.1±2.2 hour per day and flat shoes were frequently used (70.3%). The pain score was 4 (3,5) on right foot/leg and 4 (2,5) on left foot/leg. The pain score was mostly classified as moderate pain (right side 49.0% and left side 50%). (Table 1)

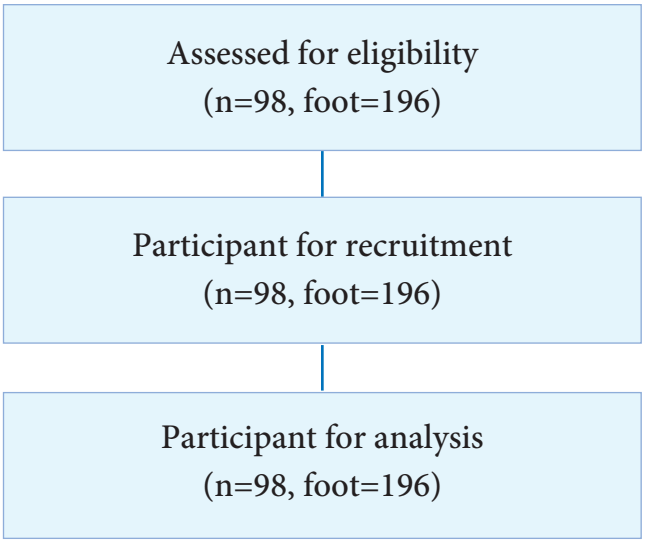



**Fig 1.** Flow of participants

The distribution of foot arch type by HII, CSI and SI are shown in fig 2. According to HII classification, bilateral normal arched foot was frequently founded (42.9%) following by bilateral pes cavus (25.5%), unilateral pes cavus (21.4%), bilateral pes planus (8.2%), and unilateral pes planus (2.0%), respectively. Meanwhile, CSI and SI classification showed bilateral normal arched foot was mostly founded (67.3% and 54.1%) following by bilateral pes planus (12.2% and 21.4%), unilateral pes planus (9.2% and 15.3%), bilateral pes cavus (6.1% and 5.1%), and unilateral pes cavus (5.1% and 4.1%), respectively.

Fig 3 shows the associated symptoms divided by the foot arch type. The associated symptoms of pes planus in HII, CSI, SI classifications and average from the three classifications were showed in fig 3a. The greatest symptoms of pes planus which averaged from HII, CSI and SI were midfoot pain (17.0%) followed by calf tightness (15.2%), and hindfoot pain (13.6%). Fig 3b shows the associated symptoms of pes cavus. The hindfoot pain (22.4%) was the mostly found in pes cavus averaged from HII, CSI and SI that followed by calf tightness (17.0%), and midfoot pain (15.1%). While the most associated symptoms of normal arched foot were hindfoot pain (17.3%) followed by back pain (17.0%), and leg pain (15.0%) showed in fig 3c.

The factors associated with moderate to severe pain (pain NRS ≥ 4) are shown in table 2. The BMI ≥ 23 kg/m$^2$ had a significant odds ratio (OR = 3.23, 95%CI 1.63 - 6.41, p-value = 0.001). In contrast, the OR of flat shoe had a statistical significance (OR = 0.49, 95%CI 0.24 - 0.98, p-value = 0.045).

## DISCUSSION

The most prevalent foot arch type by three-footprint evaluation (HII, CSI, SI) in 5$^{th}$ year medical students was bilateral normal arched feet. The most common associated symptom of pes planus was midfoot pain, however, both pes cavus and normal arched foot were hindfoot pain. The risk factor associated with moderate to severe pain was BMI ≥ 23 kg/m$^2$ (overweight and obesity) by WHO Asian BMI classification.

This study showed the most prevalent foot arch type was bilateral normal arched feet (HII 42.9%, CSI 67.3%, SI 54.1%). However, the second and third level of foot arch type were different following each classification. The HII classification showed normal arched foot, followed by pes cavus, and pes planus, respectively. Similarly, the previous study in the medical students of Nobel Medical College, Nepal, showed normal arched foot followed by pes cavus and pes planus, respectively.[10] In contrast with CSI and SI classification, this study showed that a normal arched foot was the most prevalent, then pes planus, and pes cavus, respectively. Likewise, the previous study in medical students of Mahatma Gandhi Medical College and Research Institute, India, and in the physiotherapy students of Isra Institute of rehabilitation sciences, Pakistan, showed the most prevalent foot arch type was normal arched foot followed by pes planus and pes cavus, respectively.[11,12]

In Thailand, a study in 3$^{rd}$ year medical students of Chiang Mai University showed the prevalence of pes planus by CSI classification was bilateral sides (38%) and unilateral side (24%).[5] In CSI classification, this study showed the distribution of pes planus was bilateral sides (12.2%) and unilateral side (9.2%). This may be because the cut-off point of CSI classification for pes planus diagnosis was different between the studies. However, the study in physiotherapy students of PDVVPF's, College of Physiotherapy, India, showed bilateral pes planus 11.25% by navicular drop test, arch index, and foot posture index.[13] Despite the prevalence of bilateral pes planus being similar in this study, they used the footprint measurement differently.

Pes planus present with a flattening of the medial longitudinal arch of foot. The plantar pressure of pes planus was high at the medial midfoot area during walking.[14,15]

**TABLE 1.** Demographic data

| Variable | Frequency (%) |
|---|---|
| Age (year) (mean ± SD) | 22.9 ± 1.9 |
| Gender | |
| Female | 48 (49.0) |
| Male | 50 (51.0) |
| BMI (kg/m²) (mean ± SD) | 22.3 ± 4.6 |
| Standing/ walking duration per day on studying day (mean ± SD) | 8.1 ± 2.2 |
| Shoe type on working day | |
| Flat shoe | 71 (70.3) |
| Sneaker shoe | 16 (15.8) |
| Sport shoe | 13 (12.9) |
| Sandal | 1 (1) |
| Pain score (median (P25, P75)) | |
| Right foot/leg | 4 (3,5) |
| Left foot/leg | 4 (2,5) |
| Pain score classification | |
| Right foot/leg | |
| No pain (NRS = 0) | 3 (3.1) |
| Mild (NRS 1-3) | 36 (36.7) |
| Moderate (NRS 4-6) | 48 (49.0) |
| Severe (NRS 7-10) | 11 (11.2) |
| Left foot/leg | |
| No pain (NRS = 0) | 5 (5.1) |
| Mild (NRS 1-3) | 35 (35.7) |
| Moderate (NRS 4-6) | 49 (50.0) |
| Severe (NRS 7-10) | 9 (9.2) |

**Abbreviations:** BMI = body mass index, NRS = numeric rating scale
Definitions of shoe type: flat shoe = a shoe with flat heels or no heels, sneaker shoe = a casual rubber-soled shoe, sport shoe = a shoe designed to be worn for sports, exercising, or recreational activity, sandal = an open-toed shoe consisting of a sole strapped to the foot
Definition of shoe type on working day was the same pair of shoes that the medical students always wear during study period.

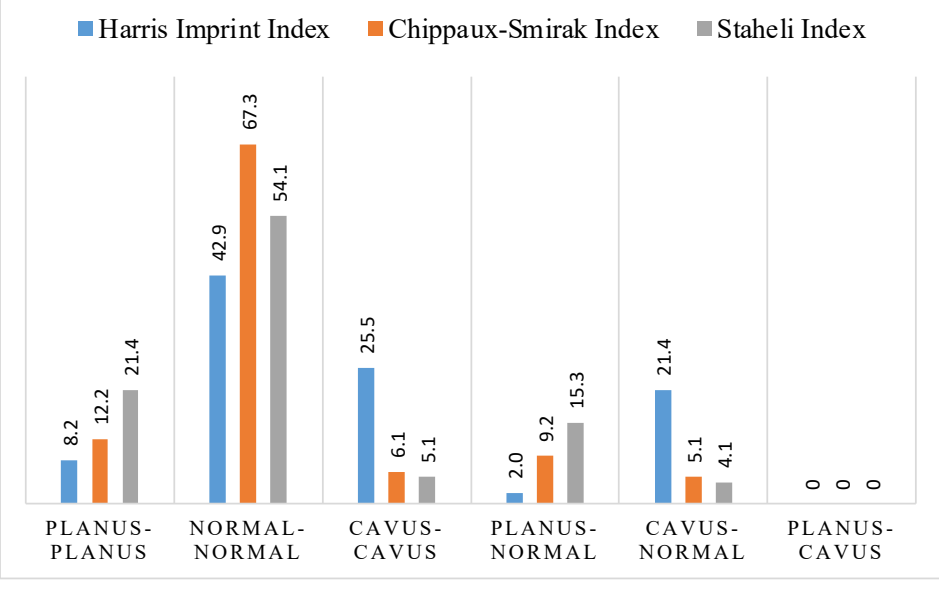
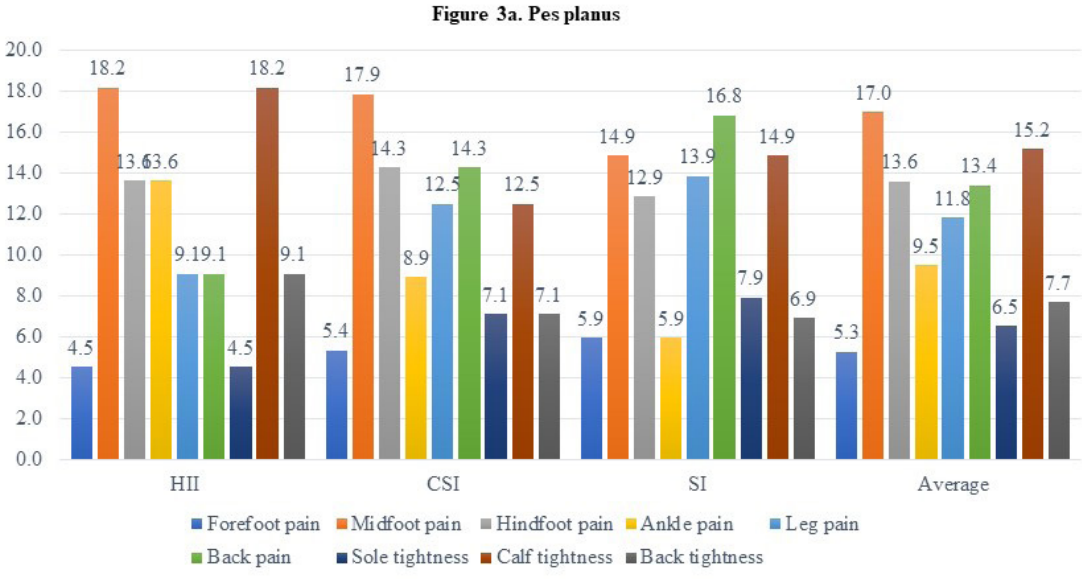
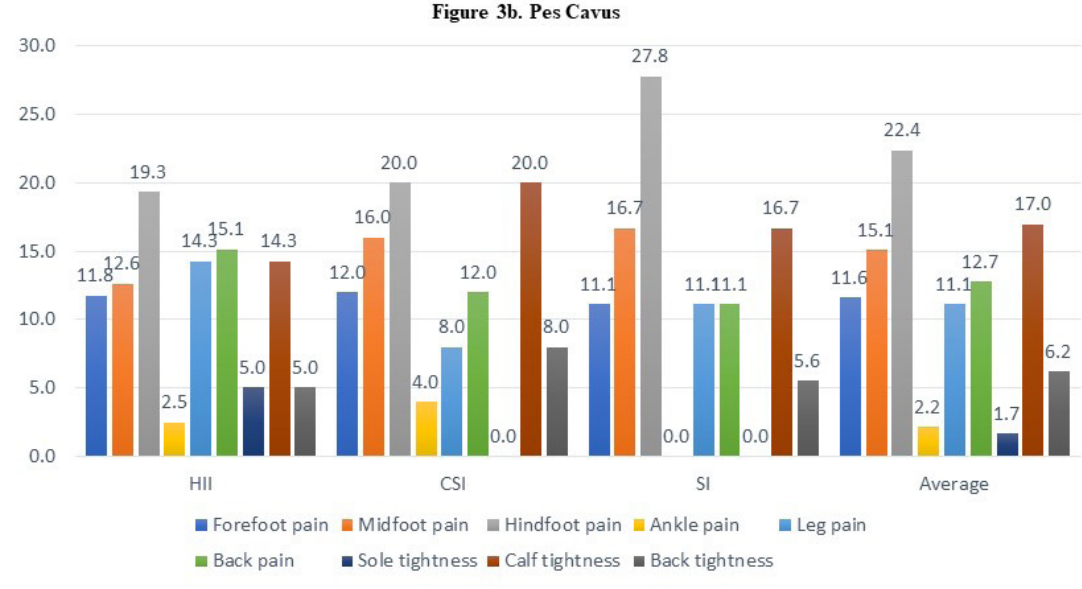



**Fig 2.** Distribution of foot arch type (%) by Harris imprint index (HII), Chippaux-Smirak index (CSI), and Staheli index (SI)



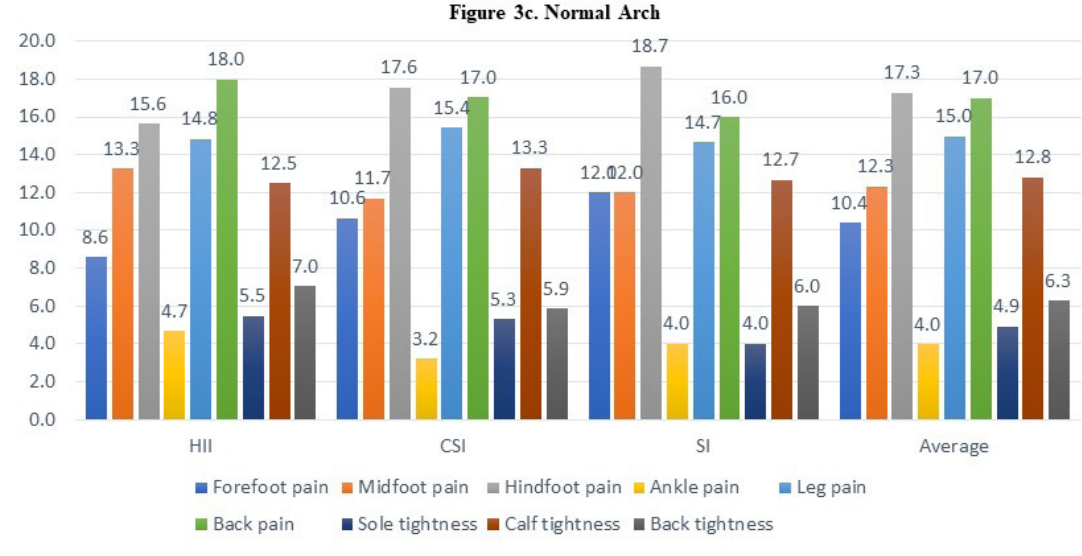




**Fig 3.** The associated symptoms (%) divide by foot arch type: Pes Planus (3a.), Pes Cavus (3b.), Normal arch (3c.)

**TABLE 2.** Factors associated with moderate to severe pain (NRS ≥ 4)

| Factors | Odds ratio | 95%CI | p-value |
|---|---|---|---|
| Gender | 0.97 | 0.55 - 1.72 | 0.929 |
| BMI ≥ 23 kg/m$^2$ | 3.23 | 1.63 - 6.41 | 0.001 |
| Standing/ walking duration ≥ 8 hours per day | 0.61 | 0.32 - 1.15 | 0.123 |
| Shoe type on study day | | | |
| Flat shoe | 0.49 | 0.24 - 0.98 | 0.045 |
| Sneaker shoe | 1.14 | 0.52 - 2.49 | 0.742 |
| Sport shoe | 1.31 | 0.55 - 3.11 | 0.540 |
| Sandal | 1.00 | - | - |
| Arch of foot type by Harris imprint index | | | |
| Pes planus | 1.07 | 0.39 – 2.88 | 0.898 |
| Pes cavus | 1.06 | 0.58 - 1.92 | 0.852 |
| Arch of foot type by Chippaux-Smirak index | | | |
| Pes planus | 0.90 | 0.42 - 1.92 | 0.786 |
| Pes cavus | 0.25 | 0.08 - 0.74 | 0.012 |
| Arch of foot type by Staheli index | | | |
| Pes planus | 1.00 | 0.53 - 1.87 | 0.993 |
| Pes cavus | 0.24 | 0.07 - 0.81 | 0.021 |

**Abbreviation:** BMI = body mass index
Definitions of shoe type: flat shoe = a shoe with flat heels or no heels, sneaker shoe = a casual rubber-soled shoe, sport shoe = a shoe designed to be worn for sports, exercising, or recreational activity, sandal = an open-toed shoe consisting of a sole strapped to the foot
Definition of shoe type on working day was the same pair of shoes that the medical students always wear during study period.

Therefore, this study mostly found the midfoot pain in the medical students with pes planus. However, pes cavus is characterized by an abnormally high medial longitudinal arch of foot. The plantar pressure of pes cavus was high at the heel and lateral forefoot area during walking.[15] Thus, the students with pes cavus mostly had hindfoot pain in this study. Low back pain was found in all groups of foot arch type. A previous study showed patients with pes planus had intermittent low back pain about 15% while this study had about 13.4%.[16] Interestingly, the previous study showed that foot posture was not associated with low back pain.[17]

Almost half of the medical students had moderate to severe pain (NRS ≥ 4) in their foot or leg. The researcher would like to evaluate the risk factors that are associated with moderate to severe pain. Moreover, the previous study showed that in patients with moderate to severe pain classification (NRS ≥ 4) their quality of life and functions might be interfered with.[9] This study found that medical students with overweight to obesity classification was a significant risk factor for moderate to severe pain (OR = 3.23, 95%CI 1.63 - 6.41, p-value = 0.001). Similarly, the previous study showed severe obesity was associated with the foot pain compared with the control group (OR 4.2, p<0.001).[18] Obesity in men and overweight to obesity classification in women were associated significantly with foot pain.[19] Flat shoes could help to reduce the foot pain. Therefore, medical students may be advised to control their BMI and choose flat shoes to prevent their foot pain.

Limitation of this study, the other foot conditions as hallux valgus, callus, and the shoe conditions as comfortable level in wearing, inappropriate shoe size that could cause their pain were not included. Also, the effect of pain on learning ability, quality of life, and psychological problems were not evaluated.

## CONCLUSION

Bilateral normal arched feet were mostly found in 5th year medical students, Faculty of Medicine, Thammasat University. Midfoot pain in pes planus and hindfoot pain in pes cavus and normal arched foot were the most common symptoms and BMI was a risk factor.

### Author contributions

Conceptualization: Paecharoen S. Methodology: Paecharoen S, Kritsanapraneet T. Formal analysis: Paecharoen S. Project administration: Paecharoen S, Kritsanapraneet T. Visualization: Paecharoen S. Writing – original draft: Paecharoen S. Writing – review and editing: Paecharoen S, Kritsanapraneet T. Approval of final manuscript: all authors.

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# Effects of Supervised Plyometric Training on Neuromuscular and Knee Functions for Late Phase Rehabilitation Program in Patients with Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial

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## ABSTRACT

**Objective:** To determine the effects of plyometric training programs on neuromuscular and knee functions during the late phase rehabilitation following anterior cruciate ligament (ACL) reconstruction.

**Materials and Methods:** Thirty participants, post-ACL reconstruction, were randomly assigned at their 6-month follow-up visit into two groups: 15 participants in each group (resistance or plyometric training group). Each group underwent two training sessions weekly for 8 weeks. The participants were assessed at baseline and after completed the training period for the single leg 6-meter timed hop, knee joint position sense, static and dynamic balance, isokinetic muscle strength and the International Knee Documentation Committee Subjective Knee Form.

**Results:** Post an 8-week training period, both groups showed improvements in the single leg 6-meter timed hop. Notably, the limb symmetry index for this hop in the plyometric group was significantly higher than the resistance group {18.2% (10.2, 26.1) vs 6.2% (-2.0, 14.5) respectively}. The plyometric group also demonstrated significantly better knee joint position sense {-3.1° (-4.3, -1.9) vs -0.8° (-2.0, 0.4) respectively}and the unipedal stance on a stable surface with eyes closed {13.9 sec (2.7, 25.2) vs -2.6 sec (-14.3, 9.1) respectively} than the resistance group.

**Conclusion:** Plyometric training in the late phase of ACL rehabilitation program has proven to be a suitable and effective approach for enhancing neuromuscular and knee functions.

**Keywords:** Anterior cruciate ligament reconstruction; plyometric; neuromuscular functions (Siriraj Med J 2024; 76: 353-365)

## INTRODUCTION

The anterior cruciate ligament (ACL) is one of the most injured in sports, especially those that involve rapid movement, jumping or landing.[1,2] Patients following an ACL injury encountered several knee functions deficit and knee laxity.[1] Arthroscopic ACL reconstruction is a common procedure to restore knee stability following an ACL injury.[2,3] Post-reconstruction, many patients struggle with muscle strength and neuromuscular deficits, contributing to difficulties in returning to sports and an increased risk of re-injury.[4-8]

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Rehabilitation is crucial for recovery after ACL reconstruction, and is typically divided into early, intermediate and late phases.[3] While early and intermediate phases have been well-studied such as accelerated rehabilitation or using blood flow restriction training, data on late phase rehabilitation is limited.[4,9,10] Late phase training programs after ACL reconstruction focus on enhancing muscle strength and neuromuscular functions to support increased physical activity.[10,11] Although resistance training has been a traditional method for improving muscle strength,[5] it may not effectively improve lower limb power and proprioception, which are vital neuromuscular functions for returning to sports after ACL reconstruction.[11,12] In addition,

The plyometric training program, consisting of jumping and landing movements, incorporates a stretch-shortening cycle (SSC).[13] This type of training has been used to improve neuromuscular function.[14] Literature reviews reveal studies reporting positive effects of plyometric training following ACL reconstruction.[15-18] However, there is a scarcity of randomized controlled trial focusing on plyometric training.[17,18] Therefore, this study aimed to determine the effects of plyometric training programs on neuromuscular and knee functions during the late phase of rehabilitation after ACL reconstruction. The hypothesis is that plyometric training may lead to significant improvements in neuromuscular and knee functions compared to resistance training.

## MATERIALS AND METHODS

### *Study Design and Setting*

This randomized controlled trial was conducted from April 2022 to March 2023 at Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The approval of the study protocol from the institutional review board (COA no. Si 264/2022) and was registered with the Clinical Trails Registry (TCTR20220608003).

### *Participants*

This study enrolled patients who had follow-up at their 6-8 months after undergoing unilateral ACL reconstruction using both of difference autografts: bone-patellar tendon-bone or hamstring tendon autografts. Recruitment occurred at Siriraj Hospital during clinical follow-ups. Eligible participants were aged 18 to 45 years at enrollment. To qualify for the study, subjects needed to demonstrate passive knee extension within 3° of the nonsurgical side, passive knee flexion within 5° of the unaffected side, a pain rating scale of less than 2 out of 10 during daily activities, and a limb symmetry index of isokinetic muscle strength exceeding 60% of the nonsurgical side. Patients with a history of fractures or dislocations in the lower extremities, multi-ligament knee injuries, inflammatory joint diseases, and cognitive neuromuscular impairments were excluded. Additionally, a less than 80% compliance (attending fewer than 13 out of 16 (80%) training sessions) was also reason for exclusion from the study. Assessments were conducted at baseline and after completing an 8-week training program. Measurements included the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF), static and dynamic balance, knee joint position sense, isokinetic muscle strength and single leg 6-meter timed hop test. All functional tests were assessed by highly skilled sports scientist at Siriraj Hospital. All patients provided written consent before participating in this study.

### *Randomization and Interventions*

All participants were operated on at Siriraj Hospital by the same surgeon and underwent ACL reconstruction using either autografts. Following surgery, they participated in a standard rehabilitation protocol, starting with the early phase of rehabilitation overseen by highly skilled sports scientists until enrollment in the study. At their 6-8 months follow-up visit, eligible patients were randomly assigned into two groups through a computer-generated block of four: the resistance training group or the plyometric training group. After baseline testing, participants of both groups received instruction and supervision for their respective exercise training programs from highly skilled sports scientist of Division of Sports Medicine, Department of Orthopaedic Surgery, Siriraj Hospital, and under the guidance of Dr. Napasakorn Chuensiri who holds the Certified Strength and Conditioning Specialist (CSCS). The participants were asked to perform maximum or explosive movement in all exercise. Moreover, sports scientists provided effective feedback to participants of their training. In addition, the participants did not receive a home exercise program. The training regimen for both groups involved two sessions per week over an eight-week period, with each session comprising a, 10-minute for dynamic warm up, 40-minute exercise protocol, and 10-minute for cool down.

### *Resistance training protocol*

Participants were instructed to exercise following a resistance training protocol based on based on the American College of Sports Medicine's guidelines.[18] This protocol involved exercises at 75% of their 1-repetition maximum (RM), consisting of 3 sets of 10 repetitions each, with a minute's rest between sets. The program

included four exercises: squats, side lunges, step ups, and heel raises. Participants used dumbbells as external loads during these exercises. The intensity, set at 75% of their 1RM, was calculated both at the baseline and after four weeks of the training period.

### *Plyometric training protocol*

The plyometric protocol was designed with an intensity of 80-100 foot contacts per training session, in line with recommendations by *Buckthorpe et al.*[20] This protocol included four exercises, each performed in four sets with five repetitions, and a two-minute rest between sets. The 8-week training protocol was split into two phases. The first phase of the plyometric training program compromised four exercises: squat jumps, ankle hops, step-up jumps, and lateral bound stick landings. After the initial 4 weeks, the patients moved to the second phase, which included squat jumps to a box, ankle jumps, step-up alternate jumps, and lateral bounds. All exercises were performed using bodyweight.

### *Outcome Measures*

The patient-reported outcome measure was assessed using the Thai version of the IKDC-SKF. This 18-item questionnaire assess knee symptoms, functions and sports activities, with scores ranging from 0 to 100.[21] Higher scores indicate better knee function. Test-retest reliability was excellent (ICC = 0.92).[21]

The unipedal stance test, used to assess static balance, involved four positions; standing on one leg on a stable surface with eyes open, the same with eyes closed, standing on one leg on an unstable surface which used foam balance pad cushion thickened with smooth surface (39 cm x 24 cm x 6 cm) with eyes open, and finally, the same with eyes closed. Participants were asked to stand on one leg with their arms crossed over their chest. The duration for which they could maintain each position without uncrossing their arms, moving their foot from the starting position, rotating their foot on the ground, opening their eyes during the closed-eye trials, or reaching a maximum of 45 seconds, was timed using a stopwatch.[22] Each position was attempted three times on both legs, starting with the unaffected knee, followed by the affected side, and the best time of each trial was recorded in seconds.

Dynamic balance was assessed using the modified star excursion balance test (mSEBT).[23] Participants were instructed to stand on one leg at a central point on the floor, with three reach lines arranged in a 'Y' shape, labeled anterior, posteromedial and posterolateral. They were instructed to reach as far as possible along each line with a light touch, and then return the reaching leg to the center. The test was repeated three times for both legs, starting with the unaffected knee, followed by the affected side, recording the best reach distance in centimeters for each direction.

Knee joint position sense, an indicator of knee proprioception, was assessed using an isokinetic dynamometer (CONTREX MJ multijoint module 2018, Physiomed, Germany).[23] The seat was set with their hip and knee flexed at 90°. With their eyes closed, their knee was initially flexed to 90° and then passively moved to 45° of knee flexion. Participants were asked to remember this target position for 5 seconds before returning to the starting position. Then, the knee was passively moved again, and participants pressed a button when they believed their knee reached the previous target angle. The difference in knee angles was recorded. Each leg was tested twice, starting with the unaffected knee, followed by the affected side. The consistency of the test showed good test-retest reliability (ICC=0.78).[24]

Muscle strength was assessed using an isokinetic dynamometer to measure peak extensor and flexor torque of the knee.[24] Prior to isokinetic muscle strength testing, participants warmed up for 5 minutes on a stationary bicycle at 60-70 revolutions per minute without resistance. After warming up, they were instructed to seated with an isokinetic dynamometer attached to their hip and knee flexed 90°. A shoulder pad across the chest and a seat strap on the middle of the thigh helped minimize body movement during the test. Participants first performed 15 repetitions at an angular velocity of 180°/sec as an additional warm-up, followed by three repetitions of maximum effort tests at an angular velocity of 60°/sec, with a 30-second rest period in between. The testing was conducted twice on each leg, starting with the unaffected knee and then the affected side. The best time for each leg was also recorded.

Hopping time was evaluated using the single leg 6-meter timed hop test.[25] Participants began by standing on a single leg at the starting position and then hopped as quickly as possible over a distance of 6 meters, with the timer stopping as they crossed the finish line. Each participant performed this test twice on both legs, starting with the unaffected knee, followed by the affected side.[25] The single leg 6-meter timed hop test demonstrated good test-retest reliability in patients in this patients group (ICC = 0.82).[26]

### *Sample Size and Statistical Analysis*

The sample size calculation for this study was performed using G*power software version 3.1.9.2, focusing on

the primary outcome of knee proprioception, based on results from a previous study.[17] In that study the mean in the experimental group was 4.3 and 6.7 in the control group. The standard deviation was 2.4. The type I error was set at 0.05, the power at 80% and the effect size at 0.5, resulting in a sample size of 13 in both groups.

Descriptive statistics were analyzed to compile participant characteristics. Data was checked for a normal distribution using Shapiro-Wilk test. The test revealed no significant deviation from a normal distribution. For categorical data, frequencies and percentages were used, while the means and standard deviations were reported for continuous data. To assess differences between groups, Chi-squared tests were applied for categorical data, and independent t-tests were used for continuous data.

The analysis of outcome measures was conducted using mixed model ANOVA. This was followed by LSD post-hoc comparisons to determine significant differences between the groups. Statistical analysis was performed using PASW software for Windows version 18. P-values of less than 0.05 were considered statistically significant.

## RESULTS

As illustrated in Fig 1, 30 patients successfully participated in this study and were randomly allocated during their 6-8 months follow-up visit into two groups.

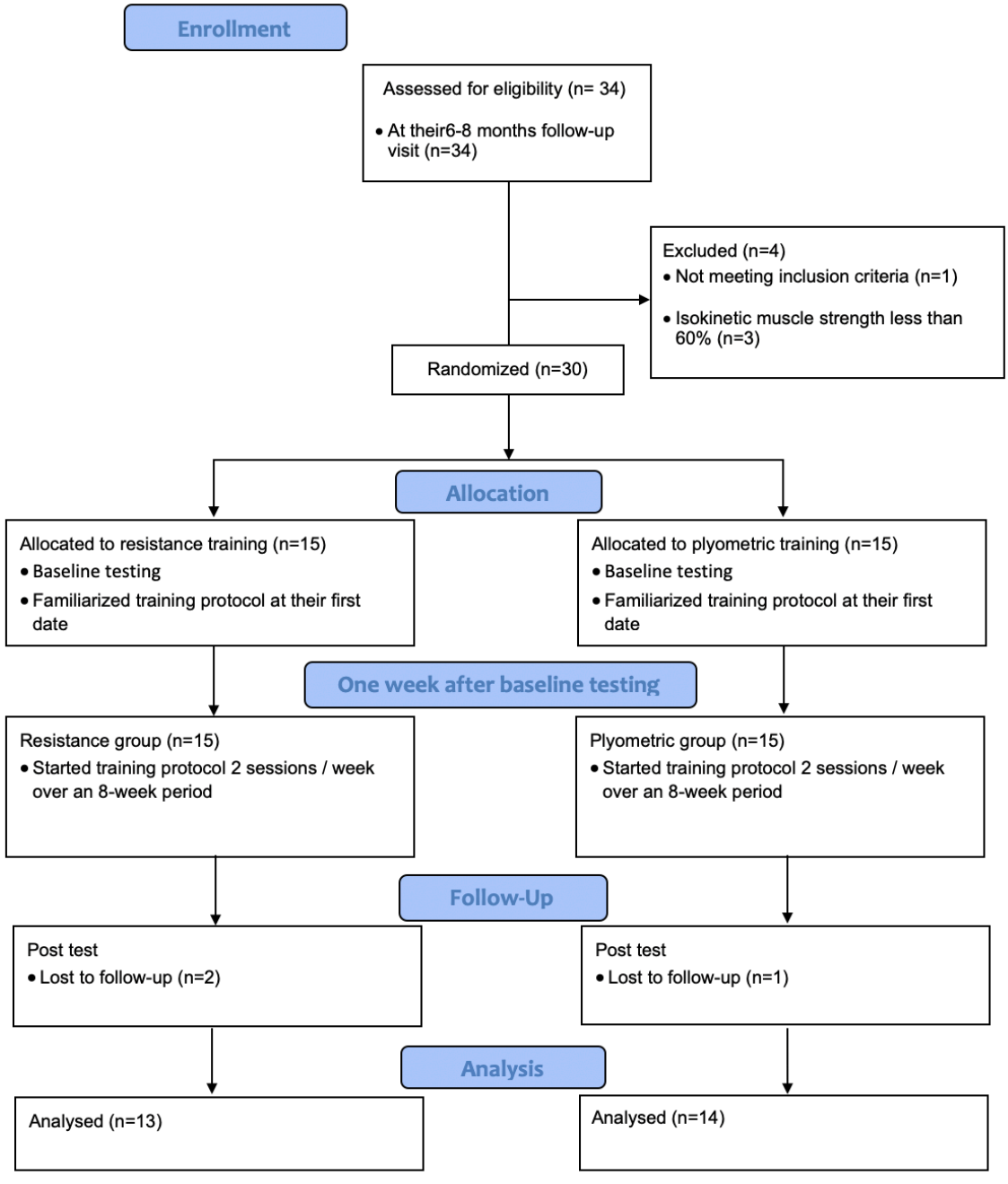


**Fig 1.** CONSORT flow chart of study enrollment

After completed baseline testing, each participant was familiarized with their training protocol from the first date of their enrollment in this study. After one week, participants started their training protocol, and received one-on-one training sessions with highly skilled sports scientist. Participants underwent a total of 16 training sessions over an 8-week period, compliance with the 16 training sessions was closely monitored. Three participants who were lost to follow-up dropped out of this study. The remaining twenty-seven participants, who attended more than 13 out of 16 (80%) training sessions and reported no serious adverse events, pain or accidents that exceeded the indicated threshold, were included in the analysis.

The characteristics of the participants, categorized into groups is presented in Table 1. There were no significant differences in the characteristics of patients between the two groups. The study group compromised 27 participants as the mean time elapsed from surgery to study enrollment was 6 months. All participants were classified as engaging in recreational activity levels. Baseline measurements of isokinetic muscle strength revealed no significant differences between the groups.

In the plyometric group, the single leg 6-meter timed hop improved significantly (p=0.041) more, -1.1 sec (95% CI; -1.6, -0.7) than in the resistance group, -0.5 sec (95% CI: -1.0, -0.1). In the plyometric group, the LSI percentage improved significantly (p=0.041) more, 18.2% (10.2, 26.1), than in the resistance group, 6.2% (95%CI: -2.0, 14.5). (Fig 2)

The plyometric group demonstrated significantly improved in the knee joint position sense for the affected (p=0.009) more, -3.1° (95% CI; -4.3, -1.9) than in the resistance group, -0.8° (95% CI; -2.0, 0.4). The unaffected of the plyometric group also showed significantly improved (p=0.015) more, -1.3° (95% CI; -2.1, -0.5) than in the resistance group, 0.1° (95% CI -0.7, 0.9) (Fig 3)

The plyometric group's unipedal stance test, one leg stance on a stable surface with closed eyes for the affected leg improved significantly (p=0.045) more, 13.9 sec (95% CI; 2.7, 25.2) than in the resistance group, -2.6 sec (95% CI; -14.3, 9.1). (Table 2) Dynamic balance using the mSEBT, the plyometric group showed a tendency to improve in anterior direction, the posterolateral direction and composite scores for affected leg more effectively compared to the resistance group. (Table 2)

There were no significant changes in either group regarding isokinetic muscle strength in knee extension and flexion (Table 3).

The IKDC-SKF did not change significantly in the resistance and plyometric groups {5.5% (-3.0, 13.9) and 6.6% (-1.6, 14.8) respectively}.

## DISCUSSION

This study compared resistance and plyometric training programs regarding effects on neuromuscular and knee functions during the late phase of rehabilitation following ACL reconstruction, which occurred 6-8 months post-operation. The key finding of this study is that improvements in the LSI of this hop were significant only in the plyometric group, and improved significantly greater than the resistance group. In addition, the plyometric group also showed significant greater in knee joint position sense of both legs and static balance on a stable surface with closed eyes for the affected leg than the resistance group. While the late phase ACL rehabilitation program traditionally uses resistance training for optimizing neuromuscular response to strength training, this study indicates that, plyometric training, known for inducing specific neural patterns through SCCs, could be a superior method for enhancing functional performance. These findings confirm the positive effects of plyometric training in late phase rehabilitation post-ACL reconstruction.

In this study, the single leg 6-meter timed hop (6MTH) served as a measure of functional performance and lower limb power. Both the resistance and training groups showed significant improvements in 6MTH, indicating enhanced lower limb power. This improvement is attributed to increased motor unit recruitment, stimulating fast-twitch fibers and growth hormone secretion[34], which are crucial for muscle activation enhancement. However, the plyometric group exhibited greater improvement in 6MTH. Plyometric training including unilateral and bilateral jumping which is ascribed to the SSCs inherent in plyometric training, where the eccentric phase stretches muscle spindles, and increasing afferent nerve firing. The rate of muscle spindle stretch dictates the signal intensity sent to the spinal cord, with faster stretches leading to greater motor recruitment.[12,32] Additionally, the LSI in the plyometric group was 91% when comparing the operated leg to the normal leg, which is significantly higher than that in the resistance group. This LSI level, surpassing 90% cutoff, is a critical factor in deciding whether to return to sports activities post ACL reconstruction.[27] These findings showed that plyometric training can positively influence decisions regarding clearance to return to sports after ACL reconstruction.

Knee joint position sense is the important factor to improve the LSI. Our study demonstrated that knee joint position sense in both legs improved significantly after an 8-week plyometric training program, more so than with resistance training. Plyometric training is crucial for enhancing knee joint position sense.[14] Plyometric training consists of jumping and landing, which continuously stimulates mechanoreceptors, Golgi tendon organs, and

**TABLE 1.** Physiological characteristics and anthropometry variables in patients post-ACL reconstruction before and after 8 weeks training in the resistance and plyometric groups (n=27)

| Characteristics | All data (n=27) | Resistance (n = 13) | Plyometric (n = 14) | p-value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 24 (88.9%) | 12 (92.3%) | 12 (85.7%) | 0.586 |
| Female | 3 (11.1%) | 1 (7.73%) | 2 (14.3%) | |
| Age (years) | 29.0 ± 7.2 | 28.2 ± 6.8 | 29.8 ± 7.7 | 0.583 |
| Weight (kg) | 72.9 ± 9.6 | 70.9 ± 10.3 | 74.6 ± 8.9 | 0.325 |
| Height (cm) | 171.9 ± 6.2 | 172.3 ± 6.4 | 171.4 ± 6.0 | 0.719 |
| Body mass index (kg/m$^2$) | 24.6 ± 2.7 | 23.8 ± 2.9 | 25.4 ± 2.5 | 0.149 |
| Side of affected knee | | | | |
| Right | 13 (48.1%) | 6 (46.2%) | 7 (50.0%) | 0.842 |
| Left | 14 (51.9%) | 7 (53.8%) | 7 (50.0%) | |
| Follow up period (months) | 6.2 ± 0.4 | 6.2 ± 0.4 | 6.2 ± 0.4 | 0.922 |
| Tegner activities scale | | | | |
| 5 | 2 (7.4%) | 1 (7.7%) | 1 (7.1%) | |
| 6 | 2 (7.4%) | 0 (0%) | 2 (14.3%) | 0.366 |
| 7 | 23 (85.2%) | 12 (92.3%) | 11 (78.6%) | |
| Sports type | | | | |
| Football | 20 (71.4%) | 10 (71.4%) | 10 (71.4%) | |
| Basketball | 2 (7.1%) | 1 (7.1%) | 1 (7.1%) | 0.504 |
| Badminton | 2 (7.1%) | 0 (0%) | 2 (14.3%) | |
| Other | 3 (10.7%) | 2 (14.3%) | 1 (7.1%) | |
| Graft type | | | | |
| BPTB | 8 (29.6%) | 4 (28.6%) | 4 (28.6%) | 0.901 |
| HS | 19 (70.4%) | 9 (69.2%) | 10 (71.4%) | |
| Combined procedure | | | | |
| No | 13 (46.4%) | 5 (35.7%) | 8 (57.1%) | |
| Meniscectomy | 10 (35.7%) | 6 (42.9%) | 4 (28.6%) | 0.524 |
| Meniscus repair | 5 (17.9%) | 3 (21.4%) | 2 (14.3%) | |
| Extension peak torque | | | | |
| Affected (Nm) | 147.9 ± 44.0 | 148.8 ± 40.8 | 147.1 ± 48.3 | 0.927 |
| Unaffected (Nm) | 183.3 ± 47.7 | 182.6 ± 42.1 | 184.0 ± 54.1 | 0.942 |
| LSI (%) | 80.3 ± 9.9 | 80.9 ± 8.8 | 79.8 ± 11.2 | 0.764 |

**Abbreviations:** BPTB - bone patellar tendon bone; HS - hamstring; LSI - limb symmetry index

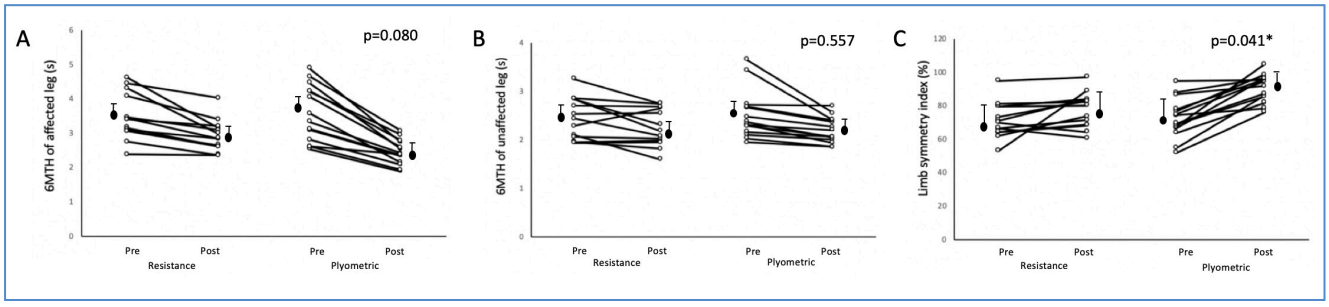


**Fig 2.** Scatterplots demonstrating paired data of individual changes in single leg 6-meter timed hop in affected (A), unaffected (B), and limb symmetry index (C) in response to the resistance group (n=13) and the plyometric group (n=14). *The statistic significantly difference of the Time * Group interactions ($p < 0.05$).

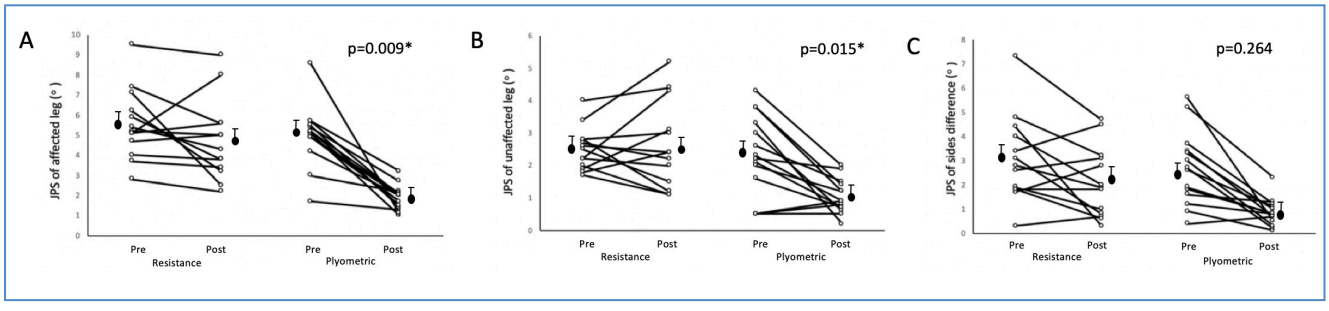


**Fig 3.** Scatterplots demonstrating paired data of individual changes in joint position sense in affected (A), unaffected (B), and limb symmetry index (C) in response to the resistance (n=13) and plyometric group (n=14). *The statistic significantly difference of the Time * Group interactions ($p < 0.05$).

muscle spindles around the knee joint. This repetitive stimulation increases the sensitivity of sensory responses and the perception of knee joint.[14,28] Previous studies corroborate these findings, showing that athletes with post-ACL reconstruction experienced improved knee joint position sense following neuromuscular training programs that included jumping exercises[17] Similarly, female athletes showed improved knee proprioception after a 6-week plyometric training period.[29] In addition, improvements in the Golgi tendon organ positively affect the reduction of force on the knee joint.[28] These findings found that such training plays a vital role in developing knee proprioception, which is crucial for returning to sports and reducing the risk of re-injury after ACL reconstruction.

Moreover, balance is a major factor that affects functional mobility in patients post-ACL reconstruction,[30,31] which is often impaired due to neuromuscular damage from injury and subsequent reconstruction. In this study improvements in static balance, measured by the unipedal stance test, were significantly larger in the plyometric group compared to the resistance group. Plyometric training played a crucial role in improving balance, primarily by repeatedly stimulating the afferent sensory pathways during the plyometric training period.[18] In addition, when visual input is removed, the nervous system must rely on increases reliance on proprioceptive feedback from joints and muscles to maintain balance.[30] Its indicated that the plyometric group demonstrated greater improvement in proprioceptive feedback than resistance training group. Furthermore, the dynamic balance of the mSEBT indicate that the plyometric group tended to show greater improvement in the anterior, posterolateral direction and composite scores for affected leg more effectively compared to the resistance group. These results are attributable to mSEBT's reliance on feed-forward control and visual feedback until toe touch, triggered by knee joint perception.[30] This feedback provides information about limb position, movement, and spatial orientation, crucial for maintaining balance.[32] Plyometric training has been shown to enhance the sensitivity of the afferent feedback pathway.[32] Moreover, the percentage change of composite score summaries of this study were greater than the minimal detectable change (10.4 vs 7.2 respectively).[33] These findings support the beneficial effects of incorporating plyometric exercises into rehabilitation programs for individuals recovering to improve balance.

In this study, peak isokinetic torque of the knee appeared to improve under both training protocols. However, no statistically significant difference was observed from the baseline, nor was there a notable difference between the groups. This lack of significant improvement could be attributed to participants already having undergone resistance protocol training in the early

**TABLE 2.** Static and dynamic balance in patients after ACL reconstruction before and after 8 weeks training in the resistance and plyometric group.

| Variables | Resistance group (n=13) | | | Plyometric group (n=14) | | | ANOVA statistic | | | Effect size | T-test p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Time | Group | Time*Group | | |
| Unipedal stance | | | | | | | | | | | |
| SOE | | | | | | | | | | | |
| Affected (sec) | 40.4 ± 8.8 (37.3, 43.5) | 42.7 ± 5.7 (39.6, 45.8) | 2.3 (-2.1, 6.6) | 43.7 ± 4.0 (40.7, 46.7) | 44.8 ± 0.8 (41.8, 47.8) | 1.1 (-3.1, 5.3) | 0.276 | 0.080 | 0.693 | 0.003 | 0.718 |
| Unaffected (sec) | 41.9 ± 7.2 (39.5, 44.4) | 44.0 ± 3.4 (41.6, 46.5) | 2.1 (-1.4, 5.6) | 43.9 ± 4.0 (41.6, 46.3) | 45.0 ± 0.0 (42.6, 47.4) | 1.1 (-2.3, 4.4) | 0.190 | 0.224 | 0.665 | 0.004 | 0.688 |
| SCE | | | | | | | | | | | |
| Affected (sec) | 18.2 ± 16.9 (9.9, 26.4) | 15.6 ± 12.7 (7.3, 23.8) | -2.6 (-14.3, 9.1) | 13.0 ± 13.6 (5.1, 21.0) | 26.9 ± 15.7* (19.0, 34.9) | 13.9† (2.7, 25.2) | 0.168 | 0.446 | 0.045 | 0.078 | 0.012 |
| Unaffected (sec) | 21.0± 15.8 (12.3, 29.7) | 21.9 ± 14.2 (13.2, 30.6) | 0.9 (-11.4, 13.2) | 17.7 ± 15.7 (9.2, 26.0) | 28.0 ± 16.5 (19.5, 36.2) | 10.2 (-1.6, 22.1) | 0.198 | 0.764 | 0.279 | 0.023 | 0.073 |
| UOE | | | | | | | | | | | |
| Affected (sec) | 31.3 ± 17.1 (18.6, 35.8) | 27.2 ± 15.9 (22.7, 39.9) | 4.1 (-8.1, 16.2) | 24.5 ± 17.4 (16.2, 32.7) | 39.6 ± 10.6 31.3, 47.9) | 15.1 (3.4, 26.9) | 0.027 | 0.515 | 0.195 | 0.033 | 0.079 |
| Unaffected (sec) | 33.1 ± 13.4 (26.5, 39.7) | 33.0 ± 13.8 (26.4, 39.7) | -0.1 (-9.4, 9.3) | 31.3 ± 12.4 (24.9, 37.7) | 41.9 ± 7.2 (35.5, 48.3) | 10.6† (1.6, 19.6) | 0.109 | 0.280 | 0.105 | 0.052 | 0.033 |
| UCE | | | | | | | | | | | |
| Affected (sec) | 3.1 ± 1.7 (1.1, 5.0) | 4.9 ± 3.6 (3.0, 6.8) | 1.9 (-0.8, 4.6) | 2.8 ± 1.3 (1.0, 4.7) | 6.2 ± 5.3 (4.4, 8.0) | 3.4 (0.8, 6.0) | 0.007 | 0.573 | 0.418 | 0.013 | 0.318 |
| Unaffected (sec) | 4.8 ± 4.0 (2.3, 7.3) | 5.9 ± 5.3 (3.4, 8.4) | 1.1 (-2.5, 4.6) | 3.9 ± 1.7 (1.4, 6.3) | 7.0 ± 5.9 (4.6, 9.4) | 3.1 (-0.3, 6.5) | 0.093 | 0.941 | 0.414 | 0.013 | 0.209 |

**TABLE 2.** Static and dynamic balance in patients after ACL reconstruction before and after 8 weeks training in the resistance and plyometric group. (Continue)

| Variables | Resistance group (n=13) | | | Plyometric group (n=14) | | | ANOVA statistic | | | Effect size | T-test p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Time | Group | Time*Group | | |
| The modified star excursion balance | | | | | | | | | | | |
| ANT | | | | | | | | | | | |
| Affected (cm) | 56.0 ± 5.8 (52.5, 59.5) | 59.0 ± 5.2 (55.5, 63.0) | 3.0 (-1.9, 7.9) | 55.9 ± 6.0 (52.6, 59.3) | 63.1 ± 7.5 (59.8, 66.5) | 7.2† (2.5, 11.9) | 0.004 | 0.234 | 0.218 | 0.030 | 0.005 |
| Unaffected (cm) | 60.1 ± 6.4 (56.3, 63.7) | 62.9 ± 6.3 (58.9, 66.3) | 2.8 (-2.1, 7.6) | 50.9 ± 4.7 (56.7, 64.1) | 64.7 ± 7.0 (60.9, 68.4) | 4.9 (0.2, 9.5) | 0.027 | 0.625 | 0.537 | 0.008 | 0.267 |
| PM | | | | | | | | | | | |
| Affected (cm) | 75.9 ± 8.1 (71.6, 80.3) | 80.0 ± 8.8 (75.7, 84.3) | 4.1 (-2.1, 10.2) | 75.1 ± 7.4 (70.8, 79.3) | 80.7 ± 6.9 (76.5, 84.9) | 5.6 (-0.3, 11.6) | 0.026 | 0.974 | 0.714 | 0.003 | 0.529 |
| Unaffected (cm) | 79.9 ± 7.4 (75.6, 84.3) | 82.1 ± 9.3 (77.8, 86.4) | 2.2 (-4.0, 8.3) | 77.7 ± 7.3 (73.5, 81.9) | 81.6 ± 6.9 (77.7, 86.4) | 3.9 (-2.0, 9.6) | 0.162 | 0.524 | 0.689 | 0.003 | 0.517 |
| PL | | | | | | | | | | | |
| Affected (cm) | 69.8 ± 10.6 (64.7, 74.8) | 74.8 ± 8.9 (69.7, 79.8) | 5.0 (-2.1, 12.1) | 67.9 ± 7.6 (63.0, 72.7) | 78.1 ± 8.8 (73.3, 83.0) | 10.3† (3.4, 17.1) | 0.003 | 0.768 | 0.288 | 0.023 | 0.044 |
| Unaffected (cm) | 74.9 ± 9.2 (70.0, 79.7) | 78.1 ± 9.3 (73.2, 82.9) | 3.2 (-3.6, 10.1) | 70.8 ± 5.7 (66.1, 75.5) | 80.4 ± 10.0 (75.7, 85.0) | 9.6 (3.0, 16.2) | 0.009 | 0.709 | 0.187 | 0.035 | 0.050 |
| Composite | | | | | | | | | | | |
| Affected (%) | 78.7 ± 6.8 (75.8, 82.7) | 83.5 ± 6.6* (80.2, 87.2) | 4.8 (0.1, 9.4) | 77.9 ± 4.7 (74.7, 81.1) | 87.0 ± 5.6 (83.2, 90.1) | 9.1† (4.6, 13.6) | <0.001 | 0.401 | 0.189 | 0.034 | 0.028 |
| Unaffected (%) | 83.9 ± 6.1 (80.6, 87.2) | 87.1 ± 7.3 (83.9, 90.4) | 3.2 (-1.4, 7.9) | 81.7 ± 3.9 (78.6, 84.9) | 88.9 ± 5.9 (83.8, 90.4) | 7.1 (2.7, 11.6) | 0.002 | 0.899 | 0.228 | 0.029 | 0.072 |

**Abbreviations:** SOE - Stable with opened eyes; SCE - Stable with closed eyes; UOE - Unstable with opened eyes; UCE - Unstable with closed eyes; ANT - anterior; PM - posteromedial; PL - posterolateral; 95%CI - 95% confidence interval

*The statistic significantly difference of the Time * Group interactions ($p < 0.05$).

†The difference change between group in independent t test were statistically significant ($p < 0.05$)

**TABLE 3.** Isokinetic muscle strength in patients post-ACL reconstruction before and after 8 weeks training in the resistance and plyometric group.

| Variables | Resistance group (n=13) | | | Plyometric group (n=14) | | | ANOVA statistic | | | Effect size | T-test p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Time | Group | Time*Group | | |
| Peak torque of extension | | | | | | | | | | | |
| Affected (Nm) | 148.8 ± 40.8 (122.4, 175.1) | 159.0 ± 43.4 (132.7, 185.4) | 10.3 (-27.0, 47.5) | 147.2 ± 48.3 (121.8, 172.5) | 165.5 ± 54.6 (140.1, 190.8) | 18.3 (-17.6, 54.2) | 0.272 | 0.852 | 0.757 | 0.002 | 0.313 |
| Unaffected (Nm) | 182.6 ± 42.1 (153.2, 212.1) | 201.8 ± 53.1 (172.3, 231.2) | 19.3 (-22.5, 60.8) | 184.0 ± 54.1 (155.6, 212.4) | 196.7 ± 59.8 (168.4, 225.1) | 12.7 (-27.4, 52.8) | 0.274 | 0.899 | 0.825 | 0.001 | 0.372 |
| LSI (%) | 81.0 ± 8.8 (74.3, 87.6) | 82.4 ± 16.4 (75.7, 89.1) | 1.4 (-8.0, 10.9) | 79.8 ± 11.2 (73.3, 86.2) | 83.8 ± 10.4 (77.4, 90.3) | 4.1 (-5.1, 13.2) | 0.405 | 0.967 | 0.690 | 0.003 | 0.510 |
| Torque average @ 0.2 second of extension | | | | | | | | | | | |
| Affected (Nm) | 137.7 ± 46.5 (114.8, 160.6) | 131.0 ± 41.4 (108.1, 153.9) | -6.7 (-39.1, 26.7) | 114.9 ± 37.8 (92.8, 137.0) | 119.1 ± 38.7 (97.1, 141.2) | 4.2 (-27.0, 35.4) | 0.913 | 0.128 | 0.629 | 0.005 | 0.171 |
| Unaffected (Nm) | 159.8 ± 54.1 (132.7, 186.9) | 169.8 ± 47.6 (142.7, 196.9) | 10.0 (-28.3, 48.3) | 142.6 ± 50.4 (116.5, 168.8) | 143.5 ± 42.2 (117.4, 169.2) | 0.9 (-36.1, 37.8) | 0.684 | 0.107 | 0.732 | 0.002 | 0.108 |
| Peak power of extension | | | | | | | | | | | |
| Affected (W) | 153.7 ± 44.7 (125.8, 181.6) | 166.9 ± 45.7 (139.0, 194.8) | 13.2 (-26.2, 52.6) | 154.6 ± 50.8 (127.8, 181.5) | 174.5 ± 57.4 (147.6, 201.4) | 19.9 (-18.1, 57.9) | 0.231 | 0.756 | 0.808 | 0.001 | 0.416 |
| Unaffected (W) | 190.0 ± 46.2 (159.0, 221.0) | 211.6 ± 55.6 (180.5, 242.6) | 21.6 (-22.3, 65.4) | 193.2 ± 56.6 (163.3, 223.1) | 207.0 ± 62.4 (180.5, 242.6) | 13.8 (-28.5, 56.0) | 0.249 | 0.963 | 0.799 | 0.001 | 0.118 |
| Peak torque of flexion | | | | | | | | | | | |
| Affected (Nm) | 103.7 ± 27.0 (85.0, 122.5) | 111.6 ± 28.0 (92.8, 130.3) | 7.8 (-18.7, 34.4) | 98.2 ± 36.6 (80.1, 116.2) | 110.3 ± 40.3 (92.2, 128.4) | 12.1 (-13.5, 37.7) | 0.282 | 0.710 | 0.817 | 0.001 | 0.363 |
| Unaffected (Nm) | 109.7 ± 30.6 (91.2, 128.1) | 122.3 ± 33.3 (103.9, 140.7) | 12.6 (-13.4, 38.7) | 107.4 ± 32.2 (89.7, 125.2) | 112.8 ± 35.8 (95.1, 130.6) | 5.4 (-19.7, 30.5) | 0.322 | 0.518 | 0.690 | 0.003 | 0.169 |
| LSI (%) | 95.9 ± 13.3 (87.7, 104.0) | 95.3 ± 15.2 (87.1, 103.5) | -0.5 (-12.0, 11.0) | 90.7 ± 15.7 (82.8, 98.6) | 95.1 ± 14.0 (87.3, 103.0) | 4.4 (-6.7, 15.5) | 0.626 | 0.505 | 0.537 | 0.008 | 0.364 |

**TABLE 3.** Isokinetic muscle strength in patients post-ACL reconstruction before and after 8 weeks training in the resistance and plyometric group. (Continue)

| Variables | Resistance group (n=13) | | | Plyometric group (n=14) | | | ANOVA statistic | | | Effect size | T-test p value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Baseline (mean ± SD) (95% CI) | Post-test (mean ± SD) (95% CI) | Δ change (95%CI) | Time | Group | Time*Group | | |
| Torque average @ 0.2 second of flexion | | | | | | | | | | | |
| Affected (Nm) | 97.6 ± 41.4 (78.2, 117.0) | 102.0 ± 28.8 (82.6, 121.4) | 4.4 (-23.0, 31.9) | 86.9 ± 37.7 (68.1, 105.6) | 91.6 ± 29.8 (72.9, 110.3) | 4.7 (-21.7, 31.2) | 0.633 | 0.270 | 0.988 | 0.001 | 0.989 |
| Unaffected (Nm) | 101.7 ± 36.3 (82.2, 121.3) | 112.7 ± 32.9 (93.1, 132.3) | 10.9 (-16.7, 38.6) | 90.8 ± 37.4 (71.9, 109.6) | 92.6 ± 33.6 (73.7, 111.4) | 1.8 (-24.9, 28.4) | 0.509 | 0.110 | 0.634 | 0.005 | 0.194 |
| Peak power of flexion | | | | | | | | | | | |
| Affected (W) | 108.7 ± 26.7 (89.7, 127.7) | 115.1 ± 27.8 (96.1, 134.1) | 6.4 (-20.4, 33.3) | 103.3 ± 37.0 (83.0, 119.6) | 111.3 ± 41.7 (96.1, 134.1) | 9.9 (-16.0, 35.8) | 0.384 | 0.552 | 0.851 | 0.001 | 0.929 |
| Unaffected (W) | 114.2 ± 29.9 (95.7, 132.7) | 125.8 ± 2332.7 (107.3, 144.2) | 11.6 (-14.5, 37.7) | 110.5 ± 33.4 (92.7, 128.3) | 117.0 ± 36.0 (99.2, 134.8) | 6.5 (-18.7, 31.6) | 0.322 | 0.495 | 0.777 | 0.002 | 0.156 |

**Abbreviations:** LSI - limb symmetry index; 95%CI - 95% confidence interval

phase of rehabilitation prior to this study. Additionally, the IKDC-SKF showed no statistically significant changes after the 8-week training period. However, the mean score of IKDC-SKF for the resistance and plyometric groups were 81% and 88% respectively, indicating a high level of knee function in daily or sport activities.[14]

In addition, while previous research often focused on plyometric training in competitive athletes,[16-18, 29] this study highlights its benefits for recreational athletes. Importantly, all participants were able to perform the training without any adverse effects following one-one training sessions. However, our study has some limitations. First, it mostly recruited male patients which may limit the generalizability of the findings to female populations. Second, requiring all participants to have quadriceps muscle strength greater than 60% of the unaffected leg which crucial in ensuring a baseline level of strength. Therefore, the participant had received an adequate muscle strength training program before participating in this study. Last, all participants were in a recreational athlete which may had a good skill for plyometric training. Future studies could explore the efficacy of this protocol in non-athletes.

## CONCLUSION

The late phase rehabilitation program, incorporating plyometric training has proven to be effective in improving neuromuscular and knee functions greater than the conventional resistance training in ACL reconstruction patients. This supervised training program can be safely executed without any adverse effects, making it suitable even for recreational level athletes.

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### Author contributions

Wacharapol and Napasakorn were developed the theory and designed the experimental in consultation with Pisit. All authors were involved in data collection and contributed to the interpretation of the results. Wacharapol and Napasakorn took the lead in drafted and prepared the manuscript. All authors provided critical feedback and approved the final version of the manuscript.

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# Sponge-incorporated VS Multilayer Padding Long Leg Cast to Prevent Pediatric Heel Pressure Injury: A Randomized Controlled Trial

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## ABSTRACT

**Objective:** To measure and compare the incidence of cast-related pressure injuries at the heel between sponge-incorporated long leg cast and multilayer padding cast following orthopedic lower extremity surgery.

**Materials and Methods:** Patients aged 1 to 18 years who were scheduled for elective lower extremity soft tissue surgery were recruited. They were equally randomized into two groups: sponge-incorporated cast (Group 1) and multilayer padding cast (Group 2). A multilayer padding cast, consisting of five layers of Webril®, was applied to the heel and bony prominence areas. At the 2nd and 4th weeks postoperatively, cast-related heel pressure injuries were evaluated using the 2016 National Pressure Ulcer Advisory Panel (NPUAP) staging system. Changes in alignment and other complications were also recorded.

**Results:** 100 patients were recruited. At two weeks postoperatively, the incidence of cast-related heel pressure injuries in Group 1 was 4/46 cases (8.7%), with all cases being stage 1. In Group 2, there were 6/54 cases (11.1%), with 3 cases in stage 1 and 3 cases in deep tissue pressure injury (p=0.479). At four weeks postoperatively, Group 1 had 6/46 cases (13%), with 4/46 cases (8.7%) being stage 1 and 2/46 cases (4.3%) being deep tissue pressure injuries. Group 2 had 6/54 cases (11.1%) (p>0.99), with all cases being stage 1. There was no statistical difference in loss of alignment. No serious complications, such as compartment syndrome or neurovascular injury, were found.

**Conclusion:** The incidence of cast-related heel pressure injury was comparable between sponge padding cast and a multilayer cotton padding cast.

**Trial registration:** This study was registered in ClinicalTrails.gov (TCTR20220207002).

**Keywords:** Long leg cast; cast complications; sponge-incorporated cast, pressure injury (Siriraj Med J 2024; 76: 366-372)

## INTRODUCTION

Cast immobilization is a common and effective treatment for the postoperative management of fractures and lower extremity soft tissue surgeries in pediatric patients. However, there are many cast-related complications such as thermal injuries, skin breakdown, pressure injuries, infections, blisters, dermatitis, neurological injuries, and compartment syndrome. One of the most common complications is pressure injury, which has been reported in 6.3% to 15% of children with cerebral palsy casts. Nearly 50% of pressure injuries occur in the heel area within the first four weeks after the application of a long leg cast or A-frame cast.[1] The initial stage of a pressure injury develops in the superficial tissues, presenting with purple or maroon discoloration. Later stages may progress to involve subcutaneous tissue, muscle, and bone, potentially causing osteomyelitis.[2] Significant pain and disability are common. The ulcer may become infected and require

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surgical debridement.[3] It is also associated with additional costs and increased loss of school or work days due to cast removal or other secondary procedures.[4] Patients who are obese or unable to communicate effectively, such as those who are obtunded, sedated, or very young, are at increased risk of complications during cast treatment.[5] Comorbidities that impair mobility may also increase the risk for cast-related complications.[6] Patients with cerebral palsy and spina bifida who have never been casted exhibit an increased risk for cast-related pressure injuries.[7]

Few previous studies reported a decrease in cast-related complications by using foam padding and wool felt padding.[1,8-11] One study of lower extremity casts in patients who were receiving chemotherapy, or those who had presented with heel soreness, reported that foam padding decreased the rate of pressure injuries.[9] Another retrospective study of foam padding in postoperative lower extremity casting reported a decrease heel pressure injuries, but the study had several limitations.[2]

To date, no Level I study has compared the incidence of pressure injuries in sponge-padded casts with multilayer-padded casts. Therefore, we hypothesized that sponge-incorporated casts would decrease the rate of heel pressure injuries compared to multilayer padding casts in children following orthopedic lower extremity surgery.

## MATERIALS AND METHODS

This prospective, randomized controlled trial was conducted at a tertiary university hospital. Approval was obtained from the hospital ethics committee (study no. Si 710/2020), and all patients provided written informed consent. The study was conducted from September 2020 to October 2022. Patients aged 1-18 years who underwent elective soft tissue surgery and postoperative immobilization with long leg casting were included. Patients with preexisting wounds in the heel area or impaired sensation, such as those with myelomeningocele, were excluded. Subjects were randomized using computer-generated sequencing to receive either a sponge-incorporated long leg cast or a multilayer padded long leg cast (Fig 1). After surgery, the circular cast was applied by one of three pediatric orthopedic staff members who used the same padding technique.

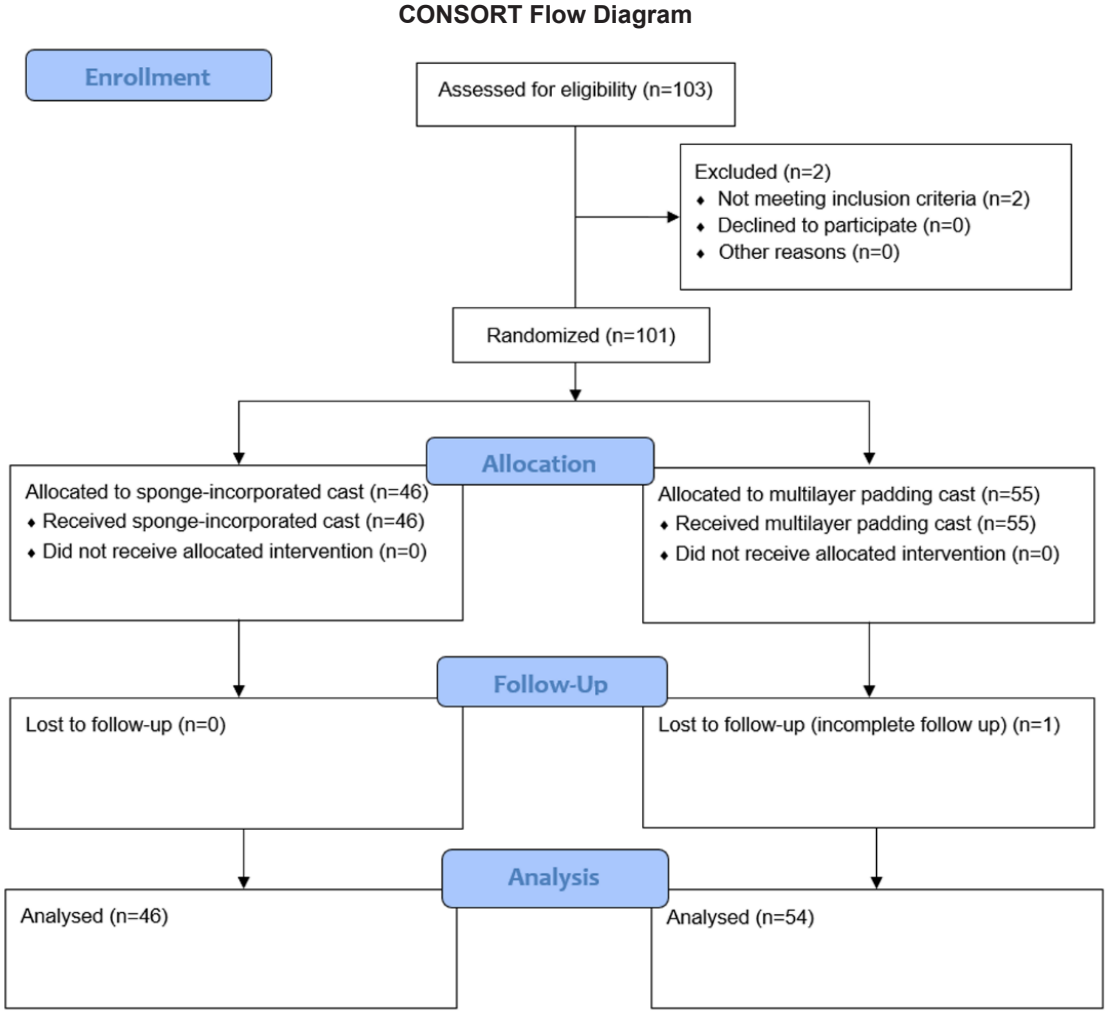


**Fig 1.** The Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram.

The sponge-incorporated cast included two layers of Webril® applied from the toes to mid-thigh, followed by a one-centimeter-thick sponge applied at the heel area (Fig. 2). An additional single layer of Webril® was applied to cover the sponge, and two more layers of Webril® were added at the medial and lateral malleolus, fibular head, patella, and upper border of the cast. Next, a fiberglass (Scotch cast 3M®) cast was applied from the toes to the mid-thigh. The multilayer padding cast consisted of three layers of Webril® padding from toes to mid-thigh, with two additional layers at the bony prominences and the upper border of the cast. The padding technique in both casts was the same, except in the heel area where the sponge-incorporated cast used a sponge, whereas the multilayer padding cast used an additional two layers of Webril® instead. In both groups, the cast was applied during full knee extension and in a neutral plantigrade foot position. Postoperative protocols were the same for all patients. The sponge padding used in this study (Jolly®) was low-density sponge and commercially available. It is a porous, lightweight, flexible synthetic material made of polyurethane that conforms well to bony prominences. The heel was defined as the area at the posterior of the foot, extending from the Achilles tendon insertion to the apex of the calcaneal bone on the plantar surface.

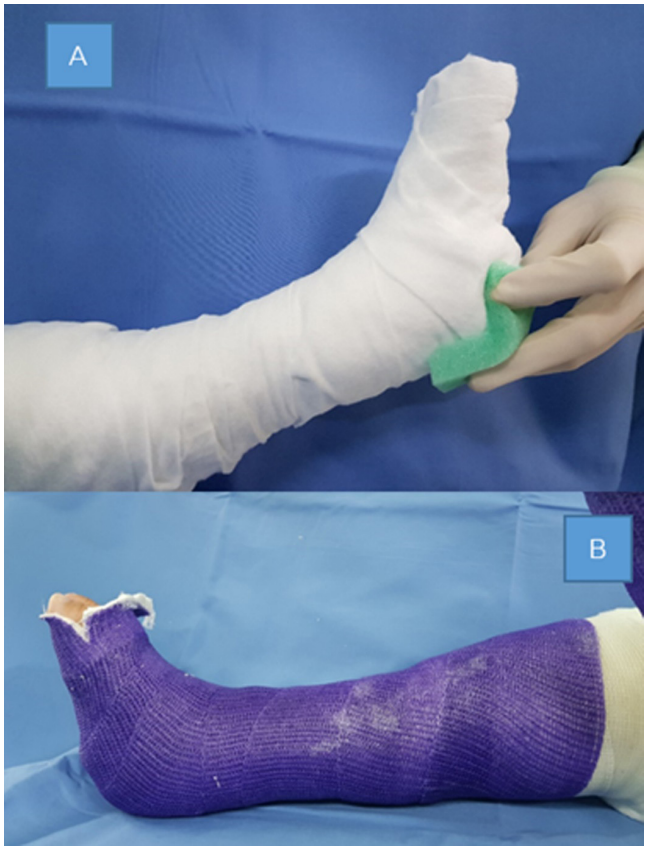


**Fig 2.** (**A**) The sponge padding was applied at patient's heel. (**B**) Sponge-incorporated long leg cast.

The primary outcome was the incidence of heel pressure injury at two and four weeks postoperatively. Demographic information, including age, gender, body weight, height, side and operative procedure, were recorded. Cast condition, other areas of pressure injury, other complications and alignment of the knee and ankle were also recorded during the follow-up period. The cast was removed by a technician and sent to be evaluated for pressure injury in another room by an orthopedic resident who was blinded to the intervention. Pressure injury was evaluated using the 2016 NPUAP Pressure Injury Staging System 10, ranging from stage 1 to 4 and deep tissue pressure injury (DTPI). Stage 1 was intact skin with a localized area of nonblanchable erythema, which may appear differently in darkly pigmented skin and also presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Stage 2 was partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Stage 3 was full-thickness skin loss, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges), is often present. Slough and/or eschar may be visible. Stage 4 was full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer. Lastly, deep tissue pressure injury (DTPI) was Intact or nonintact skin with localized area of persistent nonblanchable deep red, maroon, purple discoloration, or epidermal separation revealing a dark wound bed or bloodfilled blister.

Total time for long leg cast immobilization in this study was 4 weeks. In cases that patients have heel pressure injury at 2 weeks postoperatively, the cast will be opened in a window fashion at the pressure injury area, bivalved, and the immobilization will continue until 4 weeks.

### Statistical analysis

The statistical analysis was performed using SPSS version 18. The independent t test was utilized to compare body weight between groups. The chi-square test was utilized to compare operative procedure between groups. The Mann-Whitney test was utilized to compare age, height and body mass index between groups. The Fisher exact test was utilized to compare side and incidence of pressure injury between groups.

## RESULTS

The result of 100 cases, 46 patients were allocated to the sponge-incorporated long leg cast group (Group 1) and 54 patients were allocated to the multilayer padding

long leg cast group (Group 2). Two patients were excluded because of impaired sensation due to myelomeningocele. There were no significant differences in demographic characteristics between two groups (Table 1). The operative procedures in Group 1 were tendo-achilles lengthening (TAL) 78.3%, hamstring release 6.5%, tendon transfer 4.3%, and combined procedures 10.9%. The operative procedures in Group 2 were tendo-achilles lengthening (TAL) 64.8%, hamstring release 7.4%, tendon transfer 9.3%, and combined surgical procedures 18.5%.

In Group 1, at 2 weeks postoperatively, the incidence of heel pressure injury was 4/46 (8.7%), all of which were stage 1 heel pressure injuries. At 4 weeks postoperatively, 6/46 cases (13%) had pressure injuries, with 4/46 (8.7%) being stage 1 and 2/46 cases (4.3%) being deep tissue pressure injuries. In Group 2, at 2 weeks postoperatively, the incidence of heel pressure injury was 6/54 cases (11.1%), with 3/54 (5.5%) being stage 1 and 3/54 cases (5.5%) being deep tissue pressure injuries. At 4 weeks postoperatively, 6/54 cases (11.1%) were stage 1 (Tables 2 and 3). There was no statistically significant difference in either group at 2 or 4 weeks postoperatively. Additionally, there was no statistically significant difference between cerebral palsy and non-cerebral palsy patients. (Table 4)

The pressure injury primarily occurred at the heel, followed by the ankle, thigh, foot, and leg. One patient was lost to follow-up. At two weeks postoperative, there were no reports of loss of alignment exceeding 10 degrees in both groups. Additionally, there were no serious complications such as compartment syndrome and neurovascular injury in either group.

**TABLE 1.** Patient demographic data and operative procedure

| Variables | Sponge-incorporated cast (n = 46) | Multilayer padding cast (n=54) | P-value |
|---|---|---|---|
| Gender (Male) | 29(63.0%) | 30(55.6%) | 0.542 |
| Age (yr) † | 8(6 – 12.25) | 7(5.8 - 10) | 0.183 |
| Weight (kg) † | 26.7(17.1 – 40.6) | 21.8(15.9 – 41.1) | 0.233 |
| Height (cm) ‡ | 128.4±26.5 | 122.9±25.1 | 0.305 |
| BMI (kg/m$^2$) † | 17.4(14.3 – 21.7) | 16.4(14.9 – 21.5) | 0.809 |
| Side (Right) | 21(45.7%) | 27(50.0%) | 0.692 |
| Communicable | 45(97.8%) | 48(88.9%) | 0.120 |
| Comorbidities | | | |
| Cerebral palsy | 18(39.1%) | 29(53.7%) | 0.063 |
| Healthy | 16(34.8%) | 17(31.5%) | 0.832 |
| Procedure | | | |
| Tendo-Achilles lengthening (TAL) | 36(78.3%) | 35(64.8%) | 0.185 |
| Hamstring release | 3(6.5%) | 4(7.4%) | >0.999 |
| Combined surgery | 5(10.9%) | 10(18.5%) | 0.401 |
| Tendon transfer | 2(4.3%) | 5(9.3%) | 0.447 |

†Median(Q1-Q3), ‡Mean±SD

**TABLE 2.** Outcome measurement at 2 weeks postoperatively

| Variables | Sponge-incorporated cast [N (%)] | Multilayer padding cast [N (%)] | P-value |
|---|---|---|---|
| **Heel pressure injury** | 4/46 (8.7%) | 6 /54(11.1%) | 0.479 |
| **Heel ulcer NPUAP staging** | | | |
| Stage 1 | 4/46 (8.7%) | 3/54 (5.5%) | NA |
| Stage 2 | 0 (0%) | 0 (0%) | |
| Stage 3 | 0 (0%) | 0 (0%) | |
| Stage 4 | 0 (0%) | 0 (0%) | |
| DTPI[1] | 0 (0%) | 3/54 (5.5%) | |
| **Anatomic location** | | | NA |
| Heel | 4 (80%) | 3 (37.5%) | |
| Foot (Other) | 0 (0%) | 0 (0%) | |
| Thigh | 0 (0%) | 1 (12.5%) | |
| Ankle | 1 (20%) | 3 (37.5%) | |
| Knee | 0 (0%) | 1 (12.5%) | |
| Leg | 0 (0%) | 0 (0%) | |

[1] DTPI, Deep tissue pressure injury

**TABLE 3.** Outcome measurement at 4 weeks postoperatively

| Variables | Sponge-incorporated cast [N (%)] | Multilayer padding cast [N (%)] | P-value |
|---|---|---|---|
| **Heel pressure injury** | 6/46 (13%) | 6/54 (11.1%) | >0.999 |
| **Heel ulcer NPUAP staging** | | | |
| Stage 1 | 4/46 (8.7%) | 6/54 (11.1%) | NA |
| Stage 2 | 0 (0%) | 0 (0%) | |
| Stage 3 | 0 (0%) | 0 (0%) | |
| Stage 4 | 0 (0%) | 0 (0%) | |
| DTPI[1] | 2/46 (4.3%) | 0 (0%) | |
| **Anatomic location** | | | NA |
| Heel | 6 (85.7%) | 6 (85.7%) | |
| Foot (Other) | 0 (0%) | 0 (0%) | |
| Thigh | 0 (0%) | 0 (0%) | |
| Ankle | 1 (14.3%) | 1 (14.3%) | |
| Knee | 0 (0%) | 0 (0%) | |
| Leg | 0 (0%) | 0 (0%) | |

[1] DTPI, Deep tissue pressure injury

**TABLE 4.** Compare heel pressure injury in cerebral palsy and non-cerebral palsy patients

| Heel pressure injury | Sponge-incorporated cast | Multilayer padding cast | P-value |
|---|---|---|---|
| At 2 weeks (n=10) | | | |
| Cerebral palsy | 3 | 3 | 0.662 |
| Non cerebral palsy | 1 | 3 | 0.333 |
| At 4 weeks (n=12) | | | |
| Cerebral palsy | 0 | 3 | 0.276 |
| Non cerebral palsy | 6 | 3 | 0.474 |

## DISCUSSION

The use of sponge-incorporated casts and multilayer padding casts following elective surgery aimed to reduce the incidence of cast-related heel pressure injuries. We compared the incidence of cast-related heel pressure injuries in pediatric patients between sponge-incorporated long leg casts and multilayer padding long leg casts following elective surgery. The incidence of heel pressure injuries in the sponge-incorporated long leg cast group was 8.7% at two weeks and 13% at four weeks of follow-up. In the multilayer padding cast group, the incidence was 11.1% at both two weeks and four weeks of follow-up. There were no statistically significant differences between the groups at either time point.

Previous studies have described several techniques to reduce the incidence of pressure injuries.[6,8-12] Murgai et al.[1] conducted a retrospective study of foam padding in postoperative lower extremity casting and reported a reduced incidence of heel pressure injuries from 4.3% to 0.9%. DiFazio et al.[8] showed a reduction in cast-related skin complications with the placement of felt padding at the heel inside lower extremity casts from 17.1 per 1,000 casts to 6.8 per 1,000 casts. Forni et al.[9] also demonstrated a significant reduction in the incidence of pressure sores with polyurethane foam placed at the heel during lower extremity cast application in patients that underwent chemotherapy or patients who were presented with heel soreness. Our study was the first randomized controlled trial to compare the incidence of heel pressure injuries in long leg casts among pediatric orthopedic patients who underwent soft tissue surgery procedures. We controlled the padding technique using either sponge or 5 layers of Webril®. Both techniques were comparable in preventing heel pressure injuries.

We classified the stage of heel pressure injury using the 2016 NPUAP pressure injury staging system.[7,13] We found that the incidence of heel pressure injuries in our study was higher than in previous studies. This outcome is based on the pediatric population in this study, which had less ambulation during the casting period. Some patients had long leg casts bilaterally, and some patients had neurological problems, making it difficult for them to use gait aids. Most patients with heel pressure injuries in both the sponge-incorporated long leg cast and multilayer padding cast groups were at stage 1. Pressure injuries mainly occurred at the heel, but a few were found at the ankle, thigh, foot, or knee, similar to previous reports.[1,8,9]

Cast-related pressure injuries occur at areas of increased pressure underneath the cast, leading to decreased perfusion, ischemia, and necrosis. These areas of localized tissue injury usually occur over bony prominences where there is minimal muscle and adipose tissue overlying the bone, leaving these areas susceptible to impaired circulation. Pressure injuries commonly occur in patients who do not mobilize well. Long leg casts impair mobility, and impairment in mobility prevents patients from relieving pressure by movement or changes in body position, increasing the risk for pressure ulcer formation. Patients with static encephalopathy, spasticity, difficulty communicating and expressing pain, high BMI, and poor nutrition are also at increased risk of pressure injuries.[1,7,8]

Our study has some limitations. First, we included patients who underwent soft tissue surgery, so the results may vary in other bony procedures. Second, this study involved three pediatric orthopedic surgeons, which could result in variations in techniques. Future studies may include non-operative patients and other bony procedures.

## CONCLUSION

The incidence of cast-related heel pressure injury was comparable between sponge padding cast and a multilayer cotton padding cast.

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### Author contributions

P.E. designed the study and collected the data. T.L. involved in data collection, analysis of data and did manuscript drafting. C.C., T.A. and J.W. wrote the paper in the aspect of review and edited the manuscript. T.L. and P.E. provided final approval of the manuscript version submitted.

## DECLARATIONS

### Ethics approval and consent to participate

The institutional review board (IRB) and departmental data safety monitoring board (DSMB) approved and monitored this study.

### Consent for publication

Informed consent was obtained from all parents included in this study.

### Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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# Does The Lengthening Frequency Affect The Outcome of Distraction Osteogenesis? Comparing Two Times a Day with Four Times a Day Lengthening Protocol

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## ABSTRACT

**Objective:** Distraction osteogenesis (DO) is a well-known technique. The traditional method utilized the lengthening frequency of four times a day (QID). Many mechanical factors may affect the DO outcome. However, the effect of distraction frequency has not been proven clinically. Therefore, we aim to investigate whether the two times a day (BID) and QID lengthening frequency affect the healing index and complications of the DO.

**Materials and Methods:** We retrospectively reviewed patients who had undergone DO from 2010 – 2021. The patient was divided into BID and QID groups. Demographics, lengthening outcomes, and complications between the two groups were compared. We used the inverse probability of treatment weighting (IPTW) to determine the effect of treatment.

**Results:** The median healing index (HI) of the patients whose lengthening was done QID is 41.36 (IQR 32.72 - 67.68) days/cm, and BID is 49.12 (IQR 35.28 - 62.54) days/cm, which did not differ significantly. The Odds ratio of achieving HI < 45 days/cm for patients receiving QID lengthening compare to BID is 1.12 (95% CI 0.31-3.99, p = 0.862). The IPTW did not show a difference in average treatment effects between QID and BID lengthening. The rates of minor and major complications were not significantly different between the two groups (26.1% in QID group and 32.1% in BID group).

**Conclusion:** The frequency of QID and BID lengthening results in comparable HI and complications for patients who undergo DO. However, prospective research is needed to evaluate the effect of frequency differences in a clinical setting.

**Keywords:** Distraction osteogenesis; limb lengthening; healing index; lengthening frequency (Siriraj Med J 2024; 76: 373-380)

## INTRODUCTION

Distraction osteogenesis (DO) is a well-known method in orthopedic surgery.[1,2] This technique creates new bone formation using the principle of Tension-Stress. Under a slow and gradual traction force, the cells in the distraction gap become metabolically active, leading to osteogenesis.[3,4] DO is used in adult and pediatric patients. In adults, it is used mainly for bone defects caused by trauma, infection, or tumor. In pediatric patients, conditions such as congenital limb deficiency,

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physeal arrest, or osteomyelitis that result in limb length discrepancy (LLD) are major indications.[5,6]

DO includes the initial, distraction, and consolidation phases. The rate and frequency during distraction have been shown to affect the quality of osteogenesis.[3,4,7] In a detailed animal model study, It was demonstrated that the optimal speed for lengthening is around 1 mm per day. In addition, increasing the frequency of distraction may improve osteogenesis, but this has not been proved in a clinical study. Many factors can also affect the healing index (HI), for examplem, the patient's age, the extent of the lengthening, the lengthened bone segment, the device used, and etiologies.[7-10] Many devices have been used for DO. The two most commonly used devices were the ring external fixator and the monolateral fixator. These can be combined with some form of internal fixation to reduce time in the external fixator, called integrated lengthening.

In our institution, a lengthening frequency of four times a day (QID) is the standard method. However, some patients do not fully follow the protocol and prefer a lower frequency of distraction. Therefore, two times a day (BID) lengthening was used in some patients. However, the effect of lengthening frequency has not been tested clinically. Therefore, here our objective is to compare the results and complications between the lengthening frequency of BID and QID.

## MATERIALS AND METHODS

### *Study design and setting*

The institutional review board has approved this retrospective cohort study. Patients who underwent DO in our institution over ten years from January 2010 to January 2020 were recruited.

### *Participants and data collection*

The inclusion criteria for this study are patients who received DO at our institution. All types of devices used, consolidation methods and all etiologies for DO were included. Patients were excluded if a concurrent correction for deformity was also performed. Patients who did not have clinical and radiological follow-up until the DO process was complete were also excluded. At the time of operation, demographic data such as age, body weight, body height, and gender were collected. The patient's diagnosis was collected. DO data were recorded, including bone segment, devices used, consolidation method, lengthening rate, and lengthening frequency. The decision to use a mono-lateral fixator or Illizarov apparatus and the lengthening frequency was up to the surgeon's preferences. Radiographs were reviewed for initial bone length, length gain, and callus quality. All complications during and after the DO process were recorded.

### *Outcome measurement*

The healing index (HI) is the primary outcome of this study. It is computed by dividing the number of days spent on DO by the length of the developed callus in centimeters (cm).[8,11] In our study, the duration of DO starts on the day of osteotomy and ends when the callus is fully consolidated, and full weight bearing is permitted for the patient. HI should be less than 45 days/cm to achieve optimal treatment time.[12] External fixator index (EI) is calculated similarly, but the period is from applying the external fixator until it was removed.

Secondary outcomes involve the quality of the callus formed and the complications that occur. The callus quality is assessed using the callus's shape, density, and pathway according to Li et al.[13] The callus shape is classified into fusiform, cylindrical, concave, lateral, and central. Fusiform and cylindrical shapes were grouped as "Good callus shapes".

The callus pathway was categorized into four distinct types: sparse, homogeneous, heterogeneous, and lucent. Each of these categories is subsequently subdivided into three density levels: low, intermediate, and normal. Homogeneous and heterogeneous types with intermediate and normal density callus are grouped as "Good callus density". The callus score when the external fixator was removed was also recorded.[14] Complications were classified into problems, obstacles, minor and major complications according to Paley et al.[5] The subsidence of the callus is defined as the change in callus > 10% or angulation > 10 degrees.[14]

### *Treatment protocol*

*Osteotomy technique:* All patients received the same technique for osteotomy. We did an osteotomy at the metaphysodiaphyseal area of the distal femur and proximal tibia. The bone was drilled, and the osteotomy was completed with an osteotome. We checked the osteotomy completion by slight distraction under a fluoroscope.

*External fixator application:* Two types of exernal fixators were used in our patients. The decision to use the Illizarov frame or monolateral fixators is based on surgeon's preferences. For the Ilizarov frame, it was assembled and applied to the bone proximally and distally. Transosseous elements that engage at least four cortices in each segment using Shanz pins and wires were inserted according to the safe zone. For the monolateral fixator,

we inserted three Shanz pins, size 5.0 mm – 6.0 mm, into the proximal shaft and the distal shaft area.

*Lengthening Protocol:* The initial phase is seven days for all patients. The patient and caregiver were then instructed to manually distract the device BID (0.5 mm x two steps) or QID (0.25 mm x four steps). Both groups utilize the same rate of one mm/day.

*Follow-up and Consolidation methods:* Serial radiographs and clinical exams were scheduled every two weeks. If the patient complains of pain or has a reduced range of motion, the rate can be modified. The actual distraction rate was calculated when the distraction is fisnished by dividing the length gained by the days used. After reaching the desired length, if plate fixation or casting were chosen as a consolidation method, the external fixator was kept until some ossification of the lengthening site was observed, then converted to plate or casting. However, the cut point for conversion to plate/cast consolidation is up to the surgeon's preferences. After solid consolidation was observed, the patients were allowed to bear weight.

### Statistical analysis

A histogram and the Shapiro-Wilk test were used to investigate data distribution patterns. The independent T-test was used to test normally distributed continuous data with mean ± SD. The Mann-Whitney U test was used to evaluate nonnormally distributed continuous variables with median and interquartile range (IQR). Categorical data were provided as counts and percentages, and Fisher's exact probability test was used to test them. The statistical significance level was chosen at p 0.05. STATA 16 (StataCorp, LLC, College Station, TX, USA) was used for all statistical analyses.

We use the inverse probability of treatment weighting (IPTW) to balance baseline covariates between the two treatment groups. The IPTW is a propensity score method that will weigh treatment effects with the probability of receiving treatments to account for potential selection biases in the non-randomized study. The IPTW was calculated based on baseline covariates, including options of conversion for consolidation, external fixator type (Ilizarov or Monolateral fixator), the etiology being congenital limb deficiency, the magnitude of length gain, distraction rate, patient's age, and bone lengthed (femur or tibia). Subsequently, the average treatment effects (ATE) between the QID and BID groups for HI, the probability of having good callus density and shape, and complications were calculated under IPTW. Any covariates demonstrating a weighted absolute Standardized Difference (STD) of greater than 10% were included for a double robustness adjustment in the weighted analysis.

## RESULTS

We included 72 patients in our study. The demographic data of patients who received BID and QID lengthening is compared in (Table 1). There were significantly more male patients in the QID group. More patients in the QID group were lengthened with Illizarov frame and converted to cast for consolidation. Sixteen patients ( 21.6%) had LLD from congenital causes, which comprised six Fibular hemimelia (8.1%), four Congenital femoral deficiency (5.4%), three Tibial hemimelia (4.1%) and three Hemihypertrophy (4.1%). Fifteen patients (20.3%) had limb undergone DO due to physeal injury from either traumatic or infectious causes. Eight patients (10.8%) had chronic osteomyelitis (COM), requiring DO to reconstruct the bone defect. We used DO for Congenital tibial dysplasia in four cases (5.4%). The remaining 31 patients have various causes leading to LLD, which are six Perthes diseases (8.1%), six Developmental hip dysplasia (8.1%), four Syndrome associated (5.6%), three Blount's disease (4.1%), three Posteromedial tibial bowing (4.1%), three Bone tumor (4.1%), two skeletal dysplasia (2.7%), two Malunion (2.7%), one Arthrogryposis (1.4%), and one Cerebral palsy (1.4%). The lengthening outcomes and complications of the two groups are compared in (Table 2), showing no significant differences between the two groups.

*Effects of Lengthening Frequency on Healing Index*

A higher proportion of patient in QID group achieved H-index < 45 days/cm; QID group (27 out of 46 patients, 58.7%) vs. BID group (12 out of 28 patients, 42.9%). However the difference did not reach statistical significant, P = 0.2786). Subgroup analysis for factors that influence HI were evaluated by univariate and multivariate analysis (Table 3). QID lengthening has an OR of 1.89 ( 95%CI 0.73-4.90, p = 0.188) for achieving HI <45 days/cm. The multivariable analysis results in OR of 1.12 (95%CI 0.31-3.99, p = 0.862). Influencing factors were adjusted using IPTW to determine the average effect of lengthening frequency treatment (QID vs. BID) (Fig 1). QID lengthening did not have a significant impact on HI (52.8±24.0 days/cm vs. 50.5±17.1 days/cm, Average treatment effect (ATE) = 2.3 (-5.8 to 10.4), p = 0.577). In other words, if all patients received QID lengthening instead of BID lengthening, the HI would be about 2.3 days/cm more. QID lengthening also did not significantly affect achieving good callus shape and density.

*Effects of Lengthening Frequency on Complications*

The complication rate of DO, which included Problems (28.57% vs. 19.57%, p = 0.404), Obstacles (39.28% vs. 28.26%, p = 0.443), Minor and Major complications

**TABLE 1.** Demographic data of patients receiving distraction osteogenesis by lengthening frequency

| Demographic data | 2 times/day (BID) (n=28, 37.8 %) | | 4 times/day (QID) (n=46, 62.2 %) | | P-value |
|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | |
| Clinical characteristics | | | | | |
| Age (years) | 15.3 | 8.6 | 13.4 | 9.8 | 0.410 |
| Sex (n,%) | | | | | |
| Male | 9 | 32.1 | 27 | 58.7 | 0.033* |
| Female | 19 | 67.9 | 19 | 41.3 | |
| Body weight (kg) | 42.7 | 18.6 | 38.9 | 18.0 | 0.384 |
| Body height (cm) | 144.2 | 20.9 | 137.2 | 22.8 | 0.187 |
| Bone lengthened (n, %) | | | | | |
| Femur | 17 | 60.7 | 24 | 52.2 | 0.630 |
| Tibia | 11 | 39.3 | 22 | 47.8 | |
| Lengthening device (n, %) | | | | | |
| Ilizarov frame | 16 | 57.1 | 37 | 80.4 | 0.038* |
| Wagner frame | 12 | 42.9 | 9 | 19.6 | |
| Consolidation method (n, %) | | | | | 0.020* |
| No conversion | 2 | 7.1 | 6 | 13.0 | |
| Conversion to Casting | 12 | 42.9 | 34 | 73.9 | |
| Conversion to plate fixation | 14 | 50.0 | 6 | 13.1 | |
| Etiologies of LLD[1] (n, %) | | | | | 0.138 |
| Congenital limb deficiency | 9 | 32.1 | 7 | 15.2 | |
| Physeal injury | 6 | 21.4 | 9 | 19.6 | |
| Chronic osteomyelitis | 1 | 3.6 | 7 | 15.2 | |
| Congenital pseudarthrosis of tibia | 0 | 0.0 | 4 | 8.7 | |
| Other acquired causes | 12 | 42.9 | 19 | 41.3 | |

[1]LLD, Limb length discrepancy; Normally distributed continuous data were compared using an Independent T-test. Categorical data were analyzed using Fisher's Exact Test for small sample sizes and Pearson's Chi-Square Test for larger samples.

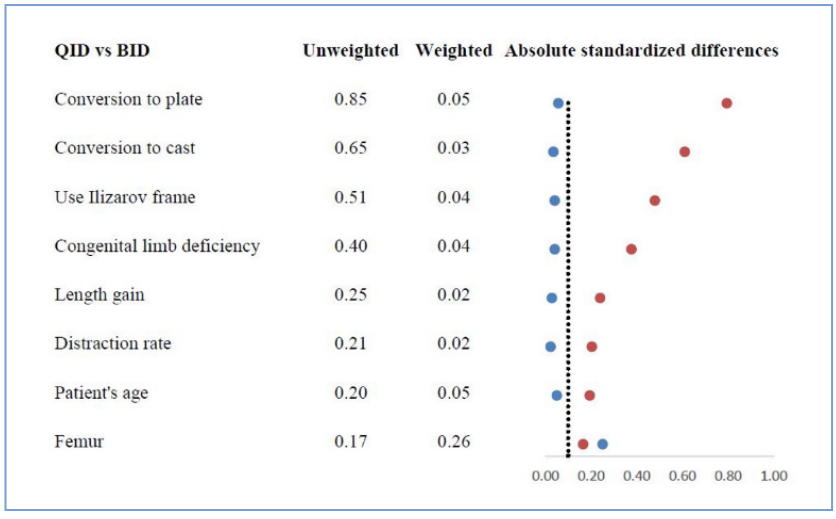


**Fig 1.** An inverse probability of treatment weighting (IPTW) graph showing the weighted effect of variables affecting the Healing Index before (Red dot) and after (Blue dot) adjusting.

**TABLE 2.** Lengthening outcomes and complications of patients receiving distraction osteogenesis by frequency of distraction

| | 2 times/day (BID) (n=28, 37.8 %) | | 4 times/day (QID) (n=46, 62.2 %) | | P-value |
|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | |
| **Lengthening data** | | | | | |
| Initial Bone length (cm) | 31.62 | 8.68 | 29.44 | 8.67 | 0.299 |
| Length gain (cm) | 6.14 | 2.40 | 5.55 | 2.31 | 0.294 |
| Lengthening rate (mm/days) | 0.71 | 0.15 | 0.75 | 0.19 | 0.391 |
| **Lengthening outcomes** | | | | | |
| Healing index < 45 days/cm (n, %) | 12 | 42.9 | 27 | 58.7 | 0.279 |
| **Callus qualities** | | | | | |
| Achieved Good callus density (n, %) | 9 | 32.14 | 15 | 32.6 | 1.000 |
| Achieved Good callus shape (n, %) | 11 | 39.28 | 26 | 56.52 | 0.231 |
| Callus score | 5.89 | 1.75 | 6.57 | 1.71 | 0.108 |
| Callus subsidence (n, %) | 9 | 32.14 | 18 | 39.13 | 0.623 |
| **Complications** | | | | | |
| Problems (n, %) | 8 | 28.57 | 9 | 19.57 | 0.404 |
| Obstacles (n, %) | 11 | 39.28 | 13 | 28.26 | 0.443 |
| Minor and Major complications (n, %) | 9 | 32.14 | 12 | 26.09 | 0.604 |

Normally distributed data was compared with an Independent T-test. Categorical data was compared with Fisher's Exact Test.

**TABLE 3.** Univariable and multivariable logistic regression for factors predicting good healing index (<45 days/cm)

| Characteristics | Univariable analysis | | | | Multivariable analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | uOR | 95%CI | | p-value | mOR | 95%CI | | p-value |
| Conversion to plate | 0.49 | 0.17 | 1.41 | 0.187 | 0.59 | 0.16 | 2.29 | 0.736 |
| Illizarov | 2.29 | 0.81 | 6.45 | 0.117 | 3.56 | 0.85 | 14.96 | 0.083 |
| Congenital causes | 0.32 | 0.10 | 1.04 | 0.060 | 0.13 | 0.02 | 0.72 | 0.019 |
| Length > 5 cm | 2.13 | 0.84 | 5.41 | 0.110 | 2.22 | 0.72 | 6.81 | 0.163 |
| Rate < 0.7 mm/day | 2.12 | 0.83 | 5.42 | 0.118 | 3.09 | 0.97 | 9.81 | 0.056 |
| Age < 10 | 1.33 | 0.518 | 3.433 | 0.551 | 3.16 | 0.69 | 14.48 | 0.137 |
| Femur | 2.12 | 0.83 | 5.40 | 0.114 | 3.93 | 1.11 | 13.97 | 0.034 |
| QID[1] lengthening | 1.89 | 0.73 | 4.90 | 0.188 | 1.12 | 0.31 | 3.99 | 0.862 |

[1]QID, 4 times per day

(32.14% vs. 26.09%, p = 0.604) did not differ between the BID and QID lengthening group. (Table 2). Using IPTW, the result shows no significant effect of QID vs. BID lengthening on minor and major complications (Table 4).

## DISCUSSION

This is the first study to clinically evaluate the effects of lengthening frequency on distraction osteogenesis (DO) for limb lengthening. We found that BID and QID lengthening did not significantly affect HI, callus quality, and minor and major complications.

### *Effects of Lengthening Frequency on Distraction Osteogenesis Outcomes*

Mechanical factors have been shown to affect callus healing in DO significantly.[1,3,7,8,15,16] The optimal distraction rate and mechanical techniques, such as distraction–compression, have improved osteogenesis in animal studies.[17,18] However, the frequency of distraction appears to be of lesser interest and is used most frequently as a standard number. A classic in vivo study by Ilizarov[3] showed that increasing the frequency of distraction positively affects osteogenesis activity; however, the frequency studied was one time/day, four times/day, and 60 times/day. Our study compares BID with QID lengthening, which might explain why the multivariate analysis shows a slight trend towards a better chance of achieving HI < 45 days/cm for the QID group, but the difference is not statistically significant. Therefore, the frequency difference might need to be greater to yield different clinical outcomes.

Mizuta et al. studied the frequency of distraction in a tibial open-edge osteotomies. They reported a higher bone mineral density in the distraction area and a shorter external fixator time for patients who received eight-step distraction compared to four-step.[15] A recent computational modeling study by Fu et al.[19] suggested that a variable distraction rate could improve osteogenesis. Therefore, even though a BID lengthening frequency may cause less patient burden and confusion, it may not be the most suitable frequency of distraction.

The quality of callus formation has been associated with a decrease in HI and the subsidence rate of the callus.[13,14] Although a higher frequency of distraction should lead to better callus quality due to improved osteogenesis activity, it did not show a significant result in a clinical setting. It is well known that many factors can affect the quality of HI and callus. The sample size may not be big enough, and the heterogeneity of patients is high, which may lead to a nonstatistically significant result.

The median healing index in our study is 42.8 days/cm, which is comparable to other studies that did not use an intramedullary magnetic nail for lengthening.[5,8,10,11,20-22] One of the significant factors influencing HI in our study is the bone lengthened being the femur. This is consistent with the findings of De Bastiani et al., Maffulli et al and Koczewski et al.[10,11,22] The femur has more muscle enveloping the bone, resulting in a more robust blood supply and improved osteogenesis.

We found that congenital etiologies had a significantly lower probability of having HI<45days/cm. Maffuli et al. also observed a higher HI for congenital limb deficiency compared to acquired causes.[10] Congenital limb deficiency is characterized not only by bone shorthening, but also by soft tissue contracture and joint instability. Therefore, complications frequently arise in these patients that may

**TABLE 4.** Average treatment effects (ATE) between QID and BID lengthening groups

| Outcomes | QID[1] | | BID[2] | | Δ[3] ATE[4] | 95% CI | *p*-value |
|---|---|---|---|---|---|---|---|
| Primary outcome (mean±SD) | | | | | | | |
| Healing index (days/cm) | 52.8±24.0 | | 50.5±17.1 | | 2.3 | -5.8 to 10.4 | 0.577 |
| Secondary outcome (Risk, 95%CI) | | | | | | | |
| Good callus shape | 0.57 | 0.43 to 0.71 | 0.50 | 0.31 to 0.70 | 0.06 | -0.18 to 0.30 | 0.614 |
| Good callus density | 0.34 | 0.21 to 0.48 | 0.41 | 0.22 to 0.60 | -0.07 | -0.30 to 0.17 | 0.577 |
| Minor and major complications | 0.27 | 0.14 to 0.40 | 0.24 | 0.13 to 0.37 | 0.02 | -0.16 to 0.20 | 0.813 |

[1]QID, 4 times/ day; [2]BID, 2 times/ day; [3]Δ, differences; [4]ATE, Average Treatment Effects

lead to increased HI. The inherent growth potential abnormality may also be a contributing factor.

Age is one of the most discussed factors regarding osteogenesis. We found that younger patients (less than ten years old) are more likely to achieve HI < 45 days/cm. Many studies also show that older patients tend to have a higher HI with various cutpoints from ten to 18 years of age.[8-10,22,23] The younger individual has a thicker periosteum and more robust blood supply with a higher re-modeling potential, leading to improved healing of the distraction site and decreased HI. Although our study did not achieve a significant statistical result, we agreed that the patient's age has a significant impact on the result of DO.

The increase in lengthening magnitude is also associated with a lower HI. Although the time in the distraction phase depends on the length needed, the time in the consolidation phase does not increase in the same proportion. This result is also evidenced in other studies.[8,9,22] The device used for DO also affects HI. Aaron et al.[24] found that the use of the Ilizarov apparatus resulted in a significantly lower healing index compared to the Wagner device. Our study reports the same result but without statistical significance.The Ilizarov method can provide a biomechanically stronger construction because it can incorporate fixation of wires and pins, resulting in greater engagement of the cortex.[25] A more stable construct may contribute to a better mechanical environment and osteogenesis.

The distraction rate is typically one mm/day. However, many studies show that the actual distraction rate achieved is less than that and ranges from 0.5 – 0.8 mm/day.[26-29] Balci et al. found that the lengthening speed of 0.56 mm/day is optimal for lengthening in congenital tibial dysplasia.[30] We also reported a mean distraction rate of 0.73 mm/day and found that a distraction rate < 0.7 mm/day results in almost statistically strong odds of achieving good HI. The importance of the distraction rate should be further investigated as the widely recommended rate of one mm/day might not be the most suitable for all patients.

*Effects of Lengthening Frequency on Distraction Osteogenesis Complications*

Our study reported a high rate of total complications. However, it is generally accepted that limb lengthening procedures are associated with many difficulties.[5,7-10,24] Ankle equinus frequently accompanies tibial lengthening and is one of the most common complications.[31] Our study reveals a similar result with the most common problems being ankle equinus and pin tract infection. However, most of these problems were successfully treated during the DO period. Minor and major complications persist after the DO period and are considered significant for the patient's outcome. We found that BID and QID lengthening results in similar minor and major complication rates. However, since not many patients faced significant complications, we may need more patients in a study to achieve a statistically significant difference.

*Limitations*

There are some limitations to our study. First, the DO in our research was done using either the Ilizarov apparatus or the monolateral fixator device. However, there are other methods for lengthenging, such as magnetic intramedullary nail lengthening and other integrated techniques, which also show promising results.[27,32-34] Therefore, the results may not be directly applicable to other distraction techniques, and warrant further research. Second, many factors contribute to HI. Although we tried to control these factors using IPWT, we may still need a larger number of patients for a more accurate result. Furthermore, the heterogeneity of patients in the study might result in non-significant findings. A more extensive study focused on an interested subgroup, such as congenital limb deficiency, is still needed. Finally, although we cannot verify the effect of the lengthening frequency in this study, we still believe that it contributes significantly to the results of the DO. Therefore, further prospective studies are needed to prove the result.

## CONCLUSION

BID and QID lengthening results in comparable HI and complications for patients who undergo distraction osteogenesis with either the Ilizarov or monolateral fixator. However, more research is required to evaluate the effect of lengthening frequency in a clinical setting.

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## DECLARATIONS

On behalf of all authors, the corresponding author states that there is no conflict of interest

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# Development of Machine Learning Algorithms for Predicting Preoperative and Postoperative Venous Thromboembolism in Patients Undergoing Surgery for Spinal Metastasis

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## ABSTRACT

**Objective:** This study aims to develop and compare machine learning models (MLMs) for predicting venous thromboembolism (VTE) in patients undergoing surgery for spinal metastasis. The study evaluates the predictive capabilities of MLMs for preoperative and postoperative VTE within different time frames.

**Materials and Methods:** A total of 334 patients undergoing surgery for spinal metastasis were included, with a mean age of 57.6 years and 57.2% being male. The investigation assessed postoperative VTE prevalence within 30 and 90 days, with pulmonary embolism (PE) and deep vein thrombosis (DVT) rates at 20% and 80%, respectively. Key patient-related factors—age, body mass index, preoperative ambulatory status, albumin level, hemoglobin level, partial thromboplastin time, and operative time—were considered potential predictors of VTE.

**Results:** The postoperative VTE prevalence was 8.98% within 30 days and 13.47% within 90 days. Age, body mass index, preoperative ambulatory status, albumin level, hemoglobin level, partial thromboplastin time, and operative time emerged as significant VTE predictors. The gradient boosted tree algorithm was the best-performing MLM for predicting VTE within 90 days, with AUC values of 0.77 preoperatively and 0.71 postoperatively. For predicting VTE within 30 days, the support vector machine model was most effective, with AUCs of 0.72 preoperatively and 0.68 postoperatively.

**Conclusion:** Predictive analytics and MLMs effectively predict preoperative and postoperative VTE in patients undergoing surgery for spinal metastasis. Identified key factors and MLM performance metrics offer valuable insights for risk assessment and preventive measures in this patient population.

**Keywords:** Development; machine-learning algorithms; prediction; venous thromboembolism; surgery; spinal metastasis (Siriraj Med J 2024; 76: 381-388)

## INTRODUCTION

Patients with cancer have a 4-6.5 times increased risk of developing venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE).[1-3] The incidence of VTE in spine surgery was reported to range from 0.15-29.38%[4], and the incidence of VTE among patients undergoing surgery for spinal metastasis was 9.48%-11%.[5,6] This data demonstrates that

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patients undergoing surgery for spinal metastasis are at far greater risk for developing VTE. The development of VTE in cancer patients is associated with both increased morbidity and mortality compared to non-cancer patients[3], and the cost of treatment is high.[7]

The two commonly used clinical assessments for VTE risk stratification among surgical patients are the Rogers score[8] and the Caprini risk assessment model.[9] The current models' lack of specificity and limited predictive accuracy for this subgroup necessitate a more focused and refined approach to risk assessment.[10,11]

Enter the realm of machine learning (ML), a subdivision of artificial intelligence that thrives on its capacity to decipher complex patterns within large datasets, a challenge often faced in medical research. ML's inherent capability to integrate and analyze multifaceted clinical data presents a promising avenue to enhance predictive models' accuracy significantly. Previous research has validated ML's potency in predicting adverse outcomes in spine surgery, setting a precedent for its application in VTE risk prediction.[12]

The urgency for advanced predictive analytics is clear: the current gap in precise VTE risk assessment for spinal metastasis surgery patients could be narrowed by employing machine learning models. By developing various MLM algorithms, this study aims to address this gap, offering potentially more accurate predictions for preoperative and postoperative VTE. Not only could this lead to better patient outcomes, but it also stands to optimize the use of healthcare resources and inform preventive strategies, thereby ameliorating the burden of VTE in oncological surgery. In doing so, we align our efforts with the evolving landscape of precision medicine, where patient care is increasingly informed by data-driven insights.

## MATERIALS AND METHODS

### *Guidelines*

We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines, and the Guidelines for Developing and Reporting Machine Learning Models in Biomedical Research.[13,14]

### *Source of data*

The data were obtained from the medical database of the Department of Orthopedic Surgery. We identified consecutive patients retrospectively who underwent spinal surgery between January 2009 and December 2020.

### *Participants*

Participants were selected based on the following criteria: (1) a confirmed diagnosis of spinal metastases classified under the International Classification of Diseases, 10th Revision, Thai Modification (ICD 10-TM) with the specific codes C79.5 and C79.8, (2) being 18 years of age or older, and (3) a documented history of undergoing surgical intervention for spinal metastases located in the cervical, thoracic, lumbar, or sacral regions, which was categorized under the International Classification of Diseases, 9th Revision, Clinical Modification (ICD 9-CM) with the procedural codes 03.0, 03.4, 03.09, 81.0, and the range of 81.00 to 81.08.

We excluded patients with a history of VTE, who had major surgery or major trauma within one month before surgery, who were pregnant, or who had a genetic abnormality, such as anticoagulation proteins C and S, antithrombin III deficiency, or factor V Leiden mutation.

### *Outcome and predictive variables*

The primary outcome of our study was the incidence of postoperative venous thromboembolism in patients with spinal metastasis at 30- and 90-days following surgery.

The following risk factor variables for VTE were identified from previous studies: gender[15,16], age[15-19], diabetes mellitus (DM)[20], hypertension (HT)[16], chronic kidney disease (CKD)[21,22], American Society of Anesthesiologists (ASA) classification[23], body mass index (BMI)[15,24,25], preoperative ambulation status[15,19], preoperative albumin level[23], preoperative hemoglobin level[5], preoperative partial thromboplastin time (PPT)[5], spinal surgery location[15], operative time[6,23], and postoperative blood transfusion.[26-28]

We divided the variables into two groups: the first one using only pre-operative data of patients, and the latter including intra-operative and post-operative data such as blood loss, operative time, etc. Patients with symptomatic venous VTE, as documented in the medical database, were used as the dependent variable in this investigation.

### *Preprocessing*

Multiple imputations with chained equations imputed missing preoperative laboratory characteristics with less than 25% missing data. A class weighting strategy was also used to ensure that the trained model would take each class into account equally despite class imbalance. To reduce the influence of different variable units and quantity levels, we scale numerical variables to a standard

deviation of one and a mean of zero, and we employ dummy encoding for categorical variables. We also get rid of outliers whose lab values are three standard deviations from the average lab value at our hospital.

### *Algorithm training and validation*

For the development and evaluation of our models, we opted for a suite of algorithms including random forest, neural network, logistic regression, gradient boosted tree, support vector machine, XGBoost, decision tree, and stochastic gradient descent. These were implemented using the Python 3.9 programming language and the Scikit-learn 1.0.1 library, which is distributed under a permissive open-source BSD license.

In the process of preparing the dataset for analysis, we performed both manual and automated tuning of hyperparameters via grid and random search methods to ensure the highest predictive accuracy during a fivefold internal cross-validation for each algorithm. The data were split into an 80:20 ratio for training and testing purposes, with the training set being utilized to fit the models, which were then validated through a fivefold cross-validation approach. To counteract any imbalance across the classes, a class weighting technique was employed during model training

The efficacy of the algorithms was assessed using the test set, scrutinizing metrics such as the area under the receiver operating characteristic (ROC) curve (AUC), the F1-score, overall accuracy, and calibration loss. The ROC curve is critical for illustrating the trade-off between the true positive and false positive rates that arise from various thresholds in the predictive model. An AUC score between 0.7 and 0.8 denotes fair model performance, while a score above 0.8 is indicative of good performance. The F1-score—a harmonic mean of precision and recall—reaches its optimal value at 1.0, representing impeccable precision and sensitivity. To evaluate a model's precision, we also analyzed the confusion matrix, which juxtaposes actual versus predicted outcomes. Given that different metrics may present certain trade-offs, such as the balance between precision and recall, the AUC was primarily used for selecting the most suitable model for practical application.

### *Statistical analyses*

The baseline demographic and clinical characteristics of study patients were summarized using descriptive statistics. Continuous data, such as partial thromboplastin time and operative time, are presented as mean plus/minus standard deviation. All other evaluated factors are reported as number and percentage. Study data were recorded and calculated using Microsoft Excel software (Microsoft Corporation, Redmond, WA, USA).

## RESULTS

A total of 334 patients were included in this study. The mean age of study patients was 57.6 years, and 191 (57.2%) of them were men. The postoperative prevalence of VTE within 30 and 90 days of surgery was 30 (8.98%) and 45 (13.47%), respectively (PE 20%, and DVT 80%). Patients who developed VTE were younger, had lower BMI, were not able to ambulate preoperatively, had a higher albumin level, and had a higher hemoglobin level. Other baseline demographic/clinical characteristics and patient outcomes are shown in Table 1. The most common primary tumor sites were lung (27.5%), breast (17.4%), and prostate gland (12.9%) (Table 2).

Regarding VTE prediction within 30 days before spinal surgery, the gradient boosted tree algorithm showed age, preoperative ambulatory status, BMI, albumin level, hemoglobin level, and PTT to be predictive factors (Fig 1). This algorithm had the best AUC (0.77) with accuracy (proportion of correct predictions within the test set) of 0.88, precision (proportion of positive predictions that were indeed positive) of 1, recall (proportion of actual positive values found by the classifier) of 0.11, and F1 score (harmonic mean between precision and recall) of 0.2 (Table 3).

Concerning VTE prediction within 90 days before spinal surgery, the support vector machine algorithm had the best AUC (0.72) with accuracy, precision, recall, and F1 scores of 0.58, 0.25, 0.82, and 0.38, respectively.

Regarding VTE prediction within 30 days after spinal surgery, the gradient boosted tree algorithm showed age, BMI, albumin level, hemoglobin level, PTT, and operative time to be predictive factors (Fig 2). This algorithm had the best AUC (0.71) with accuracy, precision, recall, and F1 scores of 0.88, 0.1, 0.11, and 0.2, respectively.

Concerning VTE within 90 days after spinal surgery, the support vector machine algorithm has the best AUC (0.68) with accuracy, precision, recall, and F1 scores of 0.86, 1.00, 0.09, and 0.17, respectively.

## DISCUSSION

This study including cancer patients with spinal metastasis who underwent spinal surgery. The incidence of postoperative VTE events was 13.5%. Zacharia, et al.[5]

**TABLE 1.** Baseline Characteristics of Patients Undergoing Surgery for Spinal Metastatic Disease, n=334

| Variable | Characteristic | Total | 30-day VTE | | 90-day VTE | |
|---|---|---|---|---|---|---|
| | | N=334 | No, N=304 | Yes, N=30 | No, N=289 | Yes, N=45 |
| Sex | Male | 191 (57.2%) | 178 (58.6%) | 13 (43.3%) | 171 (59.2%) | 20 (44.4%) |
| | Female | 143 (42.8%) | 126 (41.4%) | 17 (56.7%) | 118 (40.8%) | 25 (55.6%) |
| Age (Years) | <65 | 241 (72.2%) | 218 (71.7%) | 23 (76.7%) | 206 (71.3%) | 35 (77.8%) |
| | 65-79 | 86 (25.7%) | 79 (26%) | 7(23.3) | 76(26.3%) | 10 (22.2%) |
| | >79 | 7 (2.1%) | 7 (2.3%) | 0 | 7(2.4%) | 0 |
| Body mass index ($kg/m^2$) | <25 | 258 (77.2%) | 233 (76.6%) | 25 (83.3%) | 223 (77.2%) | 35 (77.8%) |
| | 25-30 | 62 (18.6%) | 59 (19.4%) | 3 (10%) | 55 (19%) | 7 (15.6%) |
| | >30 | 14 (4.2%) | 12 (4%) | 2 (6.7%) | 11 (3.8%) | 3 (6.6%) |
| American Society of Anesthesiologists Classification | 1-2 | 195 (58.4%) | 181 (59.5%) | 14 (46.7%) | 171 (59.2%) | 24 (53.3%) |
| | 3-5 | 139 (41.6%) | 123 (40.5%) | 16 (53.3%) | 118 (40.8%) | 21 (46.7%) |
| Comorbidities | Diabetes | 51 (15.3%) | 46 (15.1%) | 5 (16.7%) | 44 (15.2%) | 7 (15.6%) |
| | Hypertension | 119 (35.6%) | 106 (34.9%) | 13 (43.3%) | 99 (83.2%) | 20 (16.8%) |
| | Chronic kidney disease | 15 (4.5%) | 14 (4.6%) | 1 (3.3%) | 14 (4.8%) | 1 (2.2%) |
| Preoperative ambulatory activity status | No | 187 (56%) | 165 (54.3%) | 22 (73.3%) | 154 (53.3%) | 33 (73.3%) |
| | Yes | 147 (44%) | 139 (45.7%) | 8 (26.7%) | 135 (46.7%) | 12 (26.7%) |
| Albumin (g/dL) | <3.5 | 80 (24%) | 74 (24.3%) | 6 (20%) | 71 (24.6%) | 9 (20%) |
| | ≥3.5 | 249 (76%) | 230 (75.7%) | 24 (80%) | 218 (75.4%) | 36 (80%) |
| Hemoglobin (g/dL) | <10 | 40 (12%) | 35 (11.5%) | 5 (16.7%) | 34 (11.8%) | 6 (13.3%) |
| | ≥10 | 294 (88%) | 269 (88.5%) | 25 (83.3%) | 255 (88.2%) | 39 (86.7%) |
| Partial thromboplastin Time (Sec.) | | 26±3.6 | 26.12±3.63 | 25.03±3.88 | 26.14±3.65 | 25.21±3.72 |
| Index spinal location | Cervical | 33 (9.9%) | 26 (8.6%) | 7 (23.3%) | 25 (8.7%) | 8 (17.8%) |
| | Thoracic | 186 (55.7%) | 175 (57.6%) | 11 (36.7%) | 167 (57.8%) | 19 (42.2%) |
| | Lumbar | 112 (33.5%) | 100 (32.8%) | 13 (40%) | 94 (32.5%) | 18 (40%) |
| | Sacral | 3 (0.9%) | 3 (1.0%) | 0 (0%) | 3 (1.0%) | 0 (0%) |
| Operative Time (min.) | | 192.04±65.93 | 192.49±65.66 | 187.50±69.60 | 193.32±65.58 | 183.89±68.29 |
| Postoperative blood transfusion | | 243 (72.8%) | 221 (72.7%) | 22 (73.3%) | 209 (72.3%) | 34 (75.6%) |

**TABLE 2.** Origin of the primary tumor (n=334)

| Characteristic | N (%) |
|---|---|
| Lung | 92 (27.5) |
| Breast | 58 (17.4) |
| Prostate | 43 (12.9) |
| Liver | 21 (6.3) |
| Kidney | 17 (5.1) |
| Colorectal | 14 (4.2) |
| Thyroid | 14 (4.2) |
| Hematology | 12 (3.6) |
| CholangioCA | 11 (3.3) |
| Nasopharyngeal cancer | 9 (2.7) |
| Cervix | 6 (1.8) |
| Unknown | 8 (2.4) |
| Others* | 29 (8.7) |

*pancreatic cancer 4 (1.2%), soft tissue sarcoma 4 (1.2%), Endometrial cancer 3 (0.9%), tongue cancer 3 (0.9%), bladder cancer 2 (0.6%), esophagus cancer 2 (0.3%), neuroendocrine tumors 1 (0.3%) and hard palate cancer 1 (0.3%).

conducted preoperative DVT screening in patients who were to undergo surgical treatment for spinal metastasis, and they found a 9.48% preoperative incidence of DVT. Groot, et al.[6] reported that 11% of patients developed symptomatic VTE within 90 days of surgical treatment for spinal metastasis. Based on the results of the present study, the most accurate model for predicting VTE within 30 days before or after surgery is the gradient boosted tree algorithm (AUC for preoperative prediction: 0.77, and AUC for postoperative prediction: 0.71). We also found the most accurate model for predicting VTE within 90 days before or after surgery to be the support vector machine algorithm (AUC for preoperative prediction: 0.72, and AUC for postoperative prediction: 0.68). The most important variables in these algorithms are age, BMI, preoperative ambulatory status, albumin level, hemoglobin level, PTT, and operative time. These factors are consistent with previously published studies that reported risk factors for VTE after spine surgery.[5,15,18,19,23,24,26]

Other studies have investigated models that predict complications after spine surgery. Bekelis, et al.[29] conducted a retrospective cohort study that included 13,660 patients. The 30-day incidence of DVT was only 0.6%. Increasing age, alcohol consumption, preoperative neurologic deficit, and corpectomy were found to be significantly associated with a higher likelihood of postoperative DVT. Their model to predict postoperative risk of DVT had an AUC of 0.74. Han, et al.[12] developed machine learning models for predicting adverse events following spine surgery. The incidence of DVT in their study was a low 1.8%; however, the AUC for an overall AE was 0.7 among the six individual prediction models that they had developed.

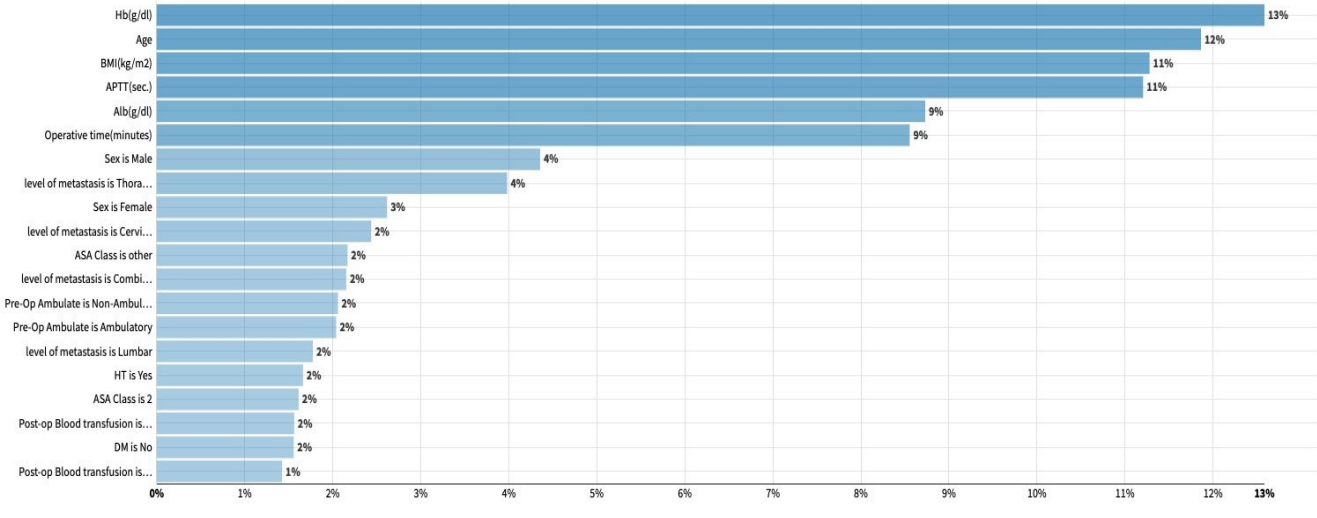


**Fig 1.** Variable importance for the preoperative prediction model.

**TABLE 3.** Machine Learning Model Performance for 30 and 90 days VTE Prediction in Patients Undergoing Surgery for Spinal Metastatic

| Metric | Machines learning algorithm | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Random forest | Logistic Regression | SVM | SGD | Gradient Boosted Trees | Decision Trees | Artificial Neural Network | XG Boost |
| **Pre op 30 days Prediction** | | | | | | | | |
| AUC | 0.62 | 0.64 | 0.59 | 0.65 | 0.77 | 0.59 | 0.63 | 0.69 |
| Accuracy | 0.88 | 0.87 | 0.88 | 0.87 | 0.88 | 0.87 | 0.87 | 0.87 |
| Precision | 1 | 0.5 | 1 | 1 | 1 | 1 | 0.5 | 1 |
| Recall | 0.11 | 0.11 | 0.11 | 0 | 0.11 | 0 | 0.11 | 0 |
| F1 score | 0.2 | 0.18 | 0.2 | 0 | 0.2 | 0 | 0.18 | 0 |
| **Pre op 90 days Prediction** | | | | | | | | |
| AUC | 0.69 | 0.63 | 0.72 | 0.66 | 0.61 | 0.56 | 0.63 | 0.56 |
| Accuracy | 0.59 | 0.59 | 0.58 | 0.7 | 0.57 | 0.16 | 0.52 | 0.57 |
| Precision | 0.24 | 0.23 | 0.25 | 0.27 | 0.21 | 0.16 | 0.21 | 0.19 |
| Recall | 0.73 | 0.64 | 0.82 | 0.55 | 0.64 | 1 | 0.73 | 0.55 |
| F1 score | 0.36 | 0.33 | 0.38 | 0.36 | 0.32 | 0.27 | 0.33 | 0.29 |
| **Post op 30 days Prediction** | | | | | | | | |
| AUC | 0.62 | 0.65 | 0.66 | 0.63 | 0.71 | 0.55 | 0.61 | 0.6 |
| Accuracy | 0.88 | 87 | 0.87 | 0.87 | 0.88 | 0.87 | 0.87 | 0.87 |
| Precision | 1 | 1 | 0.5 | 1 | 1 | 0.5 | 1 | 0.5 |
| Recall | 0.11 | 0 | 0.11 | 0 | 0.11 | 0.11 | 0 | 0.22 |
| F1 score | 0.2 | 0 | 0.18 | 0 | 0.2 | 0.18 | 0 | 0.31 |
| **Post-op 90 days Prediction** | | | | | | | | |
| AUC | 0.67 | 0.59 | 0.68 | 0.66 | 0.63 | 0.55 | 0.63 | 0.65 |
| Accuracy | 0.86 | 0.84 | 0.86 | 0.86 | 0.84 | 0.86 | 0.86 | 0.84 |
| Precision | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Recall | 0 | 0 | 0.09 | 0.09 | 0 | 0.09 | 0.09 | 0.09 |
| F1 score | 0.17 | 0 | 0.17 | 0.17 | 0 | 0.17 | 0.17 | 0 |

**Abbreviations:** AUROC = area under the receiver operating characteristic, SVM = Support Vector Machine, SGD = Stochastic Gradient Descent

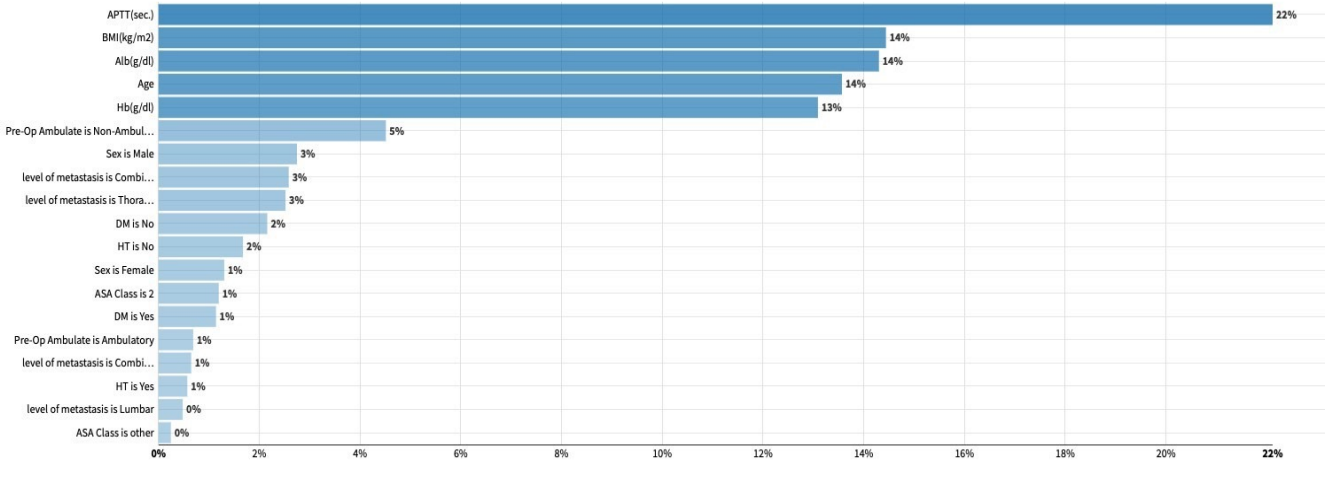


**Fig 2.** Variable importance for the postoperative prediction model.

Rogers score[8] and Caprini score[9] are two commonly used VTE risk assessment models in surgical patients. However, neither of these tools is in any way specific to spinal metastasis surgery, neither includes operative time or blood chemistry investigations, which may influence postoperative VTE development.

Previously developed prediction models included fewer risk factors due to analytic limitations. However, with the use of machine learning modeling, we were able to include 14 important risk factors in the development of our prediction algorithms. To our knowledge, this is the first study in machine learning prediction algorithm development to include both preoperative and postoperative factors in the development of algorithms that predict preoperative and postoperative VTE in patients scheduled to undergo surgery for spinal metastasis.

### Limitations

This study's findings are subject to several limitations, including the inability to differentiate between symptomatic and asymptomatic VTE, which may affect the clinical application of our predictive models. The external validity of our results is constrained by the use of data from a single institution, which may not be representative of broader patient populations. Furthermore, the potential for algorithmic overfitting and the inherent complexity of the machine learning models used could limit the interpretability and generalizability of our findings. Future research should focus on external validation with diverse cohorts, incorporate a broader array of predictive variables, and explore a range of performance metrics beyond AUC to ensure the clinical relevance of the predictive models.

## CONCLUSION

Our study affirms the utility of machine learning models in predicting VTE for spinal metastasis surgery patients, with the gradient boosted trees algorithm showing strong predictive performance for the 30-day timeframe and the support vector machine algorithm standing out for the 90-day predictions. These models have demonstrated good to fair predictive capabilities, as indicated by AUC values aligning with established thresholds. Key factors like age, BMI, and preoperative status, consistent with prior studies, have been instrumental in model accuracy, supporting their integration into clinical risk assessments to potentially enhance patient care.

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### Conflits of interest

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

### Ethics approval

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 1065/2020), and written informed consent was not obtained due to the retrospective nature of this study.

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