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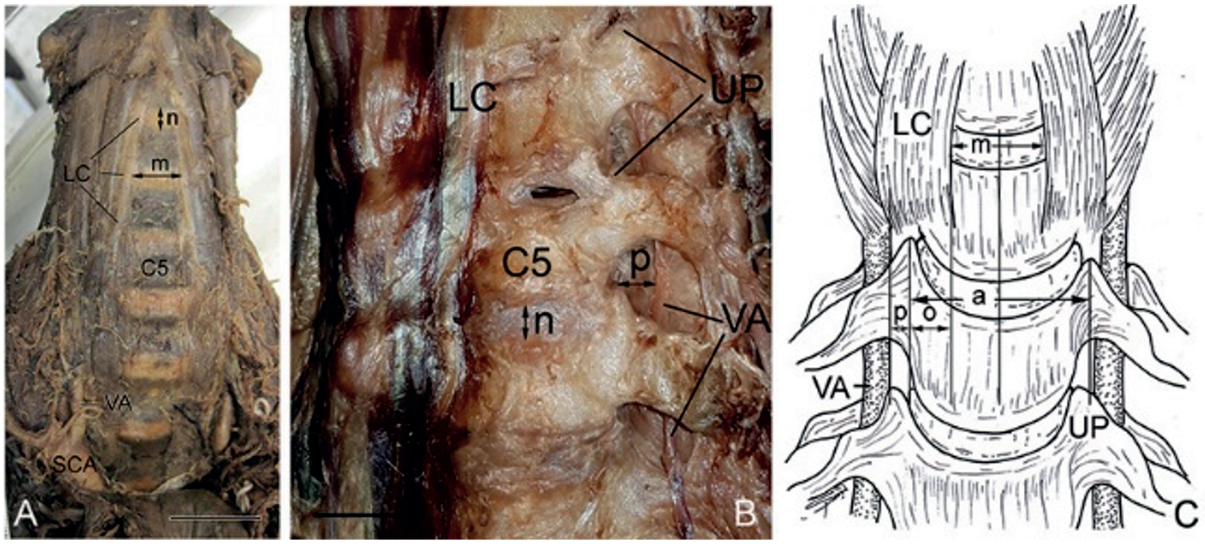

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Hidden Neuropathic Pain in Chronic Low Back Pain: Prevalence, Pattern, and Impact on Quality of Life

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ABSTRACT

Objective: A patient with Neuropathic Pain (NP) may suffer from pure NP or may have mixed nociceptive and neuropathic pain. No previous study has investigated NP among Thai patients with Chronic Low Back Pain (CLBP). This study aimed to investigate the prevalence and clinical presentation of NP, and the impact of NP on Quality of Life (QoL) in Thai Chronic Low Back Pain (CLBP) patients.

Materials and Methods: Adult patients with CLBP longer than 3 months were included. NP was detected by painDETECT questionnaire, and NP was defined as a score 19. Demographic data, pain characteristics, treatment, Oswestry Disability Index (ODI), and quality of life score (Short Form 36, SF-36) were recorded.

Results: 371 CLBP patients were enrolled. The overall prevalence of neuropathic pain was 50.1% (95% CI: 44.9-55.3%). The prevalence of NP in patients with axial low back pain, back pain with pain radiating above the knee, and back pain with pain radiating below the knee was 28.3%, 58.21%, and 59.5%, respectively. Only 48.9% of patients with NP received neuropathic pain medication. Multivariate analysis showed only older age to be associated with NP (OR: 1.017, 95% CI: 1.002-1.033). NP patients had a significantly higher ODI score. There is no difference in most dimension of SF-36 scores, except marginally higher general health and vitality dimension scores.

Conclusion: Prevalence of NP in Thai CLBP patients is high. Additionally, it is undertreated and associated with higher disability especially among patients with radiating pain above the knee. Older age is an independent predictor of NP.

Keywords: Neuropathic pain; chronic low back pain; quality of life; low back pain; Thailand. (Siriraj Med J 2022; 74: 480-486)

INTRODUCTION

In addition to being one of the most prevalent pain conditions[1,2], chronic low back pain (CLBP) is associated with high healthcare costs, reduced productivity, and disability.[3-5] Physicians generally consider CLBP to be nociceptive pain, so it is treated as such. However, several studies have reported a high prevalence of neuropathic pain (NP) in CLBP.[4,6-14]

NP and nociceptive pain are different both in their pathophysiology and their management. Additionally, the cost associated with treating neuropathic LBP is estimated to be 70% higher than the cost associated with treating nociceptive Low Back Pain(LBP).[8] A patient with NP may suffer from pure NP or may have mixed nociceptive and neuropathic pain. The recognition of the presence of NP in CLBP may represent an important advancement in

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the treatment of CLBP because NP requires treatment with agents different from those used to treat nociceptive pain. Instead of non-steroidal anti-inflammatory agents (NSAIDs) and/or skeletal muscle relaxants that are used to treat nociceptive pain, different classes of medications, such as gabapentinoids, tricyclic antidepressants, and/or selective serotonin reuptake inhibitors, were found to be more efficacious for managing NP.[6] Additionally, the treatment of NP requires comprehensive evaluation via a multimodal, multidisciplinary approach to restore function and prevent disability.[6]

No previous study has investigated NP among Thai patients with CLBP, so this study aimed to investigate the prevalence and clinical presentation of NP and to evaluate the impact of NP on quality of life in Thai CLBP patients. We used the painDETECT questionnaire to identify NP[15], the Oswestry Disability Index (ODI) to evaluate disability[16], and Short Form 36 (SF-36) to assess the quality of life (QoL).[17]

MATERIALS AND METHODS

Subject recruitment

After receiving approval from the Institutional Review Board (Si 215/2013 [EC3]), adult patients aged ≥ 18 years with CLBP for longer than 3 months during 2013-2014 were enrolled. Patients with a cognitive or mental disorder, or who had trauma, infection, or cancer at the lower back area were excluded.

Study data

After granting informed consent, study data were collected from four questionnaires, including a demographic data questionnaire, ODI questionnaire, painDETECT questionnaire, and SF-36 questionnaire. Other data that were collected included gender, age, body mass index (BMI), underlying disease, previous spinal surgery, and duration of pain. The Thai version of the ODI[18] was used to assess disability, and this questionnaire has 10 questions. The score ranges from 0 (no disability) to 100 (high disability).

There are a variety of questionnaires that can be used to detect and diagnose NP, including Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[19] and Douleur Neuropathique 4 Questions (DN4).[20] However, we chose the painDETECT tool for this study because this questionnaire was specifically designed to detect NP in patients with CLBP. The painDETECT tool has high sensitivity (85%), specificity (80%), and positive predictive value (83%).[15] There is also no need for physical examination or for medical personnel to administer this questionnaire. NP was screened by painDETECT questionnaire that had 7 questions, pain course pattern, and radiating pain items. The score ranges from 0 (low risk for NP) to 38 (high risk for NP). The presence of NP was defined as a painDETECT score greater than 19.

Quality of life was assessed using the Thai version of the Short Form 36 (SF-36) health survey.[21] This is a 36-question patient-report questionnaire that includes the following domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

Sample size calculation and statistical analysis

Hassan, *et al.* reported the prevalence of NP in CLBP to be 41%.[12] Using that prevalence rate, an alpha error of 0.05, and power of 80%, a sample size of 371 was calculated. The Chi-square test, Fisher's exact test, or Mann-Whitney U test was used to compare data between groups depending on the type and distribution of individual variables. Factors with a *p*-value less than 0.1 in univariate analysis were entered into multivariate analysis. All statistical analyses were performed using SPSS software, version 18.0, and two-tailed *p*-values less than 0.05 were considered statistically significant.

RESULTS

Three hundred and seventy-one patients (250 females, 121 males) were enrolled. The overall prevalence of NP in patients with CLBP was 50.1% (95% CI: 44.9-55.3%). The average age was 50.64±14.48 years, and the mean duration of back pain was 37.04±51.12 months. Patient characteristics, including gender, age, BMI, underlying disease, previous surgery, and pain duration, are shown in Table 1. The only variable that was found to be independently associated with a higher incidence of NP by multiple logistic regression was older age (odds ratio [OR]: 1.017, 95% confidence interval [CI]: 1.002-1.033).

Our study population (N=371) was also classified into three subgroups according to pain characteristic, as follows: 99 patients (27%) experienced predominant axial low back pain, 67 patients (18%) reported back pain and pain radiating above the knee, and 200 patients (54%) reported back pain and pain radiating below the knee. Five patients (1%) could not be classified into any category. The prevalence of NP from subgroup analysis was 28.3% (95% CI: 19.91-38.36), 58.21% (95% CI: 45.54-69.94), and 59.5% (95% CI: 52.33-66.3) for the axial pain, axial pain and pain radiating above the knee, and axial pain and pain radiating below the knee subgroups, respectively (Table 2).

Almost half (48.9%) of the patients suffering from NP were prescribed at least one neuropathic pain medication

TABLE 1. Characteristics of chronic low back pain patients.

Factors	Total (n=371)	Neuropathic pain (n=186)	Non-neuropathic pain (n=185)	*P*-value
Gender				
Female	250 (67.4%)	127 (68.3%)	123 (66.5%)	0.713
Male	121 (32.6%)	59 (31.7%)	62 (33.5%)	
Mean Age (Yr)	50.64±14.48	52.36±13.66	48.91±15.11	0.031*
BMI categories				
Obese II (> 30 kg/m^2)	34 (9.2%)	14 (7.6%)	20 (10.9%)	0.224
Obese I (25.0-29.9 kg/m^2)	109 (29.4%)	57 (30.8%)	52 (28.3%)	0.930
Overweight (23.0-24.9 kg/m^2)	68 (18.3%)	33 (17.8%)	35 (19.0%)	0.558
Normal (18.5-22.9 kg/m^2)	140 (37.7%)	74 (40.0%)	66 (35.9%)	1.000
Underweight (< 18.5 kg/m^2)	18 (4.85%)	7 (3.8%)	11 (6.0%)	0.269
Underlying disease	161 (43.4%)	78 (41.9%)	83 (44.9%)	0.633
Previous spinal surgery	8 (3.1%)	2 (1.1%)	6 (3.6%)	0.176
Mean Duration of pain (month)	37.04±51.12	38.02 ±54.65	36.05±47.44	0.573

Values are presented as mean±standard deviation or number (%), *Multiple logistic regression

TABLE 2. Show prevalence of neuropathic pain and treatment by pain location.

Pain location	Prevalence of neuropathic pain (%) (95% CI)	Neuropathic pain receiving neuropathic pain medications* (%)
Axial low back pain	28.3 (19.91, 38.36)	25
Back pain with radiating pain above knee	58.21 (45.54, 69.94)	30.8
Back pain with radiating pain below knee	59.5 (52.33, 66.3)	60.5

*considered gabapentinoid (gabapentin, pregabalin), tricyclic antidepressants or selective serotonin reuptake inhibitors

(gabapentinoid, tricyclic antidepressant, or selective serotonin-norepinephrine reuptake inhibitors). The prevalence of prescription of NP medication was 25%, 30.8%, and 60.5% in the axial low back pain, axial pain and pain radiating above the knee, and axial pain and pain radiating below the knee subgroups, respectively (Table 2).

Overall, NP was also found to be significantly associated with higher disability as measured by Oswestry Disability Index (ODI). The ODI was also found to be higher in all 3 of the aforementioned subgroups; however, only the back pain with pain radiating above the knee subgroup showed a statistically significantly higher ODI (Table 3). There was no significant difference between the NP and non-NP groups relative to SF-36 score, except for the general health dimension (47.77±7.61 vs. 46.19±7.33, p=0.020) and the vitality dimension (49.08±5.81 vs. 47.57±6.35, p=0.025), which demonstrated a statistically significantly higher score in NP patients, respectively (Table 4).

TABLE 3. Show Oswestry disability index by pain location.

Pain location	ODI neuropathic pain	ODI non-neuropathic pain	*P*-value
Over all	34.11±11.08	29.71±12.86	<0.001
Axial low back pain	29.59±11.83	26.41±12.27	0.212
Back pain with radiating pain above the knee	31.84±8.04	26.93±9.15	0.023
Back pain with radiating pain below the knee	35.92±11.39	33.58±13.45	0.146

Abbreviation: ODI; Oswestry disability index,
Values are presented as as mean±standard deviation. p-value by Chi-square test, Fisher's exact test, or Mann-Whitney U test

TABLE 4. Show quality of life scoring in each dimension of SF-36.

Dimensions	Neuropathic pain (n=186)	Non-Neuropathic pain (n=185)	*P*-value
Physical Functioning	35.90± 8.37	36.18 ±9.08	0.842
Role-Physical	35.80± 7.41	36.21± 8.51	0.937
Bodily Pain	34.49±5.34	34.78±6.69	0.673
General Health	47.77±7.61	46.19±7.33	0.020*
Vitality	49.08±5.81	47.57±6.35	0.025*
Social Functioning	37.29±7.84	38.35±9.83	0.554
Role-Emotional	30.91±9.68	31.18±10.09	0.978
Mental Health	42.20±6.77	41.53±7.66	0.520
PCS	39.01±5.374	39.02±6.24	0.654
MCS	40.83±6.38	40.43±7.20	0.470

Values are presented as mean±standard deviation. *Multiple logistic regression

DISCUSSION

The prevalence of NP in CLBP in the present study was 50%. Surprisingly, patients with back pain and pain radiating above the knee, which is what most physicians consider nociceptive pain, had the highest prevalence of NP (58.21%). Previous studies reported a prevalence of NP in CLBP that ranged from 1.6% to 80%.[4,11-13,22,23] The wide range of reported prevalence may be explained by differences in sample size, differences in the reference scores and/or type(s) of questionnaires used, and differences in the locations of pain.

Studies that used the painDETECT survey reported 1.6-50.1% prevalence of NP, while studies that used the DN4 tool reported 15-80%, and studies that used the LANSS tool reported 2.8-55%. However, Sakai, *et al.*[10] used a painDETECT NP cutoff of 13, whereas the others used an NP cutoff of 19. Interestingly, we found a 58.2% prevalence of NP among patients reporting back pain and pain radiating above the knee; however, Atta, *et al.*[11] reported only a 15% prevalence of NP among patients complaining of the same combination of pain. A possible explanation for this difference between studies

is that Atta, *et al.* used DN4 instead of painDETECT as a screening tool. Physicians usually consider radiating pain to the posterior thigh as referred pain from nociceptive low back pain. Surprisingly, patients with back pain and pain radiating above the knee had a similarly high prevalence of NP as patients with back pain and pain radiating below the knee. Moreover, and importantly, patients in the group with back pain and pain radiating above the knee had a significantly higher disability score, and a far lower proportion of patients being treated with NP medication compared to the below the knee group.

Many independent risk factors for NP in CLBP were reported from previous studies, including advanced age[4,7], female gender[4,7,14], male gender[9], pain intensity[9,14], diabetes mellitus[4,7], lumbar, abdominal, or pelvic surgery[7,23], alcohol consumption[23], Caucasian race[7], and smoking.[7] The present study found only advanced age to be an independent risk factor for NP, which is consistent with the results of studies conducted by El Sissi, *et al.*[4] and Kaki, *et al.*[7] A review of the literature is shown in Table 5.

We found that patients with NP had a higher disability than those who didn't have NP, and this finding was also previously reported.[9,13,24] Spahr *et al.* reported that CLBP patients with NP had significantly greater visual analog scale (VAS) pain scores, anxiety, depression, and psychological distress. The patients in that same study also had significantly poorer quality of life according to SF-36, including vitality, physical functioning, bodily pain, social function, and mental health.[13] In our study, there is no difference in most of the dimensions of SF-36, except vitality and general health dimensions, which were found to be statistically significantly higher in the NP group than in the non-NP group. Nevertheless, even if, the minimal clinically important difference (MCID) for these two SF-36 dimensions has not yet been established, these marginal differences (47.77±7.61 VS 46.19±7.33 and 49.08±5.81VS 47.57±6.35) are unlikely to have clinical significance. Chaisewikul, *et al.* reported the effectiveness of original and generic gabapentin in 356 patients who presented with neuropathic pain in each group. The original group enrolled 82 lumbar spondylosis with radiculopathy (23.0%), 15 herniated nucleus pulposus (4.2 %), and 52 spinal stenosis with radiculopathy (14.6%). The generic group enrolled 101 lumbar spondylosis with radiculopathy (28.4%), 16 herniated nucleus pulposus (5.1 %), and 51 spinal stenosis with radiculopathy (14.3%). The result showed the favorable response was reported in 91% in the original group and 95.2% in the generic group. Unfortunately, this study did not clearly define the exact number of patients who had chronic back pain with neuropathic pain. However, the result may help physicians choose the proper analgesic drug for neuropathic pain.[25] The other treatments including physiotherapy and Thai traditional treatment were reported. The back exercises including pelvic tilting, back extension, and knee to chest at least 3 days a week for 12 weeks can effectively relieve lower back pain and improve disabilities among patients who suffer from chronic low back pain.[26] Thepsongwat, *et al.* report the effectiveness of royal Thai traditional massage in the neck, shoulder, or back patients. This study enrolled the chronic pain patients (pain more than 6 months) for 42.6 %. The result showed 74.5% response rates in back pain and 73.5% in chronic pain participants.[27] Additionally, Verayachanku, *et al.* reported the efficacy and safety of poly-herbal formula Sahatsatara (SHT) in pain reduction in acute low back pain patients. The results show HT was not inferior to ibuprofen in pain relieving and disability in patients with acute LBP.[28]

To the best of our knowledge, this is the first study to investigate the prevalence and characteristics of NP, and the effect of NP on quality of life among CLBP patients in Thailand. The limitations of this study include its relatively small sample size and the fact that its study was conducted at a large urban national tertiary referral center. The later limitation suggests that our findings may not reflect and/or be generalizable to other care settings in Thailand. Lastly, as painDETECT is only a screening tool for NP, the positive screening is not the definite diagnosis of NP. The individual confirmation of NP by the standard guideline[29] is needed for a more definite result.

CONCLUSION

The prevalence of NP in Thai CLBP patients is high, especially in patients with back pain and pain radiating above or below the knee. Older age is an independent predictor of NP. NP is currently undertreated, especially axial pain and pain radiating above the knee.

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Competing interests:

This study was approved by the Institutional Review Board (Si 215/2013 [EC3]) and written informed consent was obtained from all participants.

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

TABLE 5. Show results of previous studies.

Author	Year	N	Tool/group	Prevalence (%)	Risk factors
Present study		371	PainDETECT >19 • Axial back pain • pain radiating proximal knee • pain radiating below the knee	50.1 28.3 58.21 59.50	advanced age
Kim et al.[9]	2017	1200	DN4 >4	41	• male • severe pain • had pain based on radiological and neurological findings
Sakai et al.[10]	2015	32	NePSQ PainDETECT ≥13	43.3 15.6	
Atta et al.[11]	2011	132	DN4 >4 • pain radiating proximal knee • pain radiating below the knee without neurologic signs • pain radiating towards the foot	 15 39 80	
El Sissi et al.[4]	2010	1134	LANSS ≥12	55	• advanced age • female • diabetes
Kaki et al.[7]	2005	1169	LANSS ≥12	54.7	• advanced age • female • increased height • white race • hypertension /Diabetes • smoking • previous back surgery • previous medications
Hassan et al.[12]	2005	100	LANSS >12	41	
Andrasinova et al.[22]	2016	63	painDETECT >19	1.6	
Spahr et al.[13]	2017	50	PainDETECT >19	48	
Sivas et al.[14]	2018	101	DN4 >4 LANSS >12	65.3 40.6	• female • occupation • VAS scores
Li et al.[23]	2018	2116	LANSS >12	2.8	• lumbar surgery • abdominal or pelvic surgery • drinking alcohol

Abbreviations: painDETECT; The painDETECT questionnaire, DN4; Self-completed douleur neuropathique 4 Questions, NePSQ; Neuropathic Pain Screening Questionnaire, LANSS; Self-completed Leeds Assessment of neuropathic Symptoms and Signs pain scale

Abbreviations

NP : Neuropathic Pain
QoL : Quality of Life
CLBP : Chronic Low Back Pain
LBP : Low Back Pain
ODI : Oswestry Disability Index
SF-36 : Short Form 36
LANSS : Leeds Assessment of Neuropathic Symptoms and Signs pain scale
DN4 : Douleur Neuropathique 4 Questions

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Multimodality-guided Transbronchial Lung Biopsy in Peripheral Pulmonary Nodules: A Comparison Between using an Electromagnetic Navigation Bronchoscopy and a Thin Bronchoscope

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ABSTRACT

Objective: To compare the diagnostic yield of using a thin bronchoscope (TB) and ENB in the diagnosis of small PPNs combined with routine R-EBUS and fluoroscopy.

Materials and Methods: Patients with a PPN less than or equal to 30 mm were randomly assigned into 2 groups: 4 mm thin bronchoscope (TB group) and 5.9 mm conventional bronchoscope with an ENB (the superDimension®) system (ENB group).

Results: In total, 49 patients were enrolled and randomized into two groups: TB group (n = 24) and ENB group (n = 25). The mean size of the PPNs was 22 mm. There was no difference in nodule size, location of the nodules, the presence of computed tomography (CT) bronchus sign, and EBUS location between the groups. The diagnostic yields were 73.9% and 66.7% in the TB group and ENB group, respectively. There was no statistically significant difference in the diagnostic yield between the two groups. Multivariate analysis showed that the diagnostic yield was significantly higher when there was also a CT bronchus sign (odds ratio 48.82, p = 0.031) and when the bronchoscope could reach a greater airway depth (odds ratio 6.21, p = 0.023). The overall complication was 2%, which was pneumothorax in one patient in the TB group.

Conclusion: Multimodality-guided techniques can improve the diagnostic yield in the diagnosis of PPNs. The PPNs larger than 2 cm with the presence of CT bronchus sign, the ENB provides a similar diagnostic yield compared to the thin bronchoscope. Further analysis and adequately powered prospective studies are required to confirm the advantages of ENB.

Keywords: Electromagnetic navigation; bronchoscopy; peripheral pulmonary nodule; navigation bronchoscopy (Siriraj Med J 2022; 74: 487-494)

INTRODUCTION

The prevalence of malignancy in various studies evaluating patients with noncalcified pulmonary nodules ranges from 2%–82%.[1-3] Peripheral pulmonary nodules (PPNs) are technically challenging to diagnose with conventional flexible bronchoscopy, which has demonstrated varying diagnostic yields, depending on a number of factors, including the size and location of nodules, the presence of the computed tomography (CT) bronchus sign, and endobronchial ultrasound (EBUS) location.

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Over the last decade, various bronchoscopic techniques have been developed to improve the diagnostic yield for the diagnosis of PPNs, including radial probe endobronchial ultrasound (R-EBUS), endobronchial ultrasound using a guide sheath (EBUS-GS), thin and ultrathin bronchoscopes, virtual bronchoscopic navigation (VBN), and electromagnetic navigation bronchoscopy (ENB). A previous study from our center reported a diagnostic yield of R-EBUS in the diagnosis of PPNs of 66.4%.[4] Combining R-EBUS with other bronchoscopic procedures, such as using a thin bronchoscope or electromagnetic navigation bronchoscopy, may improve the diagnostic yield.[5-7]

A thin bronchoscope (TB) can be advanced to the more distal bronchi compared with a conventional bronchoscope. A previous study reported a diagnostic yield of 65% from using a 3.4 mm bronchoscope with R-EBUS in the diagnosis of PPNs.[6] The ENB method uses an electromagnetic field to track a locatable guide in real time, correlating its position in the tracheobronchial tree to the patient's computed tomography (CT) scan. Several studies have reported some improvement in the diagnostic yield from using ENB, ranging from 54% to 75%.[5] The present study aimed to compare the diagnostic yield of using a thin bronchoscope and conventional bronchoscope with ENB in the diagnosis of small PPNs less than or equal to 30 mm.

MATERIALS AND METHODS

Patients

The present study was a prospective, single-center, randomized study. The inclusion criteria were patients with a small PPN defined by a size less than or equal to 30 mm in the longest diameter, with no evidence of endobronchial lesion, and who underwent bronchoscopy between April 2016 and January 2017 at the Division of Respiratory Disease and Tuberculosis, Faculty of Medicine Siriraj Hospital. The exclusion criteria were patients who were pregnant or had a contraindication for bronchoscopy or transbronchial lung biopsy (TBLB). The primary objective was to compare the diagnostic yield of using a thin bronchoscope and conventional bronchoscope with ENB in the diagnosis of small PPNs. The secondary objectives included assessing the factors affecting the diagnostic yield and complications of the procedures. All the chest radiographs and CT chest scans were reviewed. The baseline characteristic of the patients and PPNs, including the longest diameter, type of lesion, location, and the presence of the CT bronchus sign were recorded. All the patients provided their written informed consent.

The patients were randomly assigned in a 1:1 ratio into 2 groups: TB group and ENB group. The randomization sequence was computer generated in block sizes of 4. In the TB group, a thin bronchoscope (BF-MP60, 4 mm diameter, 2.0 mm working channel diameter; Olympus, Tokyo, Japan) was used. In the ENB group, a conventional bronchoscope (BF type TE2, 5.9 mm diameter, 2.8 mm working channel diameter; Olympus, Tokyo, Japan) and electromagnetic navigation system (superDimension®; Medtronic, Minneapolis, MN, USA) were used. In both groups, R-EBUS (UM-S20-20R, 20 MHz, 1.7 mm distal end diameter; Olympus, Tokyo, Japan) and fluoroscopy were used to confirm the location of the lesion and biopsy forceps before performing TBLB. The procedures in both groups were performed by a single bronchoscopist.

Procedures

Thin bronchoscope (TB group)

The bronchoscopic procedures were performed using local anesthesia with lidocaine and moderate conscious sedation with intravenous midazolam and fentanyl. When the target bronchus was located, the R-EBUS probe was inserted through the bronchoscopic working channel. When the EBUS image was obtained, TBLB was performed under fluoroscopic guidance followed by bronchoalveolar lavage. We did not perform brushing and transbronchial needle aspiration.

The bronchus level reached by the bronchoscope, the location of the R-EBUS probe related to the lesion on an EBUS image, and any procedure-related complications were recorded. The biopsy specimens were immersed in 10% formalin and analyzed by pulmonary pathologists. Pneumothorax was screened for using fluoroscopy in all patients immediately after the procedure.

The final diagnoses were established by the cytology, histopathology, and microbiology results. Malignancy was diagnosed based on the histopathology results obtained from the bronchoscopic biopsy. The diagnosis of benign diseases was confirmed by histopathology with or without microbiological evidence of infection. All patients with non-diagnostic bronchoscopy were either subjected to alternative procedures (e.g., repeat bronchoscopy, CT-guided transthoracic core needle biopsy, and surgical resection) or followed up with a combination of clinical data and CT chest for a minimum of 24 months. When an alternative diagnosis was established, these cases were considered to be a negative diagnostic yield. If the patients showed both clinical and radiological stability or improvement, the lesion was considered to be a true benign lesion.

Electromagnetic navigation bronchoscopy (ENB group)

Pre-procedural planning for identification of the target lesion, airway path, and registration points was performed after importing the CT data into the superDimension® software. The bronchoscopic techniques applied were similar to in the TB group except they were performed under real-time navigation. When the bronchoscope was located in the bronchus of interest, the locatable guide was withdrawn and the R-EBUS probe was inserted through the extended working channel (EWC). When the EBUS image was obtained, TBLB was performed under fluoroscopic guidance followed by bronchoalveolar lavage.

Statistical analyses

Initially, we decided to analyze the results using a non-inferiority design based on the diagnostic yields of TB and ENB in the diagnosis of PPNs reported in a previous study (59% and 88%, respectively). Non-inferiority of the TB method was concluded if the lower border of the 95% confidence interval (CI) for the difference in the diagnostic yields exceeded the predetermined non-inferiority border of 5%. We calculated that demonstration of non-inferiority with a statistical power of 80% at a one-sided significance level of 0.05 would require a minimum of 38 patients per group. Unfortunately, we could not recruit enough patients to carry out this study due to the limitation in material support. Thus, finally, we decided to compare the diagnostic yields of TB and ENB using Fisher's exact test. The continuous variables were presented as the mean or median and standard deviation. Pearson's chi-square test or Fisher's exact test were used to test the association between the categorical variables. The unpaired t-test was used to test the difference in means of the normally distributed quantitative variables. Results were considered statistically significant when the p-value was less than 0.05. All the statistical analyses were performed using statistical software (SPSS for Windows, version 20.0; SPSS; Chicago, IL, USA).

The study was approved by the ethics committee of our institution (Si 213/2016). Written informed consent was obtained from all patients prior to the bronchoscopic procedures.

RESULTS

We enrolled a total of 49 patients (24 patients in the TB group and 25 patients in the ENB group). There was no statistically significant differences in the characteristics of the patients between both groups except for sex (Table 1).

The diagnostic yields were 73.9% and 66.7% in the TB group and ENB group, respectively. There was no significant difference in the diagnostic yield between the two groups (p = 0.587). The final diagnoses are summarized in Table 2. The prevalence of malignancy was 71.4% (66.7% in the TB group and 76% in the ENB group, p = 0.344), in which adenocarcinoma was the most common histopathologic result. The most common diagnosis of benign disease was pulmonary tuberculosis. The diagnosis remains unknown in 2 patients (4.1%) due to their loss to follow-up. There was no significant difference in diagnostic yield regarding nodule size, location of the nodules, EBUS location, and diagnosis of malignancy. The presence of the CT bronchus sign had a higher diagnostic yield compared to the absence of the CT bronchus sign (p = 0.05).

In the non-diagnostic group, the final diagnosis was made by repeated bronchoscopy (2 cases), surgical resection (7 cases), CT-guided transthoracic core needle biopsy (1 case), and follow-up CT chest (4 cases).

The thin bronchoscope reached more distal segmental bronchi compared to the conventional bronchoscope in the ENB group, but there was no statistical significance (Table 3). PPNs were identified by R-EBUS in 89.8% of cases (87.5% in the TB group and 92% in the ENB group, p = 0.835). The mean number of TBLBs was 7 in both groups. The multivariate analysis showed that the presence of the CT bronchus sign and more distal segmental bronchi reached by the bronchoscope were associated with an improvement of the diagnostic yield, as shown in Table 5 (OR 48.82, p = 0.031 and 6.21, p = 0.023, respectively). The overall complication was 2%, which was pneumothorax that occurred in one patient in the TB group and which required chest tube drainage.

DISCUSSION

Several studies have reported that the multimodality of guided bronchoscopy can improve the diagnostic yield of PPNs.[7] In our center, we routinely use R-EBUS and fluoroscopy to confirm the location of lesions and biopsy forceps before performing TBLB. R-EBUS has demonstrated various diagnostic yields in the diagnosis of PPNs with some limitations,[7-9] including that R-EBUS is not a real-time guided procedure and the position of tip of the bronchoscope can be lost during EBUS probe withdrawal prior to introduction of the biopsy forceps. Our center previously reported a diagnostic yield of 66.4% for R-EBUS combined with fluoroscopy in the diagnosis of PPNs.[4] The combined use of R-EBUS with other guided techniques may improve the diagnostic yield.[1-3,7] The present study investigated the diagnostic yields of TB and ENB in the diagnosis of small PPNs less

TABLE 1. Characteristics of patients and pulmonary nodules.

Baseline characteristics	TB group, N (%)	ENB group, N (%)	*P* value
N	24	25	
Age, years (mean ± SD)	67 ± 13	63 ± 10	0.318
Male	16 (66.7)	9 (36)	0.032
Size, mm (mean ± SD)	20 ± 6.1	23.36 ± 6.36	0.184
Nodule size			0.477
Less than 20 mm	13 (54.2)	11 (44)	
20-30 mm	11 (45.8)	14 (56)	
Type of nodule			0.613
Solid nodule	23 (95.8)	23 (92)	
Ground glass nodule	0 (0)	1 (4)	
Subsolid	1 (4.2)	1 (4)	
Location of nodule			0.180
Right upper	6 (25)	8 (32)	
Right middle	4 (16.7)	3 (12)	
Right lower	3 (12.5)	10 (40)	
Left upper	5 (20.8)	2 (8)	
Lingula	2 (8.3)	1 (4)	
Left lower	4 (16.7)	1 (4)	
CT bronchus sign	15 (62.5)	14 (56)	0.644

Abbreviations: ENB; electromagnetic navigation bronchoscopy, TB; thin bronchoscope, SD; standard deviation, mm; millimeter, CT; computed tomography

TABLE 2. Final diagnosis.

Final diagnosis	TB group, N (%)	ENB group, N (%)	*P* value
Final diagnosis			0.344
Malignancy	16 (66.7)	19 (76)	
Adenocarcinoma	11	11	
Squamous cell carcinoma	1	2	
Adenoid cystic carcinoma	0	1	
Carcinoid tumor	1	0	
Metastatic carcinoma	2	5	
Malignant melanoma	1	0	
Benign diseases	7 (29.2)	5 (20)	
Pulmonary tuberculosis	4	3	
Organizing pneumonia	1	0	
Other benign diseases	2	2	
Undetermined	1 (4.2)	1 (4)	

TABLE 3. Bronchoscopic results.

Bronchoscopic results	TB group, N (%)	ENB group, N (%)	*P* value
Airway generation (mean ± SD)	5 ± 1	4 ± 1	0.252
EBUS location			0.835
Within the lesion	10 (41.7)	12 (48)	
Adjacent to the lesion	11 (45.8)	11 (44)	
Not seen the lesion	3 (12.5)	2 (8)	
Pieces of TBLB (mean ± SD)	7 ± 1	7 ± 1	0.275
Complications			0.488
Massive bleeding	0 (0)	0 (0)	
Pneumothorax	1 (4.2)	0 (0)	
Severe hypoxemia	0 (0)	0 (0)	
Others	0 (0)	0 (0)	

Abbreviations: SD; standard deviation, EBUS; endobronchial ultrasound, TBLB; transbronchial lung biopsy

TABLE 4. Diagnostic yield.

Variables	TB group,	ENB group, N (%)	*P* value N (%)
N	23	24	
Overall diagnostic yield	17 (73.9)	16 (66.7)	0.587
Nodule size			0.775
Less than 20 mm	9 (75)	6 (60)	
20-30 mm	8 (72.7)	10 (71.4)	
Type of nodule			1.000
Solid nodule	16 (72.7)	15 (65.2)	
Ground glass nodule	-	-	
Subsolid	1 (100)	1 (100)	
Location of nodule			0.246
Right upper	4 (66.7)	5 (62.5)	
Right middle	3 (75)	3 (100)	
Right lower	2 (66.7)	4 (44.4)	
Left upper	5 (100)	2 (100)	
Lingula	1 (50)	1 (100)	
Left lower	2 (66.7)	1 (100)	
CT bronchus sign			0.050
Presence	12 (85.7)	10 (76.9)	
Absence	5 (55.6)	6 (54.5)	
EBUS location			0.714
Within the lesion	8 (80)	9 (75)	
Adjacent to the lesion	8 (80)	7 (70)	
Not seen the lesion	1 (33.3)	0 (0)	
Diagnosis			0.460
Malignancy	12 (75)	13 (68.4)	
Benign	5 (71.4)	3 (60)	

Abbreviations: ENB; electromagnetic navigation bronchoscopy, TB; thin bronchoscope, mm; millimeter, CT; computed tomography, EBUS; endobronchial ultrasound

TABLE 5. Factors associated with diagnostic yield.

Variables	OR	*P* value
Univariate analysis		
Age	0.942	0.086
Nodule size 20-30 mm	4.5	0.028
Subsolid nodule	0.15	0.113
CT bronchus sign	6.9	0.007
Airway generation	2.24	0.115
Multivariate analysis		
Age	0.905	0.126
Nodule size 20-30 mm	0.459	0.621
Subsolid nodule	12.439	0.269
CT bronchus sign	48.82	0.031
Airway generation	6.21	0.023

Abbreviations: OR; odds ratio, mm; millimeter, CT; computed tomography

than or equal to 30 mm when combined with R-EBUS and fluoroscopic guidance. The diagnostic yield of TB was comparable to that of ENB (73.9% and 66.7%, respectively; p = 0.587).

The use of a thin bronchoscope (4 mm outer diameter) and ultrathin bronchoscope (UTB; outer diameter less than 4 mm) might reduce the limitation of R-EBUS compared with using a conventional bronchoscope because they can reach more distal segmental bronchi leading to the lesion, which would result in a more precise direction alignment with the lesion and reducing the chance of displacement of the tip of the bronchoscope.[10-13] The present study found that the use of TB with R-EBUS and fluoroscopy resulted in a higher diagnostic yield in diagnosis of PPNs less than 30 mm compared to the previous study performed at our center (73.9% and 63.8%, respectively).[4] This was similar to the study of Tanner et al., which reported that the use of TB with R-EBUS could improve the diagnostic yield in the diagnosis of PPNs compared to the use of a conventional bronchoscope (49% and 37%, respectively; p = 0.110).[10] The use of UTB combined with multimodality-guided techniques has been reported to provide a significantly higher diagnostic yield compared to the use of TB.[11-13] This advantage might be due to more distal bronchi being reached when using UTB. However, the diagnostic yields of UTB vary depending on the studies and guided methods, ranging from 40%–90%, with a yield of 24%–81% for lesions < 20 mm.[11]

The addition of ENB may have a benefit in helping physicians to identify the target bronchi leading to the lesion. ENB requires the use of a conventional bronchoscope (5.9 mm outer diameter with a 2.8 mm working channel), so the tip of the bronchoscope cannot be advanced to the more distal segmental bronchi. Using a steerable locatable guide in ENB can solve this limitation because the direction of the locatable guide can be adjusted in real time in practical situations to find the target bronchus leading to the lesion. When using ENB combined with R-EBUS, the diagnostic yield was significantly improved compared to ENB or R-EBUS alone.[7,14] The present study found that ENB with R-EBUS had a diagnostic yield of 66.7%, which was similar to our previous study of using a conventional bronchoscope with R-EBUS. Several studies have reported various diagnostic yields of ENB ranging from 65%–90%.[7,16-19] Interestingly, the results of the AQuIRE registry showed a low diagnostic yield when using ENB with R-EBUS for the diagnosis of peripheral lung lesions, which was only 47%.[20] The recent multicenter study in seven countries from the United States and Europe, The NAVIGATE study, has found the global diagnostic yield of ENB was 67.8% (69.8% in the United States and 55.2% in Europe).[21] The NAVIGATE study had some regional practice variations including differences in guided techniques, ENB experience, number of tissue biopsies, and the use of general anesthesia that likely affected the outcomes. These might reflect the diagnostic yield of ENB in real-

world practice, especially when ENB was used outside a research center. Regarding the superDimension® system, the operators need some experience in choosing and controlling the locatable guide to find the target lesion, which might have resulted in the lower diagnostic yield in the ENB group in the present study.

Most of the lesions in the present study could be visualized by EBUS (48% within the lesion and 44% adjacent to the lesion) regardless of the use of ENB (41.7% within the lesion and 45.8% adjacent to the lesion), suggesting that the use of ENB might have no additional benefit in terms of the chances of localizing the lesion. However, ENB may have benefit in shortening the time to find the lesion, which was not evaluated in the present study.

Failure to identify the lesion by R-EBUS was 12.5% and 8% in the TB and ENB group, respectively. The results of the present study were consistent with previous studies, which reported a successful navigation to PPNs with ENB of 97.4%, but the definitive diagnosis could be confirmed in only 64.9% of cases, with a sensitivity to detect cancer of 71% and a negative predictive value of 52%.[19] This discordance between the navigation success and diagnostic yield may depend on the relationship between the airways and lesion, and the actual position of the locatable guide may differ from the virtual location due to the interval duration between CT imaging and the diagnostic procedure and respiratory variation. Conscious sedation during the procedures might result in a high respiratory variation and coughing, which sometimes causes a difficulty to control the locatable guide. The meta-analysis reported that the use of general anesthesia was associated with better diagnostic yields compared to the use of conscious sedation (69.2% and 57.5%, $p = 0.02$).[18] Several studies have reported low diagnostic yields for PPNs located adjacent to the R-EBUS probe location. In contrast, we found that the EBUS location did not affect the diagnostic yield in both groups.

Multivariate analysis demonstrated that the presence of CT bronchus sign and more distal segmental bronchi reached by the bronchoscope were associated with an improvement in diagnostic yield (OR 48.84, $p = 0.031$ and OR 6.21, $p = 0.023$, respectively), which were consistent with several other studies.[16,17,21,22]

No major complications were found in the present study. The overall complication rate was 2.0%, which was similar to in a previous study.[9]

The cost of the ENB system is considerably higher than that of the TB because the ENB system requires disposable instruments, such as a locatable guide and an extended working channel. Further study is needed to identify the cost-effectiveness of these procedures.

The present study has several limitations to note. First, the study involved a single-center experience. However, there was no operable variability because all of the procedures were performed by one bronchoscopists. Second, the sample size was inadequate due to technical problems. Finally, the duration of the procedure was not evaluated in the present study.

CONCLUSION

Multimodality-guided techniques can improve the diagnostic yield in the diagnosis of PPNs. The PPNs larger than 2 cm with the presence of CT bronchus sign, the ENB provides a similar diagnostic yield compared to the thin bronchoscope. Further analysis and adequately powered prospective studies are required to confirm the advantages of ENB.

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Conflicts of interest: The authors declare they have no conflicts of interest. However, it is to be noted that the present study received material support from Medtronic, but they had no influence on the study procedures and did not have access to the study data.

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Outcomes of an Early Laparoscopic Cholecystectomy in Acute Cholecystitis, Grades I and II

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ABSTRACT

Objective: According to the accumulated benefits of laparoscopic cholecystectomy (LC) in acute cholecystitis (AC), early LC is becoming a standard management for selected patients. While patients with mild AC usually gain the advantages of this approach, removing a more inflamed gallbladder in patients with moderate AC has various results, depending on the institute where the procedure is performed. The aim of the study was to compare the outcomes between early LC in patients with grade I and II AC.

Materials and Methods: From June, 2015 to December, 2019, electronic medical records in the division of Acute Care Surgery at Siriraj Hospital in Bangkok were reviewed retrospectively. An early LC was performed consecutively in 105 cases of AC grades I and II. The overall results and the outcomes comparing grades I and II AC were evaluated.

Results: Forty-two patients were grade I (40%). Patients with grade I AC tended to be younger (56 +/- 17 years vs. 63 +/-15 years, $p = 0.03$). Among grade II patients, the late onset of more than 72 hours was the most common measure (62%). The estimated blood loss was significantly lower in grade I [30 (5-450) ml. vs. 100 (5-3,000) ml., $p = 0.018$]. The overall conversion rate was 21%, which was significantly higher in grade II AC (28.6% vs. 9.5%, $p = 0.026$). There were no differences in operating time (125 +/- 47 minutes vs. 117 +/- 44 minutes. $p = 0.365$), total lengths of stay [4 (2-7) days vs. 5 (3-28) days, $p = 0.163$], and post-operative complications (19% vs 25%, $p = 0.448$). The minor bile duct injuries occurred in four patients (3.8%), 2 cases in each group. From the multivariate analysis, grade II AC did not statistically impact the conversion (adjusted OR 2.99, 95% CI 0.5-17.6, $p = 0.225$).

Conclusion: Our study shows that the overall and evolving outcomes of early LC for grade I and II AC were safe and feasible. While a higher conversion rate and estimated blood loss attributed to grade II AC, a pre-operative severity grading can guide surgeons to accommodate their ability so as to maximize the benefits of early LC.

Keywords: Early LC; acute cholecystitis grade I; acute cholecystitis grade II (Siriraj Med J 2022; 74: 495-501)

INTRODUCTION

In 1993, Wittgen et al.[1] reported the beneficial results of laparoscopic cholecystectomy (LC) in patients who required cholecystectomy comprising acute cholecystitis (AC). At that time, most patients with AC underwent open cholecystectomy (OC). After reaching the minimally invasive age, LC became a successor of standard OC in almost all situations, including AC. The safety and feasibility of laparoscopically removal of acutely inflamed gallbladder (early LC) became more evident.[2] The accumulating evidence-based advantages of urgent cholecystectomy[3] and insignificant difference of complications compared

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with delayed LC[4] had been strongly recommended. Not only were there advantages in terms of the LOS and the cost of treatment, but early cholecystectomy also eliminated the 6-23% risk of emergency operations for non-subsided AC during the wait prior to the delayed LC.[5]

After 2007, the Tokyo guidelines[6,7] became standardized surgical management of patients with AC, according to the severity of their condition. The early LC had been suitably applied for patients with grade I and II AC whose a Charlson comorbidity index (CCI) was < 5 and an American Society of Anesthesiologists physical-status classification (ASA-PS) was < 2. These days, the outcomes of early LC are regularly published.[8,9] For mild-disease, grade I AC patients obtain the benefits of a minimally invasive cholecystectomy, without increasing the peri-operative risks. Thus, in cases of grade I AC, early LC has been recommended. As the clinical criteria of grade II AC consist of more extensive inflammation, so early LC may encounter more challenges in the operating field and end up with open conversion to OC (LOC) or some unfavorable outcomes. Consequently, a subsided gallbladder can be resected after four to six weeks in those institutions that are unfamiliar with the early LC, so as to maximize the advantages of the minimally invasive approach.

Although, there was a study comparing the outcomes of emergency LC in mild (grade I) and moderate (grade II) AC which did not differ in term of the complications (7% vs 9%, $p = 0.517$) and conversions (6% vs 6%, $p = 0.985$). The conclusion was a retrospective design from a single institution.[10] In this author's institute, which is a teaching hospital, early LC has become one of the most common urgent laparoscopic procedures. This study assessed the outcomes of early LC and compared the operative results between two grades, according to Tokyo guideline 2018 (TG18).[6] The present study also provided intra-operative details and evolvement of conversion within the institute.

MATERIALS AND METHODS

The electronic medical records of patients who were older than 15 years and in the division of Acute Care Surgery were reviewed retrospectively. Consecutive cases of grade I or II AC who were admitted for urgent LC between June, 2015 and December, 2019 were examined. The patients with suitable clinical parameters, with definite diagnostic criteria of AC in accord with the TG18, and whose pathological reports revealed acute inflammations, were enrolled in the study. Those with incomplete pre-operative data or any other pathology were excluded. The demographic details, medical history, pre-operative physiologic data, laboratory measurements, and diagnostic ultrasonography or computed tomography were collected. The research project was reviewed and approved by an Institutional Review Board, Faculty of Medicine Siriraj Hospital (Si 425/2019, 305/2021).

The patients who have any one of the following conditions: the duration of symptom of more than 72 hours, a palpable, tender mass in the right upper quadrant, white blood cell (WBC) count of more than 18,000/mm^3, marked local inflammations detected by pre-operative imaging were categorized into grade II AC. The other patients who did not consist of these criteria were in grade I. The operations were performed by acute care, colorectal, HPB, and MIS surgeons, each performed more than fifty cases of LC for gallstone diseases per year. Nevertheless, the surgeon individually decided whether to operate the AC patients. The chronological data regarding onset, peri-operation times and lengths of stay were recorded. Associated intra-operative parameters - for example, the estimated blood loss, adverse events, decisions for conversion, and additional procedure - were analyzed. Information concerning complications at follow-up clinics and emergent visits within 30 days were obtained. The overall results of early LC and the outcomes comparing grades I and II AC were evaluated.

Statistical analysis

The quantitative data were described as mean and standard deviations. The categorical variables were shown as numbers and percentage. The output of the sample size was calculated from the study of Lee W.[11] of which conversion rates of an early LC in grade I and II AC were 20% and 44%. For the evaluations between two independent proportions (two-tailed test); the proportion in group 1 = 0.200 and group 2 = 0.440. The calculated sample size was 59 in each group. Independent student t-tests were used to compare the continuous data. Chi-squared test or Fisher's exact test was used to compare categorical variables. Multivariate logistic regression was performed to identify independent clinical risk factors associated with unfavorable outcomes such as conversions or complications which were reported as odd ratio (OR) and 95% confident interval (CI) and adjusted OR and 95% CI. All p-values of less than 0.05 were considered as statistically significant. Data were recorded and analyzed using PASW statistic version 18.0 (SPSS Inc. Chicago, IL, USA).

TABLE 1. Demographic data and preoperative parameters between grade I and II AC.

	Grade I (n = 42)	Grade II (n = 63)	*P*-value
Female	24 (57.1%)	34 (53.9%)	0.749
Age (years)	56.2 ± 17.3	63.1 ± 15.2	0.030
Body temperature (Celsius)	37.5 ± 0.8	37.8 ± 0.9	0.292
Charlson comorbidity index <5	42 (100%)	61 (96.8%)	0.515
ASA classification 1 and 2	33 (78.6%)	49 (77.8%)	0.923
Body mass index (kg/m^2)	25.5 ± 3.7	25.5 ± 4.5	0.718
Positive Murphy's sign	34 (81%)	39 (61.9%)	0.038
Tenderness	42 (100%)	61 (96.8%)	0.244
Guarding	7 (16.7%)	13 (20.6%)	0.615
Mass	0 (0%)	8 (12.7%)	0.020
WBC count (cells/mcL)	13,659 ± 2,759	16,600 ± 7,586	0.001
WBC count >18,000 cells/mcL	0 (0%)	28 (44.4%)	<0.001
Total bilirubin (mg/dL)	0.7 (0.13 - 3.24)	1 (0.23 - 9.5)	0.39
Wall thickening ≥ 4 mm.	29 (69.0%)	53 (84.1%)	0.067
Positive sonographic Murphy sign	23 (54.8%)	28 (44.4%)	0.300
Positive pericholecystic fluid	19 (45.2%)	35 (55.6%)	0.300
Preoperative time (hours)	24 (3-336)	72 (5-216)	<0.001
Onset to OR >72 h	0 (0%)	39 (61.9%)	<0.001

Data were presented in n (%), mean +/- SD, or median (range).

RESULTS

Patient characteristics

One hundred and five cases were recruited for this study. The mean age was 60 (21 to 89) years. Fifty-five percent of the patients were female. Most patients had less than 5 CCI. Thirty-two (30.4%), fifty (47.6%), and twenty-three (21.9%) patients were in the ASA-PS class I, II, and III, respectively. The average onset of symptoms was at 30 hours (ranging from three hours to one week). The mean body temperature was 37.7 degrees Celsius. On physical examination, Murphy's sign was 70% positive, 23% equivocal, and 5% negative. The average white blood cell count was 15,612 (3,870-50,900) cells per cubic-millimeter. A thicker-than-4-mm. wall was revealed in 77.4% of the patients, while the rest had less than 4 mm. The sonographic Murphy's sign was positive in 61%, negative in 13%, and equivocal in 5% of the patients. For 21% of the patients, this examination was not available via CT scan or was not mentioned in the ultrasonography (US) reports. The median pre-operative time interval was 48 (3 to 336) hours. Thirty-nine patients (37.1%) received a cholecystectomy after 72 hours of onset.

Operative findings

The mean operation time was 120 minutes. The estimated blood loss was 174 ml. per case. An LC was successfully performed in 83 patients (79%), with five cases of subtotal cholecystectomy (LsC). The rate of LOC was 21% (22 cases), which included a subtotal cholecystectomy (LsOC) in two patients. The reasons for conversion involved adhesion in 14 cases (63.6%); inflammation in 11 cases (50%); contamination in 8 cases (36.3%); and bleeding in 5 cases (22.7%). Overall extra-steps were added to the standard cholecystectomy in 56 cases (53.3%), and a Jackson-Pratt drain was the most commonly implemented (39 cases). Eighteen patients (21.7%) needed either a 10 mm. clip or loop ligatures to secure their gallbladder stump. Six patients required laparoscopic suturing. In the LOC group, nine of 22 patients (41%) had an additional procedure; three had cystic duct suturing; two had a closing of their gallbladder remnant; and there was one patient requiring each of the following: IOC; cystic artery ligation; suturing a vein; and ceasing the bleeding of the liver bed.

Post-operative outcomes

The total rate of post-operative complications was 22.9% (24 cases). The most common complication was superficial surgical site infections (7 cases, 6.7%) followed by bile duct injuries and Gram-negative sepsis (4 cases, 3.8%). All four cases of bile duct injuries were minor, two patients experienced post-operative bile leakage were successfully treated by a watchful-waiting strategy. One required re-admission for hydration. Two LsC patients had retained CBD stones which were detected and treated endoscopically during follow-ups at one and six months, respectively. One of these individuals had concurrent cholecystitis and then proceeded through a completed LC uneventfully. The pathological findings revealed acute on-top chronic inflammation in 37 patients (35.2%) and there were complicated inflammations, such as gangrene, necrosis, or perforation in 33 patients (31.4%). The total LOS was 4 (2 to 28) days. In addition, there was no intra-abdominal collection, 30-day mortality, or re-operation in this study.

Comparative data between two grades

Forty-two patients were categorized in severity grade I (40%). There was no difference in the CCI and ASA-PS classification. Patients with grade I AC tended to be younger (56 years vs. 63 years, $p = 0.03$). Among the grade II patients, a late onset of more than 72 hours was the most common measure, followed by findings of suspected gallbladder perforation e.g. irregular or less-enhanced wall of gallbladder, fluid collections, marked leukocytosis, and palpable mass. The WBC counts were lower in grade I (mean difference = 2,941 cells/cubic-millimeter, $p = 0.001$). Positives in Murphy's sign was documented more in grade I ($p = 0.028$). The conversion rate was significantly higher in grade II AC (28.6% vs. 9.5%, $p = 0.026$). The EBL was slightly higher in the grade II AC. The situations that needed an extra-instrument or an add-on procedure occurred insignificantly difference between two groups. The post-operative complications were comparable between two groups including two cases of bile duct injuries in each group. In grade I, a small laceration of the right-posterior intra-hepatic duct and the duct of Luschkar were identified and then repaired laparoscopically. On the other hand, both cases of grade II were postoperative bile leakage after LOC. The median of total LOS were not considerably longer in grade II AC (5 versus four days, $p = 0.163$). As for pathology, complicated cholecystitis was more reported in grade II (36.5% vs. 23.8%, $p = 0.17$).

DISCUSSION

From the start, the results from the early and delayed LC[5] had a comparable rate of conversion (20.3% versus 23.6%) and complications. Still, 17.5% of the patients in the delayed group could not avoid emergency LC, and that procedure had a 45% conversion rate. Subsequently, early LC had widely accepted, albeit various diagnostic criteria and forms of management, and there were increased reports of better outcomes afterward. In 2013, Lee et al.[11] defined early LC as an operation performed within three days of the symptoms' onset. Their report showed that 24.5-44.2% of early LC cases had an open conversion and that 14.4-19.5% of cases had complications. The most common cause of conversion and complication was bleeding. The researchers concluded that delayed LC in AC with mild symptoms (according to the Tokyo guidelines of 2007) had the lowest rate of conversion, at 7.7%, with no different complications. Inoue K. et al.[12] reported the outcomes of early LC (classified by the Tokyo guidelines of 2013) as follows: the conversion rate of early LC in grade II AC was only 13%, with 9.8% of patients having complications and 4% having bile leakage. In 2020, Yu-Ning L. et al.[13] published the satisfactory outcomes of early LC, in accord with the TG18. Their results showed 0% and 8% conversion rate in grade I and II AC, respectively, without complications. In our cohort, a conversion rate of 9.5% and 28.5% in grade I and II, respectively. Our results were slightly higher than from the TG18, which ranged from 2.4 to 7% for grade I and 1.7 to 25.6% for grade II. A high conversion rate seems to be a significant disadvantage of an early LC from the start particularly in grade II. If we decide to commence an early LC, improvements in will occur. We hope an early LC will outrank the delayed LC eventually and become the operation of choice for operable patients with grade I and II AC.

The samples in the study were recruited from the emerging usage of the early LC epoch in the author's institute. Some conversions should be omitted later as a result of the competency of surgeons who are gaining familiarity with the inflammation. As expected, there were some changes in the particulars of conversion which appeared over time. We found that extra maneuvers were needed in only five-fifteenth of the LOC cases in the first three years of the study, whereas all four cases that were converted to OC in the last two years were associated with additional procedures. The purpose of conversions such as suturing the gallbladder stump or stopping a profuse hemorrhage have been documented, instead of simply

giving vague reasons, such as "severe inflammation" or "severe adhesion." In cases of non-converting LC, a sentinel drain was increasingly placed in the last two years of our cohort. This indicates that there were more events related to infection, bleeding, or stump-securing that were managed without an open conversion. Some conversions were omitted by laparoscopic skills such as suturing the gallbladder stump, particularly in grade II AC. However, operating surgeons should not hesitate when they encounter situations in which the advantages of the open approach will be significantly achieved. Meanwhile, the physicians should realize that severe inflammation or adhesion of the AC can be overcome by personnel with longer learning curve. In addition, early LC may be conducted in patients with grade II AC when the indications for conversions are clearer, regarding the surgeons' own abilities.

While there are no specific criteria determining the difficulty in the operating fields, the individual conversion rate of each institute is used to weigh the benefits of early LC. An early operation is quite decisive for simple AC with a low likelihood for conversion, due to the fewer inflammations in such cases. When encountering clinical parameters of marked local inflammation that is classified as grade II AC, surgeons should anticipate a more difficult cholecystectomy. In the past, surgeons would decide to convert freely when encounter the unfamiliar situations such as a markedly-inflamed or distended, gangrenous, or perforated gallbladder. The recent data tend to show that both grades could be managed comparably.[9] In our multivariate analysis for risk of conversion likewise found that grade II AC was not a factor for conversion (adjust OR 2.99, 95% CI = 0.51-17.56, $p = 0.225$). Similarly, none of the determinant was the independent risk of conversion. In addition, additional procedures might reduce the conversion, yet were not statistically significant (adjust OR 0.53, 95% CI = 0.19-1.48, $p = 0.224$). Given the controversial evidence of those clinical parameters which may predict intra-operative difficulties, Inoue K. et al. proposed a predictive criteria of difficult LC by focusing on 122 patients with grade II AC. An early LC was difficult when performed after 96 hours of onset (OR 6.32, 95% CI = 2.126-20.15, $p = 0.0009$), with a 47.1% conversion rate ($p < 0.0001$). Unfortunately, there were only two cases in our study in which early LC was started after 96 hours. However, both patients underwent successful laparoscopic procedures and had uneventful post-operative courses. As mentioned, a substantial quantity of LOC was in patients with grade II AC. While searching for more accurate predictors of open conversion, the severity grading of the TG18 can help surgeons enhance their options, in these cases, the conversion rate or the sequelae of a subtotal cholecystectomy must be discussed.

The overall complication rates were 19% in grade I and 25.4% in grade II, when comparing the series in the TG18, which were 2.9 to 9.7% in grade I and 3.1 to 28% in grade II. There were no significant differences in the operative time or the complications rate between the two groups. The most common complication was associated with non-morbidity infections. The difference of median EBL was not clinically significant (30 ml. vs. 100 ml.). The most common added step was the insertion of a Jackson-Pratt drain, followed by the procedures for securing the gallbladder stump. So, equipment like the drain, the commercial loop ligation, and/or extra-large clips and trocars should be provided for early LC in both grades I and II. Nonetheless, the drain favorably enhanced post-operative recovery via removing the residual gas and fluid which caused peritoneum tension and pain.[14]

Both cases of LsC in this study had clinical manifestations of CBD stone exacerbations and needed further endoscopic and operative management, while the two cases of LOsC had uneventful post-operative complications during the follow-ups. In a systematic review of subtotal cholecystectomy in 2015[15], most patients who underwent LC in cases of severe cholecystitis revealed only 3.1% retained stones. The laparoscopic approach produced less risk of retained stones (OR 0.5; 95% CI = 0.3-0.9), compared with the open approach. Therefore, if not too difficult, the intra-operative cholangiography can be added to the subtotal cholecystectomy so as to detect a large portion of gallbladder remnant or retained stones. However, post-operative imaging or vigilant follow-ups are the best strategy for these patients.

The limitation of our study is that it has a retrospective design. Also, variations in the area of expertise and the experience of individual surgeons who participated in the pool emergency calls also substantially affected their intra-operative decisions. As a result of the multivariate analysis, none of peri-operative parameters significantly affected the conversion. The future research about surgeon factors, such as levels of competency or numbers of emergency cases performed annually, might precisely predict the conversion of the early LC.

CONCLUSION

After urgent laparoscopy had become more widely available, the authors studied the results of early LC in grade I and II AC, according to the TG18. The benefit of an early LC is that it yielded low morbidities but slightly higher conversion rates, compared to the guidelines.

Our data supports the leverage of early LC, particularly for patients with grade I AC. While the conversion rates were significantly higher in patients with grade II AC, the adverse events were not statistically different between the two grades.

TABLE 2. Operative results between grades I AC and grade II AC.

	Grade I (n = 42)	Grade II (n = 63)	*P*-value
Operations			0.039
LC	36 (85.7%)	42 (66.7%)	
LOC	3 (7.1%)	17 (27.0%)	
LsC	2 (4.8%)	3 (4.8%)	
LsOC	1 (2.4%)	1 (1.6%)	
Conversion	4 (9.5%)	18 (28.6%)	0.026
Added procedures to cholecystectomy	20 (50%)	36 (57.1%)	0.570
Estimated blood loss (ml.)	30 (5 - 450)	100 (5 - 3,000)	0.018
Operative time (min.)	125 ± 47	117 ± 44	0.365
Complications	8 (19%)	16 (25.4%)	0.448
Bile duct injury	2 (4.7%)	2 (3.2%)	1.000
Total length of stay (days)	4 (2 - 7)	5 (3 - 28)	0.163
Complicated cholecystitis on pathologic reports*	10 (23.8%)	23 (36.5%)	0.170

*Gangrene, necrosis, or perforation

Abbreviations: LC; laparoscopic cholecystectomy, LOC; laparoscopic converted to open cholecystectomy, LsC; laparoscopic subtotal cholecystectomy, LsOC; laparoscopic converted to open subtotal cholecystectomy

TABLE 3. Risk factors for conversion.

	Crude OR (95% CI)	*P* - value	Adjusted OR (95% CI)	*P*- value
Grade II acute cholecystitis	3.8 (1.18-12.2)	0.019	2.99 (0.51-17.56)	0.225
Onset to OR >72 h	2.49 (0.96-6.48)	0.057	1.41 (0.38-5.29)	0.612
Mass	1.28 (0.24-6.85)	0.672	0.9 (0.15-5.48)	0.91
WBC count >18,000 cells/mcL	1.8 (0.66-4.91)	0.247	1.4 (0.38-5.28)	0.606
Wall thickening > 4 mm.	0.94 (0.31-2.9)	0.916	0.7 (0.21-2.34)	0.557
Added procedures	0.67 (0.25-1.64)	0.35	0.53 (0.19-1.48)	0.224

TABLE 4. Additional procedures by timelines.

Procedure	Total	2015	2016	2017	2018	2019
LC with JPD	39	1	4	7	10	17
LC with loop ligature	12	2	1	1	2	6
LC with 10-mm clip	6	1	0	2	1	2
LC with suturing	6	0	1 (GB)	0	2 (GB, bowel)	3 (cystic duct, right intrahepatic duct, duct of Luschka)
LC with unplanned IOC	4	1	2	0	0	1
LOC with added procedures	9	0	2 (IOC, stop bleed at GB bed)	3 (suture GB x 2, suture cystic duct)	1 (ligate proximal cystic artery)	3 (suture cystic duct x 2, suture vein at GB bed)

Abbreviations: LC; Laparoscopic cholecystectomy, JPD; Jackson-Pratt drain, IOC; intra-operative cholangiogram, GB; gallbladder

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Longus Colli and Vertebral Artery Guide Safety of Cervical Spine Surgery

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ABSTRACT

Objective: To improve the safety of the anterior cervical vertebral surgical approach, MRI and CT have been used and the distances between the medial borders of the longus colli (LC) to expose the uncinated process (UP) have been reported. The anatomic parameters of the LC and vertebral artery (VA) were considered here in relation to the UP to minimize complications.

Materials and Methods: Data were obtained from 60 Thai adult skeletons and 20 embalmed cadavers. Direct measurements of the dry cervical vertebrae were performed using digital Vernier calipers, while computer imaging analysis was used for the cadaveric measurements after capturing the images.

Results: No significant difference was noted in the inter-UP distance between the dry and cadaveric cervical measurements. The average UP width was 6.7 ± 0.2 mm. The average distance from the tip of the UP to the VA was 2.6 ± 0.1 mm. The calculated distance from the LC to the UP which derived from the inter-UP distance and the distance between the LC increased from C2 to C7 with an average distance of 11.9 ± 0.3 mm.

Conclusion: Within a distance of 11.9 ± 0.3 mm from the medial border of the LC, UP can be identified. Dissecting at a distance less than 10 mm posterior, 5–6 mm lateral and superior to the base of the UP can avoid VA injury and optimize the safety of the anterior cervical vertebral surgical approach.

Keywords: Cervical vertebra; uncinate process; anterior cervical surgery; vertebral artery (Siriraj Med J 2022; 74: 502-508)

INTRODUCTION

The anterior surgical approach of the cervical vertebrae is commonly used as the surgical procedure for cervical vertebral pathologies, including disc herniation, cervical spondylotic myelopathy, tumor, and infection. Several potential risks of injury after these surgeries have been reported. One of them is Horner's syndrome, which is related to cervical sympathetic trunk (CST) injury and has been reported to have an incidence of between 0.2%–4%.[1,2] The vertebral artery (VA) injury associated with cervical spine surgery has also been reported, and although it has shown a rare incidence (0.3% to 0.5%), it carries a threat of fistulas, pseudo-aneurysm, cerebral ischemia, and even death.[3-5] Neural foramen decompression during anterior cervical discectomy has been used to relieve pressure upon the affected nerve root. In this procedure, the medial border of the longus colli muscle (LC) has been suggested as a landmark for lateral dissection to

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the medial portion of the uncinate process (UP) at the uncovertebral joint and as a guided safe area of the bone, which in most patients should have been removed.[6,7] In addition, it should be done carefully to avoid injury to the CST as well as to the VA. Therefore, this study aimed to clearly delineate the surgical anatomy of the LC and its related structures (VA and UP) to aid developing safer surgery for minimizing the potential risks.

MATERIALS AND METHODS

The morphometric evaluation with known genders and ages according to the personal records of body donors was approved by the Siriraj institutional Review Board (SIRB), protocol no 629/2013. In total, 300 dry cervical spines (C3–C7) of 60 Thai adult skeletons (age range 19–83 years old; mean age 43.9 years old in 38 males and 42.4 years old in 22 females), and 20 formalin-fixed cadavers (age range 50–93 years old; mean age 68.4 years old in 10 males and 68.2 years old in 10 females) were obtained from Department of Anatomy.

Fig 1 shows the dry bone measurements performed on the UP of the cervical vertebrae, including the inter-UP distance (a), between the tip of the right and left UP, the anteroposterior (AP) distance of the UP (b), along the medial side of the UP and the width of the UP (c), at the base of the UP. For the cadaveric measurements, cadavers with a history of neck trauma and cervical vertebral operation were excluded. Along the anterior border of the sternocleidomastoid muscle (SCM), the superficial layer of cervical fascia was opened to expose the anterior view of the cervical vertebrae. The SCM was moved laterally. The coverage fat and fascia were cleaned to expose the LC and the VA as shown in Fig 2A. The cervical vertebrae and intervertebral spaces from C2 to C7 were exposed. The levels of the vertebrae were checked from the superior part by counting the disc space levels. The distance between the medial borders of the LC (m) measured at each disc space level and also its height at midline (n) were also measured. In Fig 2B, dissection of the transverse process to clearly expose the UP of each cervical vertebra and the VA at the C2–C3, C3–C4, C4–C5, C5–C6, and C6–C7 levels was performed after removing the LC. The drawing in Fig 2C shows the positions of the three measurements: the inter-UP distance (a), distance between the LC (m), and the distance between the tip of the UP and the medial wall of the VA (p). The calculation for the distance between the medial border of the LC and the tip of the UP (o) was calculated from this equation (o = a/2–m/2).

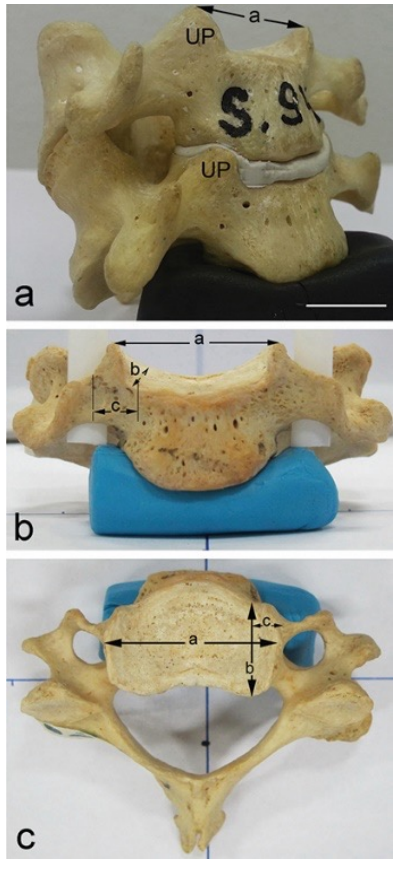

Fig 1. Cervical vertebra showing the anterolateral view (1a), anterior view (1b), and superior view (1c) , indicating the measurements, a, b, and c of the uncinate process (UP).
Scale bar is 1 cm. a, inter-UP distance; b, AP distance of the UP; c, width of the UP.

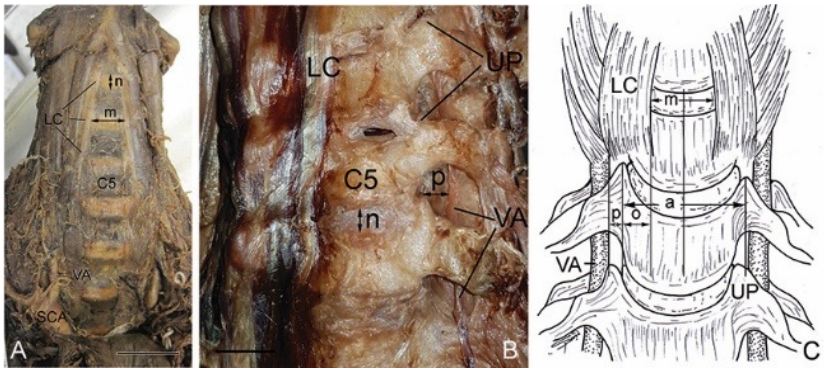

Fig 2. The anterior views of the longus colli (LC) muscles showing the measurements,: 2A) the representative cadaveric specimens along the side of the cervical spines (C5) and the vertebral artery (VA) originating from the subclavian artery (SCA); 2B) the representative cadaveric specimens after removing the LC with a clearer uncinate process of the cervical spines and VA; 2C) drawing indicating more of the measurements.
Scale bar is 2 cm (in 2A and 2B), Abbreviation: m, distance between the LCs; n, height of the intervertebral space; a, inter-UP distance; p, distance between the tip of the UP and the VA; o, distance between the medial border of the LC and the tip of the UP.

To minimizing the errors inherent in this morphometric study, all the measurements were performed using a digital Vernier caliper accurate to 0.1 mm and taken three times by a single person. In addition, they were repeated by computer image analysis with ImageJ 1.52v (National Institutes of Health, USA, http://imagej.nih.gov/ij) after capturing images of the anterior view of the cadaveric cervical vertebrae. As shown in Fig 3, each measurement of the captured image with its scale was analyzed as the "Length" by drawing with the straight line tool, such as the distance between the medial borders of the LC muscles (m). In the ImageJ program, "Analyze and Set Scale" was used for calibration (white arrow in the inset picture), and then "Analyze and Measure" was performed and the result is shown in the result table as the "Length". The repeated length measurements in the table were transferred to Excel for statistical analysis.

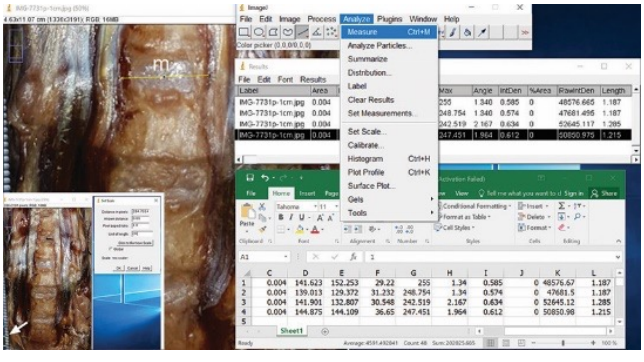

Fig 3. ImageJ 1.52 v was utilized to analyze the distance between the LCs (m). Each measurement of the captured image with scale was analyzed as the "Length" by drawing with the straight line tool, also using "Analyze and Set Scale" for setting the calibration (white arrow in the inlet picture), and then "Analyze and Measure" to show the length in the results table, which were then transferred to the Excel program for the statistical analysis.

Statistical analysis

The average of three observations was used for statistical evaluation with the SPSS software, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences in the various parameters between age groups and vertebral levels were analyzed statistically using a single factor analysis of variance (ANOVA), while differences between the two sides and the genders were analyzed with the Student's t-test, and considered statistically significant at $p < 0.05$.

RESULTS

Morphometric measurements of dry cervical vertebrae

Dry cervical vertebrae (C3–C7) were studied in a total of 60 Thai adult skeletons, comprising 38 male (63.3%) and 22 female (36.7%) specimens with a mean age of 43.56 ± 16.8 years old (range, 19 to 83 years old). All the symmetrical structures were measured bilaterally and the results are shown in Table 1. Average measurements relative to the UP were compared between genders, sides, and among age ranges. All the parameters of UP in the males were greater than in the females, with significance at $p < 0.05$. In addition, all the parameters of UP in both younger groups were less than in the older group significantly at $p < 0.05$. In Table 2, comparison of the measurements among the levels of the cervical vertebra showed significant increases when compared to C3, at $p < 0.05$. The average AP distance of the UP was 12.1 ± 0.2 mm and became widened from C3 (11.5 ± 0.2 mm) to C6 (12.5 ± 0.3 mm) but shorter at C7. Moreover, the average inter-UP distance of 27.9 ± 0.3 mm was also widened from C3 (24.39 ± 0.3 mm) to C7 (31.9 ± 0.5 mm), whereas the average width of UP of 6.5 ± 0.1 mm was shorter from C3 (6.7 mm) to C7 (6.3 mm), both in males (6.7 ± 0.2 mm) and in females (6.2 ± 0.1 mm).

TABLE 1. Average measurements of dry cervical vertebrae expressed as the mean ± SEM compared between genders, sides, and among age ranges.

Parameters (mm)	Gender		Side		Age range (years)		
	male	female	right	left	18–40	41–60	61–85
Inter-UP distance	28.7±0.5	26.7±0.4*	27.9±0.4	27.1±0.3[a]	27.4±0.3[a]	31.1±0.7	
AP distance of UP	12.7±0.2	11.0±0.2*	11.9±0.2	12.1±0.2	11.4±0.1[a]	11.6±0.2[a]	14.6±0.3
Width of UP	6.7±0.2	6.2±0.1*	6.5±0.2	6.5±0.1	6.3±0.1[a]	6.2±0.1[a]	7.8±0.2

*significant difference ($p < 0.05$) comparing gender.
[a] significant difference ($p < 0.05$) compared with the age range 61–85 years old.

TABLE 2. Comparison of measurements among levels (C3–C7) in dry cervical vertebrae and in the anterior view of cadaveric cervical vertebrae, expressed as the mean ± SEM. Abbreviations (a, b, c, m, n, o, and p) are shown in Figs 1–2.

Parameter (mm)	Level of the cervical vertebra					Average distance
Dry bone measurements	**C3**	**C4**	**C5**	**C6**	**C7**	
Inter-UP distance (a)	24.39±0.3	26.6±0.4	27.3±0.4	29.4±0.6*	31.9±0.5*	27.9±0.3
AP distance of UP (b)	11.5±0.2	12.1±0.2	12.2±0.2	12.5±0.3*	11.9±0.2	12.1±0.1
Width of UP (c)	6.7±0.1	6.6±0.1	6.5±0.1	6.4±0.2	6.3±0.1	6.5±0.1
Cadaveric measurements	**C2–C3 (C3)**	**C3–C4 (C4)**	**C4–C5 (C5)**	**C5–C6 (C6)**	**C6–C7 (C7)**	
Inter-UP distance (a)	21.4±1.0	23.2±1.0	24.3±1.1*	26.8±1.1*	30.9±1.3*	25.5±0.5
Distance between LCs (m)	9.4±0.3	13.4±0.3[a]	15.7±0.3[a]	15.9±0.3[a]	15.3±0.2[a]	13.9±0.4
Height of intervertebral space (n)	5.5±0.3	6.3±0.3	6.4±0.3[a]	6.3±0.3	6.0±0.3	6.1±0.1
UP to VA (p)	3.4±0.2	2.6±0.3*	2.4±0.2*	2.3±0.2*	2.2±0.2*	2.6±0.1
LC to UP (calculated by a/2 – m/2 = o)	10.3±0.5	10.9±0.5	11.3±0.5	12.6±0.6*	14.3±0.7*	11.9±0.3

*significant difference ($p < 0.05$) compared with the level at C3.
[a] significant difference ($p < 0.05$) compared with the distance at the space between C2–C3

Morphometric measurements of the anterior view of the cadaveric cervical vertebrae

Anterior views of the cervical vertebrae of 20 cadavers with an average age of 68.3 years old (ranging from 50 to 93 years old) were studied. Two vertical arrangements of LC lying along the anterolateral aspect of the cervical vertebrae and anterior cervical discs are shown in Fig 2A.

Table 2 presents a comparison of the measurements among the cervical vertebral levels (C2–C3 to C6–C7). The distances between the medial border of the right and left LC increased from C2 (9.4 ± 0.3 mm) to C6 (15.9 ± 0.3 mm) and decreased at C7 (15.3 ± 0.2 mm) significantly when compared to C2, at $p < 0.05$. In addition, comparisons between the genders and age range groups were also performed. The average distance between LCs was 12.5 ± 0.5 mm (13.1 ± 0.5 mm in males and 11.9 ± 0.5 mm in females; 13.4 ± 0.5 mm in the 50–60 year olds and 12.1 ± 0.5 mm in the 61–93 year olds). The height of the intervertebral space was significantly greater at C4–C5 when compared to C2–C3. The average height was 6.1 ± 0.1 mm (6.4 ± 0.1 mm in males, 5.8 ± 0.1 mm in females; 6.0 ± 0.1 mm in 50–60 year olds and 6.1± 0.1 mm in 61–93 year olds). The average distance between the LCs and the height of the intervertebral space showed no significant differences between genders and among the age ranges at $p < 0.05$.

After the LCs were removed, the inter-UP distance and the distance from the tip of the UP to the VA were measured and the results are presented in Table 2. The average inter-UP distance in the cadaveric study of 25.5 ± 0.5 mm was also widened from C3 (21.4 ± 1.0 mm) to C7 (30.9 ± 1.3 mm). The distance from the tip of the UP to the VA was measured bilaterally and showed no significant difference between genders (average 2.6 ± 0.1 mm; 2.4 ± 0.1 mm in males, 2.5 ± 0.1 mm in females), but a significant difference was found between the sides (2.6 ± 0.1 mm in the right side, 2.3 ± 0.1 mm in the left side), and age ranges (2.8 ± 0.1 mm in 50–60 year olds, 2.3± 0.1 mm in 61–93 year olds) at $p < 0.05$. Therefore, the tip of the UP was closer to the VA in the left side, and in the older specimens with an age over 60 years old. In the comparisons among the vertebral levels in Table 2, the tip of the UP was closer to the VA at C4 (2.6 ± 0.3 mm) to C7 (2.2 ± 0.2 mm) with significance at $p < 0.05$ when compared to C3 (3.4 ± 0.2 mm). The calculated

distance from the LC to the UP (indicated by "o" in Fig 2C) increased from C2 (10.25 ± 0.5 mm) to C7 (14.3 ± 0.6 mm) with an average distance of 11.9 ± 0.3 mm.

Table 3 presents a comparison of the inter-UP distance among each cervical vertebra (C3–C7) in the dry bones (average 27.9 ± 0.3) and cadaveric materials (average, 25.5 ± 0.5). There was no significant difference in each cervical vertebra between the dry bones and cadaveric materials at $p < 0.05$ as indicated with the *P* values. In addition, in Table 3, the inter-UP distance was also considered and compared to the reported results in previous studies.[5-9]

TABLE 3. Inter-UP distance of each cervical vertebra (C3–C7) expressed as the mean ± SEM, showing no significant difference between dry bones and cadaveric specimens at $p < 0.05$. Comparison of the inter-UP distance to other studies with different races and different studied materials.

Parameter (mm)	Level of the cervical vertebra					Average distance	Materials
	C3	C4	C5	C6	C7		
In this study							
Bone inter-UP distance	24.39±0.3	26.6±0.4	27.3±0.4	29.4±0.6*	31.9±0.5*	27.9±0.3	Dry bones (60 adults, M=38, F=22)
Cadaveric inter-UP distance	21.4±1.0	23.7±1.0	24.3±1.1*	26.8±1.1*	30.9±1.3*	25.5±0.5	Cadaveric study (20 adults, M=10, F=10)
P value**	0.108	0.062	0.078	0.996	0.777		
Inter-UP distance from other studies	**C3**	**C4**	**C5**	**C6**	**C7**		**Materials**
Lu et al. (1998)	19.4±1.3	20.5±1.8	21.4±1.7	23.4±1.9	25.2±2.0		Dry bones (54 adults)
Ebraheim et al. (1998)	19.4±1.3	20.5±1.8	21.4±1.7	23.4±1.9	25.2±2.0		Dry bones: (M=31)
	18.9±1.7	20.5±1.0	20.9±1.5	22.6±1.8	23.7±1.9		Dry bones: (F=23)
Park et al. (2016)	-	16.4±0.8	17.4±2.0	18.1±2.3	17.8±2.7		MRI and CT (n=120)
Guvencer et al. (2006)	23.7±3.2	24.0±3.1	25.5±3.0	28.3±4.5	-		Cadaveric radiographic study (n=12)
Guvencer et al. (2016)	23.7±3.4	24.0±3.3	25.4±3.7	27.0±3.4	29.0±3.0		CT study (M=13)
Guvencer et al. (2016)	20.8±1.0	21.9±1.7	23.7±2.0	25.5±2.3	28.1±2.4		Cardaveric study (M=13)

Abbreviations: M; male, F; female, n; number.

*significant difference ($p < 0.05$) compared with the level at C3.

** *P* value when comparing the inter-UP distance between bones and cadaveric determination.

DISCUSSION

The anterior cervical vertebral approach for decompression is widely used for many pathologies. The anatomical relationships between the LC and VA have been widely studied and marked as a safety guide to reduce the risk of complications during surgery, particularly VA injury. The anterior approach for the distracted disc space and for bone removal at the cervical vertebrae has been considered, using the UP as an important landmark.[10] The UP is located in the superior surface of the cervical vertebral body, except for C1 and C2, and also on the first thoracic vertebra.[11] In addition, the anatomical relationship between the LC and the UP is also beneficial for performing a thorough decompression of the intervertebral foramen in cases of arthroplasty. Recently, preoperative magnetic resonance imaging (MRI) and computed tomography (CT) scans have been recommended to help guide a safe dissection for Koreans by mobilizing the LC laterally 5 mm at C3–5, 6 mm at C5–6, 7 mm at C6–7, and 8 mm at C7–T1 to fully expose the UP.[5] However, these lengths may be different in other races, and there are no reports yet on the recommended lengths for Thai patients. A previous study by Raykateeraroj et al.[12] reported a greater anteroposterior (AP) distance of UP in males than in females with significance in dry cervical vertebrae. That study also reported the inter-UP distance and the width of UP. The average inter-UP distance was performed in both dry (27.9 ± 0.3 mm) and cadaveric cervical vertebrae (25.5 ± 0.5 mm) and showed no significant difference; therefore suggesting other related measurements from dry bones and cadaveric materials could be used for the calculation and might be approximately reported as a safe guideline for anterior cervical surgery in Thai patients. For each side of measurements, the distance from the medial border of the LC to the tip of the UP was calculated and the mean value was 11.9 mm and ranged from C3 (10.3 ± 0.5 mm) to C7 (14.3 ± 0.7 mm). This study includes data for both Thai dry bones and cadaveric materials with the higher numbers and race-dependent measurements presented as a guiding distance for surgery, as shown in Table 3.

In the calculation, the inter-UP distance (a) and the distance between the LC (m) was multiplied by 1/2 at each vertebral level. To locate the medial border of the left and right LC of the atlas to the bodies of the C3 to T3 vertebrae, it was assumed it was also attached to the transverse processes of the C3 to C6 vertebrae. Dissection of the LC beyond the transverse process to expose the UP was performed from the midline equally and in the same manner with the bilateral UPs. This distance was calculated because the LC had already been mobilized to fully approach and easily identify the UP during surgery. For the LC, it was necessary to identify the longest and most medial part of the prevertebral muscle during uncinectomy. Even though, using MRI and CT scans, Park et al.[5] reported that in right-handed patients, the distance from the medial border of the right LC that should be dissected laterally to expose the UP was larger than in the left side, no difference was reported in the distance to locate the bilateral UP.

In addition, the inter-UP distance showed a gradual increase from the C3 to C7 levels. Therefore, the use of fixed values for anterior decompression from the C3 to C7 levels may not be appropriate and may lead to inadequate decompression at the lower levels. In this study, to fully expose the tip of the UP, the LC had to be dissected laterally 10.3 ± 0.5 mm at C3, 10.9 ± 0.5 mm at C4, 11.3 ± 0.5 mm at C5, 12.6 ± 0.6 mm at C6, and 14.3 ± 0.7 mm at C7.

According to the reviews results in other studies and as shown in Table 3, the inter-UP distance (an important value for calculating the distance from the LC to the UP) was also compared among C3 to C7, and in different studied materials and different races. Our study showed no significant difference in the inter-UP distance between dry bones and cadaveric materials. Reports of the inter-UP distance of the cervical vertebrae of Thai, Turkish, and American people also showed quite similar values in the cadavers, radiographs[7], CT scans[8], and dry bones[6,9], which were all longer distances than in the MRI/CT findings of Park et al.[5] Therefore, the safety guidance for the anterior cervical vertebral surgical approach should be based on race. In addition, reports from cadavers and dry bones should be considered along with the MRI/CT findings before surgery and vice versa. MRI/CT of individual case would be more reliable and accurate to that specific person, while dry bone measurement my help clarify certain questions from CT/MRI.

Kim et al.[13] also used the UP as the reference point to determine its distance from the related anatomical structures because the LC was removed during the surgery. Therefore, the location of the VA should be estimated from the UP. In this study, the average distance from the tip of the UP to the VA was 2.6 mm. As mentioned above, the medial border of the LC can guide the tip of the UP within 10.25 to 14.3 mm (average distance, 11.9 mm) laterally. To avoid VA injury, considering the average UP width (6.5 ± 0.1 mm), AP distance of the UP (12.1 ± 0.1 mm), and our previous findings[12] of the UP height (6.6 ± 0.19 mm for males and 5.8 ± 0.2 mm for females), the safety point for lateral dissection at the

base of the UP could be performed less than 5–6 mm medial to the lateral margin of the UP, not deeper than 10 mm or higher than 5–6 mm.

Similar to Lu et al.[6], who reported that resection of the UP is usually performed 5–6 mm medial to the lateral margin of UP, our study also provides additional suggestion and consideration for avoiding VA injury within about 2.6 mm from the tip of the UP. Also, more caution must be taken in the midcervical region (C4–C6), which is very close to the VA, similar to previous reports.[14,15] The anatomical relationship between the LC and VA was also reported by Lu and Ebraheim[16], who suggested the need to consider an anomalous VA, which could increase the risk of injury. Therefore, the preoperative MRI and/or CT scans should be carefully reviewed about anomalous VA for safer operation. In addition, many studies have reported that an anterior cervical approach is associated with more post-operative airway embarrassment than posterior procedures and this therefore should be considered[17,18], because during this procedure, the trachea and esophagus are retracted to the contralateral side of the neck to expose the anterior aspect of the cervical spine, which can result in post-operative airway edema.

CONCLUSION

Using the UP as a reference point in relation to the LC and VA taken at the level of the C3–C7 vertebrae, the UP can be located within 11.9 ± 0.3 mm from the medial border of the LC. To avoid VA injury, the safety point for lateral dissection at the base of the UP is a distance less than 10 mm posteriorly, 5–6 mm laterally, and superiorly to the base of the UP. The LC and VA can help surgeons performing anterior cervical surgery by decreasing the rate of complications and increasing the rate of success.

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Conflict of interest: none

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Behavioral Problems in Grade One Students with Reading Difficulties in Thailand: A Cross-Sectional Study

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ABSTRACT

Objective: Children with reading difficulties face a number of challenges when entering school. Numerous studies have revealed greater behavioral and emotional problems in children with reading disorders. There is limited data on the challenges faced by young struggling readers in Thailand. This study aimed to investigate behavioral and emotional problems in grade one students, comparing between children with and those without reading problems.

Materials and Methods: A cross-sectional study was conducted of 901 grade one children in Thailand. The parental version of the Strengths and Difficulties Questionnaire (SDQ) was completed by parents along with a questionnaire of demographic data. Homeroom teachers completed the SDQ, teacher version. Reading assessments were performed to determine which students had reading difficulty.

Results: Based on reading test scores, 131 students were considered to have reading difficulty. Students with reading difficulty were found to have significantly more behavioral and emotional problems in almost all aspects of the SDQ than children who were typical readers since they had just attended the formal education system. Overall, teachers reported five times as many problems in struggling readers, while parents reported twice as many.

Conclusion: Thai grade one students with reading difficulty appear to have significantly more emotional and behavioral problems than typical readers.

Keywords: Behavioral problems; reading difficulty; reading disorder; SDQ; Thailand (Siriraj Med J 2022; 74: 509-517)

INTRODUCTION

Specific learning disorders (SLD) are neurodevelopmental irregularities that lead to learning ability impairments. The DSM V classifies SLD into three subtypes: 1) reading disorder; 2) writing disorder; 3) mathematics disorder.[1] Of all these, reading disorders (RD) are the most commonly recognized and intensively researched. Globally, the prevalence of SLD is 5–15% among school-age children across different languages and cultures. RD is the most common subtype of SLD; which accounts for 82% of total children with SLD or approximately 4 – 9 % of the population.[1,2] The prevalence rate of SLD in Thailand is in line with international research, the prevalence being between 6.4 - 15.6 %.[3-6] However, for prevalence studies in Thailand, it is necessary to explain that, in Thailand, there is currently no standardized comprehensive testing using Thai language to diagnose RD in children. The most widely used tool for diagnosis of RD is the Wide Range Achievement Test (WRAT)-Thai version which examines the accuracy of word reading, but does not measure other aspects such as fluency.[7]

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During the early elementary school years, children with RD have difficulties with spelling and reading aloud; they read slowly, guessing at or sounding out words they do not know, and making many errors. Reading skill is an essential prerequisite for academic success. Therefore, children with reading difficulties find challenges when they enter school. Not only do they achieve less academically than their peers, but their emotional and social lives are negatively impacted as well.

There is substantial literature on associations between reading difficulties and aspects of socio-emotional functioning. Research focusing on relationships between RD and internalized problems reveals that RD is associated with increased internalizing symptoms i.e., anxiety, depression, low self-esteem, somatic compliance and social withdrawal.[8-14] These symptoms were found in children from primary school to adolescence.[11] Children with RD also experience more externalizing symptoms. They are more overactive, impulsive, disruptive, defiant or aggressive than their peers who are typical readers. Moreover, reading problems were found to be associated with attention deficit hyperactive disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder. Among developmental disorders, ADHD is the most common comorbidity in children with RD; 15-40% of children with RD, also have ADHD.[8-10,12,15,16] In Thailand, research studies on the relationship between reading problems and behavior problems are limited. A study conducted an overview of medical records from 213 patients and found that 3 common developmental and emotional comorbid problems of SLD were ADHD (67.5%), developmental coordination disorder (27.2%) and adjustment disorders (14.6%).[5] However, the study was hospital-based where children with RD often had serious problems or had co-morbidities.

Although studies show associations between RD and both internalized and externalized behavior problems, there are no clear conclusions that such behavioral problems are the result of RD, or co-occurring with RD; one cognitive deficit may underlie both RD and several symptomatic behaviors.[17] A longitudinal study proposed that reading difficulties and problem behaviors appear to be independent of each other rather than problem behaviors being a consequence of reading failure supported a bidirectional causal model between reading and behavior problems.[12,18] Another longitudinal study followed a cohort of children in the UK from 2000 and found that children with specific word reading difficulties (SWRD) had behavioral challenges measured by SDQ at age 7, at the time they were just starting school. The researcher followed up this group of children for 4 years and found children with SWRD had even greater behavioral difficulties at 11 years old.[19]

Compulsory education of Thailand begins at Primary 1, corresponding to the age of 6-7 years. Systematic teaching of literacy begins when children are enrolled in this compulsory education. At present, in Thailand, RD has not been systematically screened in primary schools to provide early assistance. Therefore, children with RD who did not show any severe symptoms did not often receive service at hospital. This group of children not only needs help with reading and writing skills, but they may have emotional and behavioral issues that should be helped as well. Consequently, we were interested in a population-based study at a school. We wanted to find the prevalence and details of behavioral problems of children with or at risk of reading difficulties in their first years of school. Accordingly, the purpose of this study is to examine behavioral problems in grade 1 students at risk of RD as compared to those not at risk.

MATERIALS AND METHODS

A cross-sectional study was conducted in Pathum Thani Province, Thailand. Pathumthani is located adjacent to the Bangkok Metropolitan Region, with approximately 1.2 million people, who work in a variety of sectors including agriculture, industry, and other services. The Grade 1 students, aged 6 - 8 years, were recruited from eight primary schools in the region by purposive sampling. Schools were selected from three main affiliations: the Office of Basic Education Commission (OBEC), the Local Government Organization (LGO), and the Office of Private Education Commission (OPEC). The population selection from each school was done by distributing the number of students corresponding to each school's affiliation. In Pathum Thani province, approximately 70 % were affiliated with OBEC or LGO, and 30 % were affiliated with OPEC.[20] We decided to conduct this study during the second semester of grade one (November to December, 2018) because the data of our previous research found that children's reading ability in the first semester has an irregular distribution due to the wide variation in reading instruction in kindergarten. In the second semester of the compulsory school system, the 10th percentile cut-off point could be accurate enough to identify children with reading difficulty. Students previously diagnosed with visual impairment, e.g., blindness or low vision; hearing impairments, e.g., deafness; developmental disorders, e.g., autism, intellectual disabilities; and students who did not use Thai as a primary language were excluded.

Demographic data

Demographic data were collected by self-administrated questionnaire. The information collected includes age, gender, parental education, family income, kindergarten attendance, history of speech delay, family history of reading or writing difficulty, and parental perception of their children's reading abilities.

Assessment of reading skills

The students had their reading skills assessed by a test that was developed by Vibulpatanavong & Evans.[21] The reading tests were specifically designed for Thai students, grades 1-3. Word reading and passage reading tests were used in this study. The word reading test consisted of 60 words in a sequence from easy to difficult. Each student was instructed to read the words as quickly and accurately as possible in one minute in front of an assessor. The assessor gave a score based on the correct words that the child could read in one minute. The passage reading test comprised of three prose-style short stories, each 120 – 175 words long. Each student read aloud each story within one minute and was then scored on the basis of correct reading; each story was scored separately. The total score of the passage reading test was the sum of each passage score. The criteria for students at risk of RD was defined as having a score < 10 percentile of the sampled population in either the word reading test or in the passage section.

Assessment of behavioral problems

The assessment of behavioral problems was carried out using the Strengths and Difficulties Questionnaire (SDQ), Thai version for parents and teachers. The SDQ was designed for assessing children aged 4 - 16 years. It is comprised of 25 questions, which are divided into five subscales of five items each: 1) emotional symptoms, 2) hyperactivity/inattention, 3) conduct problems, 4) peer relationship problems, and 5) prosocial behavior. Each question of the SDQ can be answered as: not true (score of 0), somewhat true (score of 1), and certainly true (score of 2). On the first four subscales, higher scores represent more difficulties, while higher scores in the prosocial subscale indicate greater strengths.[22] The SDQ-Thai version was last updated in 2003 by Wongpiromsarn et al. Normative scores for Thai children were studied and cut off points were defined to classify children into 3 groups: normal, borderline, or problematic. SDQ was found to have high internal consistency. Cronbach's alpha for teacher and parent versions were 0.76 and 0.81, respectively.[23]

Procedures

After parental consent was given, reading assessment was performed face-to-face at school. Students had to read words and passages to the researchers one by one in a room with minimal noise. For consistency, each reading test (word, passage 1, passage 2 and passage 3) was assessed and scored by the same researcher for all children. Demographic questionnaires and the SDQ parental version were sent out to be completed by parents. The SDQ teacher versions were completed by homeroom teachers within two weeks. The reading scores were not disclosed to teachers and parents until the questionnaires were returned.

Data analysis

Data were analyzed by using STATA version14. Descriptive statistics were used, and when categorical data percentages were needed, normal distribution with mean and standard deviation were calculated for continuous data after being tested for data distribution. In comparison of data between groups, Chi square/Fisher exact tests were used for categorical data, whereas t-test/Mann-Whitney U tests were deployed for continuous data. Multivariate logistic regression model of the association between each behavioral problem and at risk of RD included gender, parental education, average family income, kindergarten school attendance, and school affiliation.

Ethical approval

Ethical approval was granted by the Human Research Ethics Committee of Thammasat University Faculty of Medicine: project number MTU-EC-PE-4-111/19.

RESULTS

Among the total of 1,127 students being sampled, 109 students were absent from the reading assessment; therefore, there were 1,018 questionnaires to be completed by parents and teachers, from which 902 sets, or 88.6 %, were returned.

According to our reading test, 132 students could be classified as at risk of RD. One student was excluded having a tested intelligence level ≤ 70; thus, the final number was 131 students, or 14.5 %.

The demographic data of students and their parents as shown in Table 1 reveals statistically significant differences of various external factors in students at risk of RD as compared to the normal group, i.e. three times males than females, parental education less than vocational college, below average family income, less attendance at kindergarten, and history of delayed speech. Although

TABLE 1. Demographic data of students at risk of RD compared to typical readers.

	At risk of RD N(%)	Typical reader N(%)	*P*-value
Gender			<0.001
Female	32 (24.4)	414 (53.8)	
Male	99 (75.6)	356 (46.2)	
Age: mean ± SD	7.0 ± 0.6	7.0 ± 0.4	0.786
Maternal education			0.023
High school or lower	94 (78.3)	498 (68.0)	
Vocational college or higher	26 (21.7)	234 (32.0)	
Father education			0.011
High school or lower	91 (79.1)	477 (67.4)	
Vocational college or higher	24 (20.9)	231 (32.6)	
Average family income per month (baht)			0.006
<10000	42 (34.7)	149 (20.4)	
10000 - 30000	58 (47.9)	387 (53.1)	
30000 - 50000	13 (10.7)	131 (18.0)	
50000 - 100000	5 (4.1)	49 (6.7)	
Kindergarten school			0.043
Attend	122 (96.8)	732 (99.1)	
Not attend	3 (2.4)	3 (0.4)	
History of delayed speech			<0.001
No	98 (86.7)	662 (95.7)	
Yes	15 (13.3)	30 (4.3)	
Family history of reading or writing difficulty: N (%)			0.178
No	102 (93.6)	685 (96.5)	
Yes	7 (6.4)	25 (3.5)	
Parent's perception of their child's reading ability			<0.001
Inferior	41 (44.1)	63 (9.7)	
Normal	51 (54.8)	542 (83.8)	
Superior	1 (1.1)	42 (6.5)	
School affiliation			<0.001
Office of Basic Education Commission	71 (54.2)	283 (36.6)	
Local Government Organization	34 (26.0)	220 (28.6)	
Office of the Private Education Commission	26 (19.8)	267 (34.7)	

parents of students at risk of RD were more aware of their children's reading difficulties than parents of typical readers, less than half of the parents realized that their children were less skilled at reading than their peers. Each school affiliation revealed a different proportion of children at risk of RD. The highest proportions of students at risk of RD were found in the OBEC, LGO, OPEC, respectively. Unexpectedly, a family history of reading or writing difficulty appeared not to affect reading skills in our study.

Table 2 shows the SDQ reported by parents and teachers, classified as problematic and non-problematic in students at risk of RD compared to typical readers. Both parental and teacher reports revealed that the proportions of student who had problematic behaviors were significantly higher in children at risk of RD than in typical readers in almost every domain of SDQ except for parentally-reported prosocial behavior. Thus, it can be concluded that overall behavioral problems are more pronounced in students at risk of RD than in typical readers.

With the use of univariate and multivariate analyses, the determined odds ratios of being at risk of RD for various behavioral domains of SDQ, reported by parents and teachers, are compiled in Table 3. The unadjusted odd ratios revealed that children at risk of RD were

TABLE 2. Number of students at risk of reading disorders whose SDQ scores were classified as problematic in various domains of behavioral problems compared to normal readers.

Domains	Classification	At risk of RD N (%)	Typical reader N (%)	*P*-value
Parent report				
Emotional problem	Normal/borderline	101 (77.1)	648 (84.2)	0.046
	Problematic	30 (22.9)	122 (15.8)	
Conduct problem	Normal/borderline	91 (69.5)	622 (80.8)	0.003
	Problematic	40 (30.5)	148 (19.2)	
Hyperactivity	Normal/borderline	96 (73.3)	658 (85.4)	<0.001
	Problematic	35 (26.7)	112 (14.6)	
Peer problem	Normal/borderline	50 (38.2)	400 (52.0)	0.004
	Problematic	81 (61.8)	370 (48.0)	
Prosocial behavior	Normal/borderline	122 (93.1)	739 (96.0)	0.144
	Problematic	9 (6.9)	31 (4.0)	
Total	Normal/borderline	85 (65.0)	614 (79.7)	<0.001
	Problematic	46 (35.1)	156 (20.3)	
Teacher report				
Emotional problem	Normal/borderline	112 (85.5)	732 (95.1)	<0.001
	Problematic	19 (14.5)	38 (4.9)	
Conduct problem	Normal/borderline	107 (81.7)	706 (91.7)	<0.001
	Problematic	24 (18.3)	64 (8.3)	
Hyperactivity	Normal/borderline	88 (67.2)	691 (89.7)	<0.001
	Problematic	43 (32.8)	79 (10.3)	
Peer problem	Normal/borderline	108 (82.4)	736 (95.6)	<0.001
	Problematic	23 (17.6)	34 (4.4)	
Prosocial behavior	Normal/borderline	97 (74.1)	701 (91.0)	<0.001
	Problematic	34 (25.9)	69 (9.0)	
Total	Normal/borderline	86 (65.7)	702 (91.2)	<0.001
	Problematic	45 (34.3)	68 (8.8)	

TABLE 3. Univariate and multivariate analysis of students at risk of reading disorders as a risk factors leading to behavioral problems.

Behavioral problem	Crude Odds ratio		Adjusted Odds ratio*	
	Odds ratio (95 % CI)	*P*-value	Odds ratio (95 % CI)	*P*-value
Parent report				
Emotional problem	1.57 (1.00 - 2.48)	0.048	1.66 (1.00 - 2.76)	0.049
Conduct problem	1.86 (1.23 - 2.81)	0.003	1.76 (1.08 - 2.85)	0.021
Hyperactivity	2.16 (1.40 - 3.35)	0.001	1.82 (1.09 - 3.05)	0.022
Peer problem	1.75 (1.20 - 2.56)	0.004	1.70 (1.11 - 2.60)	0.015
Prosocial behavior	1.80 (0.84 - 3.89)	0.132	1.19 (0.47 - 3.08)	0.706
Total	2.16 (1.45 - 3.22)	<0.001	2.37 (1.50 - 3.74)	<0.001
Teacher report				
Emotional problem	3.24 (1.80 - 5.82)	<0.001	4.05 (1.09 - 8.62)	<0.001
Conduct problem	2.53 (1.52 - 4.24)	<0.001	2.17 (1.19 - 3.95)	0.011
Hyperactivity	4.36 (2.82 - 6.72)	<0.001	4.47 (2.66 - 7.54)	<0.001
Peer problem	4.71 (2.66 - 8.33)	<0.001	4.90 (2.51 - 9.58)	<0.001
Prosocial behavior	3.58 (2.25 - 5.70)	<0.001	3.78 (2.19 - 6.48)	<0.001
Total	5.53 (3.56 - 8.59)	<0.001	5.32 (3.17 - 8.93)	<0.001

* Multivariate logistic regression model of the association between each behavioral problem and at risk of RD included gender, parental education, average family income, kindergarten school attendance and school affiliation.

likely to have more behavioral problems in all domains according to teacher reports and in conduct problem, hyperactivity and peer problem according to parental reports. Multivariate analysis was used to adjust for gender, parental education, average family income, kindergarten school attendance, and school affiliation. SDQ reports from teachers clearly indicated that even after adjustment, students at risk of RD still exhibited more behavioral problems in all domains than the other group. While SDQ reports from parents revealed the same results both before and after adjustment, children with RD were likely to display more conduct problems, hyperactivity and peer problems.

DISCUSSION

As far as we know, our study presents the first data on the prevalence of behavioral problems of Thai children at risk of RD from an early grade of school in school setting. The outcome of our research is consistent with the global findings. In our study, the SDQ scores from both parents and teachers revealed that children at risk of RD had more behavioral difficulties in almost all domains than children with typical reading skills.

The emotional problems domain from the SDQ questionnaire asked about internalizing symptoms, including somatic symptoms, anxiety, depressed mood, and self-esteem issues. Our study found that children in the at-risk group had significantly more of these problems than their peers. Teachers reported three times more internalizing problems while parents reported 1.7 times more problems in children at risk of RD. Similarly, previous research worldwide has found that at all ages; individuals with dyslexia have more internalizing symptoms, including higher level of depressive symptoms, lower level of self-esteem, and higher social and school anxiety.[8,11,24] The internalizing symptoms may be caused by feelings of incompetence and being pressured from adults. Children with reading difficulties attend school with the same willingness to learn to read as other children. However, over time, the children find themselves unable to read like their peers despite their efforts, and could not figure out what caused it, which

can lead to self-esteem problems. In addition, children are often under pressure from adults, such as teachers and parents who expect them to be successful in school. In early elementary year, it is the time when children go to school and learn to read. When parents find that their children are unable to read, they often link to their children's failure at school and tend to be anxious. They may blame the children for being inattentive and lazy due to a lack of understanding, which can exacerbate self-esteem problems and also internalizing symptoms. A previous study in Thailand found that although most parents of children with SLD had typical stress level, stress level was related with avoidance coping style.[25] Therefore, helping parents to understand and accept their children's difficulties could be beneficial for both parents and children.

For conduct problems, or externalizing symptoms, including often losing their temper, disobedience, fighting, lying, and stealing, both teachers and parents also reported significantly more challenges in children at risk of RD. These problems occurred about twice as much in at-risk children as in typical readers. Many international studies have also found that reading disabilities are associated with more externalizing symptoms, such as conduct, delinquency, and aggressive behaviors in children with reading disabilities.[8,14,26-27] Children with reading difficulties, when entering elementary school which focuses on reading and writing practice, often have trouble keeping up in class and may display task-avoidance behavior, such as ignoring teacher's instruction in the classroom, not working on assignments, and not handing in the assignments. If teachers or parents do not understand root causes of the problems, these behaviors may be interpreted as disobedience, lying, or resisting, which are described as externalizing symptoms. This avoidance behavior may also result in receiving negative feedback, such as scolding and punishment, which will intensify children's aggressive behaviors and externalizing symptoms.

Although both the questionnaires from teachers and parents reflected that at-risk children were more likely to have both internalizing and externalizing behavioral problems, the problems were more evident at school. It is worth noting that parents actually reported more children at risk with problems, but they also reported more problems in the not-at-risk children. It may be that at home, although there were more problems, the problems were unrelated to academics, while at schools; the behavioral problems were associated with learning situations.

On the Ages and Stages Questionnaire (ASQ) teachers reported problems among at-risk children most frequently in the hyperactivity domain. 32% of at-risk children had symptoms of attention deficit, hyperactivity or impulsivity while only 10% of typical readers had these problems. Epidemiological studies have consistently found that attention deficit hyperactivity disorder (ADHD) is the most common disorder co-occurring with dyslexia.[10,12,14,24] It is estimated that 15–40% of children with dyslexia are also diagnosed with ADHD. To date, it is not clear, on which exact functional processes this comorbidity is based. Some researchers proposed that children with reading difficulties struggle in learning in a classroom, and can lead to symptoms of ADHD, while some suggested that comorbid RD and ADHD was associated with a combination of the cognitive impairments according to brain function abnormalities, which are the underlying cause of both SLD and ADHD.

Deficient social skills, peer rejection and social isolation are known to accompany learning disabilities across age groups.[24,28-31] We also found this to be true, and we discovered that peer problems began to arise from the beginning of school. Social problems were especially evident in classrooms, where teachers reported five times more peer problems in children with reading difficulties than in typical readers. Problems with friends can be explained in a number of ways: RD may correlate with weakness in social interaction which causes peer problems.[12,24] Externalizing behaviors, self-regulation problems, and ADHD symptoms which are also common in children with RD may causes problems. It is interesting that the peer problem was the aspect that parents of children in both groups reported the most trouble with; fifty percent in the normal reader group and 60% in the at-risk group. This research was unable to explain why many parents were concerned about peer issues. More in-depth information should be gathered about parental concern of peer problems.

Parent and teacher reports differed regarding prosocial skills. Parents considered more than 90 percent of children in both groups to have good prosocial skills, but teachers rated the skills of at-risk children much lower than the prosocial skills of typical readers. This may be because the assessment of teachers was mostly based on behavior in the classroom. In Thailand, teachers usually have little opportunity to follow and observe students outside the classroom. Therefore, children at risk of RD who were inferior to their peers in education and faced more stress in the classroom had less opportunity to demonstrate prosocial skills, such as helping their classmates.

This research was a cross sectional study of the relationship between behavioral problems and reading

problems, so it was not possible to determine cause and effect. When the study was conducted, the children had just completed one semester of literacy training, about four months, which was too short to infer that reading problems lead to behavioral problems or vice versa. Previous research also found that children with reading difficulties had behavioral challenges shortly after starting school.[19,27] We therefore believe that emotional and behavioral problems and reading problems may be coincidental. As we know, reading problems and emotional problems can result from atypical brain functions. The abnormal brain activity of reading and emotional problems may be linked, this theory requires further study for clarification.

Previous research has revealed that without any intervention, behavioral and emotional problems worsen as a child with RD gets older.[24,30] Our study found that children with reading difficulty started having emotional and behavioral challenges shortly after attending primary school and were clearly different from general children. Thus, early intervention is essential, not only for reading impairment but also for emotional and behavioral issues for children who struggle with reading.

Our research entails some limitations. First of all, the measurements of emotional and behavioral problems were based on teachers' and parents' questionnaires which had unavoidable subjective bias. Secondly, the study took place only in Pathum Thani province, so the results may not be generalizable to the rest of Thailand. Lastly, there is currently no standard national reading assessment in Thai to determine if a child has a reading disorder (RD). We used a pre-existing test to assess reading skills and defined our at-risk group as the ten percent of students with the lowest scores. An ongoing long-term research study should learn how children in the at-risk group develop their reading skills in the future.

CONCLUSION

Students at risk of RD had more behavioral and emotional problems than children with no risk of RD, based on parental and teacher SDQ reports. The behavioral problems were more frequent in at risk RD students with the adjusted odds ratio of 1.6-4.7 according to both of teachers' and parents' reports. The major challenge reported by teachers was hyperactivity while peer problems were most often reported by parents.

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Effectiveness of the Four-Frequency Protocol of Repetitive Peripheral Magnetic Stimulation (rPMS) for Chronic Pain

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ABSTRACT

Objective: Repetitive peripheral magnetic stimulation (rPMS) is a noninvasive method of delivering a magnetic field to the periphery other than the brain. The treatment has shown positive outcomes for chronic pain and provides many advantages. This study investigated the effectiveness of the four-frequency protocol of rPMS in patients with chronic pain.

Materials and Methods: A retrospective review was conducted of patients with chronic pain treated with the four-frequency protocol. Data on patient demographics, pain characteristics, quality of life, and satisfaction were collected and analyzed.

Results: Forty-eight patients (174 sessions) were eligible for analysis. Most patients (81%) were diagnosed with chronic neuropathic pain. Upon completing the 4-week course of treatment, the mean ± SD of percentage of pain reduction was 49.7% ± 34.8%. The pain score also significantly decreased from baseline (mean difference, 3.3; 95% CI, 2.5–4.1; $P < 0.001$). Responses to treatment were observed for most patients (79.2%) and most treatment sessions (87.4%). For immediate effectiveness, the mean ± SD of percentage of pain reduction at the end of each treatment session was 46.2% ± 27.6%. Improvements in mood, function, and sleep were reported by 75.8%, 77.3%, and 79.5% of patients, respectively. Furthermore, most patients (72.5%) expressed satisfaction with the treatment.

Conclusion: The four-frequency protocol of rPMS for patients with chronic pain significantly reduced their pain scores for immediate effect and after the 4-week treatment course. A positive treatment response, an improved quality of life, and satisfaction with the therapy were found for nearly 80% of the patients.

Keywords: Chronic pain; neuromodulation; neuropathic pain; repetitive peripheral magnetic stimulation (Siriraj Med J 2022; 74: 518-529)

INTRODUCTION

Chronic pain has a considerable impact on both an individual's health and public health. It causes physical suffering and emotional distress, contributing to depressed mood, activity impairment, sleep disturbance, and increased healthcare costs worldwide.[1] Many pharmacological approaches have been developed for treating chronic pain. Particularly, chronic neuropathic pain usually required three or more drug combination treatment,[2] which may cause drug-drug interaction or additional side effects. On the other hand, nonpharmacological approach has been widely implemented into the treatment

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strategies due to high efficacy and less adverse effects. "Magnetic stimulation" is a nonpharmacological technique commonly used in clinical and research settings. The stimulation is divided into 2 noninvasive methods of delivering a high-intensity magnetic field: "transcranial magnetic stimulation" (TMS) and "peripheral magnetic stimulation" (PMS). The field is delivered to the brain by TMS and to the periphery other than the brain by PMS.

When the pulse of the high-intensity magnetic field passes into the body, it generates a voltage difference and creates an electric field, explained by the Maxwell–Faraday equation.[3,4] In turn, ions and electrons are induced to flow, affecting cell bodies in the magnetic field. Each type of cell has a different stimulation threshold. For example, the axons of neurons have a lower stimulation threshold than the cell bodies, so the magnetic stimulation affects the axons rather than neuron cell bodies.[5] The terms "repetitive transcranial magnetic stimulation" (rTMS) and "repetitive peripheral magnetic stimulation" (rPMS) describe the delivery of repetitive magnetic pulses.

In both research and clinical settings, rTMS is a commonly used technique for chronic pain treatment. There are many publications about its applications, efficacy, and safety. In contrast, rPMS has fewer studies and less extensive data on only some types of chronic pain, such as chronic neuropathic pain,[6,7] musculoskeletal injuries,[8] myofascial pain syndrome,[9,10] lumbosacral spondylotic pain,[11] and low back pain.[12,13] The rPMS technique has demonstrated positive outcomes for chronic pain and provides many advantages. It is a therapeutic device that can stimulate through any medium, does not require contact with the skin, can penetrate deep tissue, has no reported serious adverse effects, and is considered a painless method if a proper rPMS intensity is used.[14] The safety considerations relating to heating and magnetization are the same as those for rTMS.[15]

The type of PMS coils, their placement, and their parameter settings affect treatment. The type of coils affects the focus and depth of penetration into the target. Placing the coils flat and tangential to the longitudinal axis of the target structure is more effective for stimulation.[16] In rTMS, the parameter settings are relevant to safety concerns and treatment efficacy. Different parameters create a different preferential activation. The critical factors in determining the effectiveness and safety of rTMS are frequency, the total number of stimuli, duty cycle, and intensity. The term "slow" or "low-frequency" stimulation refers to stimulus rates of 1 Hz or less, which have inhibitory effects, whereas "high-frequency" stimulation refers to stimulus rates of 5 Hz or more, which have excitatory effects in the brain.[15,17] As to rPMS, there is no consensus regarding the standard protocol for parameter settings. The influence of frequency and the total number of rPMS stimuli remains inconclusive.[14] In the duty cycle, a longer "intertrain interval" may reduce the risk of excessive heating of the coils if the rPMS machine does not have a cooling system. As for the intensity parameter, many studies used suprathreshold stimulation, measured by muscle contraction, to produce proprioceptive afferents to induce neuroplasticity.[14] Many other studies used the output power at which patients perceived a significant local sensation or muscle contraction without excessive discomfort as a proper level of intensity.[6,8-10,12,13]

At the Siriraj Pain Clinic, a four-frequency protocol (FFP) of rPMS was implemented for chronic pain treatment in 2019. Patient responses have varied. Limited studies have evaluated the effects of rPMS on chronic pain, and its protocols are still controversial. The present investigation aimed to evaluate the effectiveness of the FFP on pain relief in patients suffering from chronic pain. The efficacy and safety of the FFP for this application has never been reported.

MATERIALS AND METHODS

Study design

Before this retrospective study began, its protocol was approved by the Siriraj Institutional Review Board (Si 1089/2020). Using ICD-11 code numbers, the authors searched medical records for all chronic pain patients at Siriraj Pain Clinic, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Patients

The inclusion criteria were patients of any age with chronic pain treated with the FFP of rPMS once weekly for 4 weeks. In addition, the patients were required to have had a definitive diagnosis of chronic pain for more than 3 months. The exclusion criteria were any records that lacked essential data (such as a diagnosis or pain score), patients who were treated with other or unknown PMS protocols, or PMS treatment was discontinued within the 4-week course for reasons unrelated to treatment efficacy or side effects.

The authors consecutively recruited patients from June 2019 (when the FFP protocol was introduced) to February 2021 (Fig 1).

Procedures

Patients were placed in the most comfortable and relaxed position (sitting, supine, or prone) for the particular treatment area. The equipment used to produce PMS at

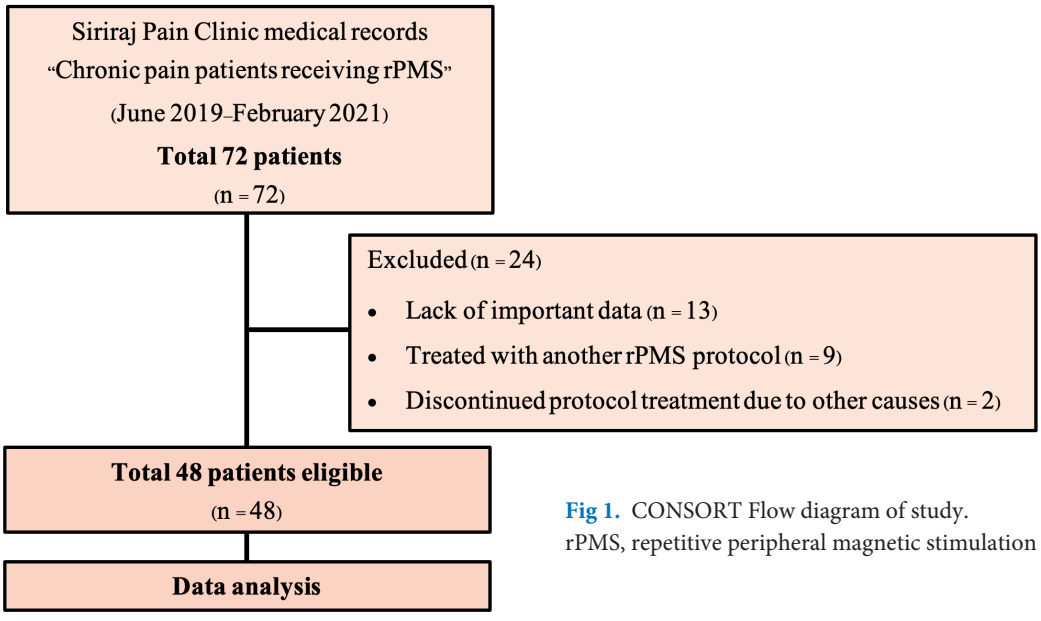

Fig 1. CONSORT Flow diagram of study.
rPMS, repetitive peripheral magnetic stimulation

Siriraj Pain Clinic was a Cool-125, active fluid-cooled, circular coil with a 12.1 cm outer diameter (MagVenture, Farum, Denmark) connected to a MagPro R30 TMS magnetic stimulator (MagVenture).

For the FFP, the machine was set at standard mode with a biphasic waveform, normal current direction, 40 pulses per train, and 40 trains per frequency. The first frequency was set at 10 Hz; each train lasted 4 s during the "On" period, while the intertrain interval (the "Off" period) was 1 s. The second to fourth frequencies were progressively increased to 20, 30, and 40 Hz, with trains lasting 2, 1.3, and 1 s, respectively; the "Off" period was 1 s. The initial treatment course comprised 4 sessions; they were held once weekly over 4 weeks. Each treatment session lasted approximately 10 minutes, with 1600 pulses per frequency and 6400 pulses per session (Fig 2). The stimulation intensity was adjusted at each session for each patient based on the patient's subjectively reported perception of the non-painful stimulation in the stimulated area.

To define the optimal stimulation intensity, pain physicians started the stimulations at 15% of the maximal output power of the machine. The power intensity was progressively in 2% to 3% increments until the patients perceived significant local or regional sensation without excessive discomfort. The authors found that the mean ± SD of stimulation intensity delivered for the initial treatment session was 32.4% ± 6.5%. Moreover, the maximum intensity was 39.3% ± 5.6%.

RPMS was delivered over the pain area depending on the pain diagnosis. For instance, with lumbar radicular pain, pain physicians started at the lumbar spine area and moved distally to cover all pain areas, by area or region. For brachial plexus injuries, treatment started at the area of injury and then moved distally to cover all pain areas, following the cervical dermatome or nerve distribution. With chronic musculoskeletal pain, treatment began at the myofascial trigger point or the most painful area before moving to cover all pain areas progressively (Fig 3).

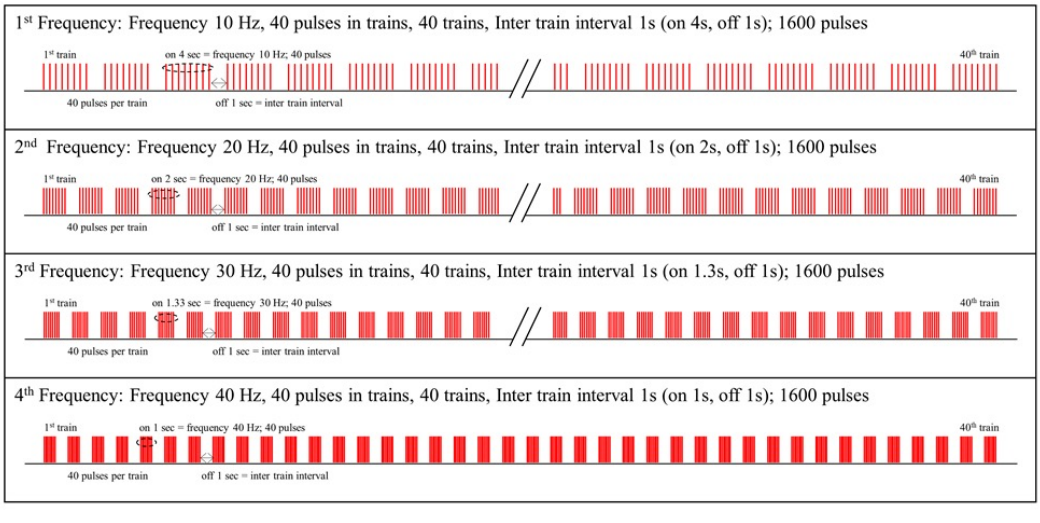

Fig 2. Diagram representing the parameters of the four-frequency protocol of stimulation.

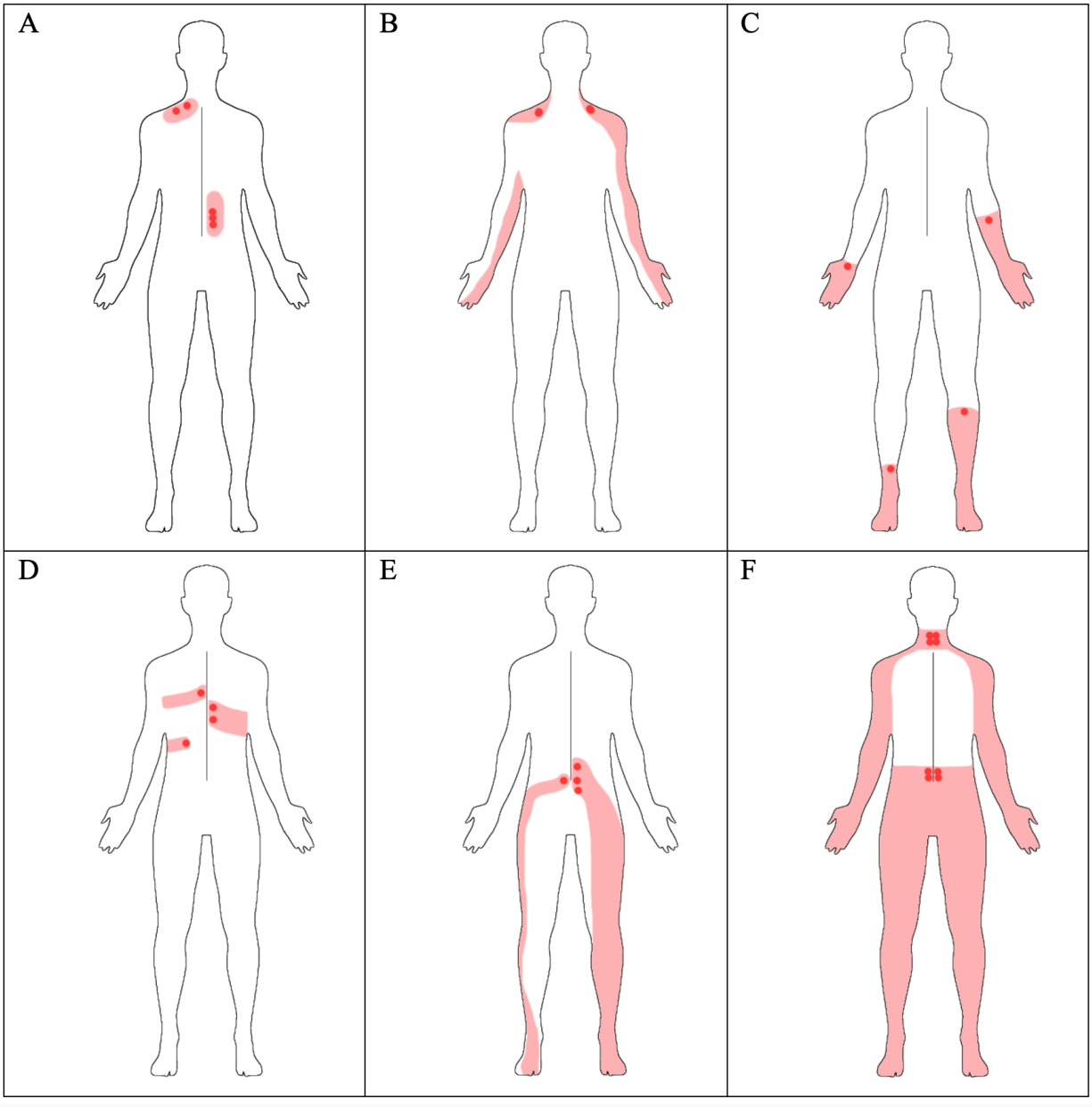

Fig 3. Diagram demonstrating the body area of stimulation. Examples for the areas of stimulation: red = starting area; pink = cover all pain areas; (A) for chronic musculoskeletal pain; (B) for chronic neuropathic pain after peripheral nerve injury; (C) for painful polyneuropathy; (D) for postherpetic neuralgia; (E) for painful radiculopathy; (F) for chronic central neuropathic pain associated with spinal cord injury.

Data collection

Demographic data (age, sex), patient characteristic data (primary diagnosis, pain diagnosis according to ICD-11, type of pain, type of neuropathic pain, area of pain, and associated disease), rPMS protocol settings, and the number of sessions were collected. Pain intensity was assessed by pain score (PS) using a numeric rating scale (0–10: 0 = no pain and 10 = worst possible pain). The PSs at baseline, before and after each treatment session, and at week 4 were recorded.

If the data were available, the authors also collected details relating to changes in quality of life (mood, function, and sleep), patient satisfaction, and adverse events.

Outcome measurements

Outcomes were evaluated at baseline (before treatment), before and after each session, and at week 4. The primary outcomes were:

1. The effectiveness of the FFP. This was measured by calculating the percentage of pain reduction relative to the PSs at baseline and week 4.
2. The number of "responders". This was defined as either:
   - the number of patients with a significant reduction in PS (PS reduction ≥ 2[18] or a percentage of pain reduction ≥ 30%) after the 4-week course of treatment; or

- the number of patients with a satisfactory response to rPMS and desiring to continue the treatment after the 4-week course.

There were 5 secondary outcomes. The first was the "immediate effectiveness" of the FFP. This was measured straight before and after each treatment session by calculating (1) the percentage of pain reduction and (2) the number of "responsive" treatment sessions, measured by the number of sessions that patient reported either significant pain relief (PS reduction ≥ 2 or a percentage of pain reduction ≥ 30%) or no pain or mild pain (PS 0–3) after treatment. The second outcome was the quality-of-life improvement, evaluated by mood, function, and sleep. As the medical records lacked appropriate quality-of-life measures, the authors defined "improvement" as when patients reported having:

- better moods (i.e., not depressed, not irritable, generally good mood, better relationships); or
- better function (i.e., able to stand, sit, walk, run, work, do activities, do activities for more extended periods); or
- better sleep (i.e., being able to sleep, a longer sleep duration, feeling fresh upon awakening).

The third outcome was patient satisfaction. This was defined as patients reporting being "satisfied" or "not satisfied" with their treatment. The fourth outcome was an analysis of factors potentially related to the number of responders and the degree of PS reduction. The factors investigated were sex; pain diagnosis; types of pain; site of stimulation (region or dermatome); and type of neuropathic, peripheral neuropathic and central neuropathic pain. The fifth outcome was adverse events stemming from the FFP.

Statistical analyses

Patient data were recorded and analyzed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). All results are presented as numbers (*n*) and percentages (%) for categorical variables and means ± standard deviations (SD) for continuous variables. The authors used the Wilson score interval for confidence interval (CI) calculations.[19] The unpaired t-test (normality) or Mann-Whitney U test (nonnormality) was used for continuous variables, and the Chi^2 test or Fisher's exact test for categorical variables. All tests were two-tailed. Results with a probability (*P*) value of < .05 were deemed statistically significant.

RESULTS

Between June 2019 and February 2021, 72 patients with chronic pain received rPMS treatment at the Siriraj Pain Clinic. Of those, 48 patients (174 sessions) were eligible for analysis. Their demographic data and pain characteristics are detailed in Table 1. The mean ± SD of the average initial PS was 6.4 ± 2.2. Chronic neuropathic pain (MG30.5) was found in 81.2% of the patients (39 of 48), while chronic peripheral neuropathic pain (MG30.51) was diagnosed in 70.8% (34 of 48).

Effectiveness of the FFP on primary outcomes

The mean ± SD of percentage of pain reduction was 49.7% ± 34.8%. The average baseline PS was 6.4 (2.2). After 4 weeks, the average PS was 3.2 (2.4). The PS significantly changed from baseline (mean difference, 3.3; 95% CI, 2.5-4.1; *P* < .001; Table 2).

Thirty-eight of 48 patients (79.2%; 95% CI, 65.7%-88.3%) were classed as "responders." No difference was found in the baseline PSs of the responder and non-responder groups (*P* = .703; Table 2).

Effectiveness of the FFP on secondary outcomes

From 174 sessions, the mean ± SD of percentage of pain reduction was 46.2% ± 27.6%. Of those sessions, 152 were classed as "responsive" (87.4%; 95% CI, 81.6%–91.5%; Table 2).

Improvement in quality of life

Some data related to the patients' quality-of-life improvements were missing. Twenty-five of 33 patients (75.8%; 95% CI, 59%–87.2%) reported an improvement in mood; 34 of 44 patients (77.3%; 95% CI, 63%–87.2%) reported an improvement in function; and 31 of 39 patients (79.5%; 95% CI, 64.5%–89.2%) reported an improvement in sleep (Table 2).

Patient satisfaction

Some data related to patient satisfaction were missing. Twenty-nine of 40 patients (72.5%; 95% CI, 57.2%-83.9%) expressed satisfaction with the treatment (Table 2).

Factors related to responder to the FFP

Sex, pain diagnoses, dermatome site of stimulation, type of pain, type of neuropathic pain, and type of peripheral neuropathic pain were not related to the number of responders to the treatment protocol. However, the regional stimulation site demonstrated a significant relation to responsiveness (*P* = .026; Table 3).

Factors related to pain score reduction of the FFP

Significant differences in responsiveness to the treatment protocol were found with only 2 factors: type of pain (*P* = .036) and stimulation site (region;

TABLE 1. Demographic data and pain characteristics of patients.

Characteristics	Values (*n* = 48)
Age (years)	63.4 ± 16.7
Sex	
Male	18 (37.5)
Female	30 (62.5)
Initial pain score	6.4 ± 2.2
Pain diagnoses	
Chronic musculoskeletal pain	9 (18.8)
Chronic neuropathic pain	39 (81.2)
Types of pain	
Nociceptive	6 (12.5)
Neuropathic	39 (81.2)
Mixed	3 (6.3)
Pain areas; sites of stimulation, over the region	
Upper extremity	8 (16.7)
Body	2 (4.1)
Back	12 (25.0)
Lower extremity	26 (54.2)
Sites of stimulation, over the dermatome	
Cervical (C)	13 (27.1)
Thoracic (T)	3 (6.2)
Lumbar-sacral (L)	32 (66.7)
Types of peripheral neuropathic pain (*n* = 34)	
Chronic neuropathic pain after peripheral nerve injury	7 (20.6)
Painful polyneuropathy	1 (2.9)
Postherpetic neuralgia	2 (5.9)
Painful radiculopathy	24 (70.6)
Types of central neuropathic pain (*n* = 4)	
Chronic central neuropathic pain associated with spinal cord injury	3 (75)
Other central neuropathic pain	1 (25)

Data are presented as mean ± SD or number (%). Mixed pain = combination of nociceptive and neuropathic pain.

TABLE 2. Effectiveness of four-frequency protocol of rPMS on primary and secondary outcomes.

		95% CI	*P*-value
Primary outcomes (*n* = 48)			
% Pain reduction (PS at 4th week vs baseline)	49.7 ± 34.8		
PS at baseline	6.4 ± 2.2		
PS at 4th week	3.2 ± 2.4		
Change from baseline	-3.3 ± 2.7	-4.1, -2.5	< .001
Responder	38 (79.2)	65.7, 88.3	
PS reduction ≥ 2	34 (70.8)		
PS reduction ≥ 30%	35 (72.9)		
Prefer to continue further treatment	20 (41.7)		
Non-responder	10 (20.8)	11.7, 34.3	
Baseline PS			.703
Responder group	6.5 ± 2.3		
Non-responder group	6.2 ± 1.6		
Secondary outcomes			
Immediate effectiveness (*n* = 174)			
% Pain reduction (PS at pre vs post treatment)	46.2 ± 27.6		
Responsive	152 (87.4)	81.6, 91.5	
Non-responsive	22 (12.6)	8.5, 18.4	
Improvement of quality of life			
Improvement of mood (*n* = 33)	25 (75.8)	59.0, 87.2	
Improvement of function (*n* = 44)	34 (77.3)	63.0, 87.2	
Improvement of sleep (*n* = 39)	31 (79.5)	64.5, 89.2	
Satisfaction (*n* = 40)	29 (72.5)	57.2, 83.9	
Adverse events (*n* = 174)			
(Pain at ankle became worse, PS 6→10)	1 (0.6)		

Data are presented as mean ± SD or number (%).

P = .009; Table 3). Nevertheless, nearly all other factors demonstrated a good reduction in pain after treatment (Table 3 and Fig 4).

Adverse events

Only 1 adverse event was observed for the whole cohort (1 of 174 sessions; 0.6%; Table 2). A patient in the "non-responder" group received all 4 sessions of rPMS. Although good outcomes with no adverse effects were reported for sessions 1, 2, and 4, an increase in pain was experienced in session 3. Pain in the ankle (the same side as the PMS) worsened, with the PS rising from 6 to 10 after treatment. The pain was subsequently relieved by oral medication (the PS dropped from 10 to 4).

DISCUSSION

Effectiveness of the FFP

The FFP of rPMS effectively decreased the PSs of patients with chronic pain 4 weeks after the initiation of treatment, with an approximately 50% pain reduction. Furthermore, the PS reduction was significantly different from baseline (mean difference, 3.3; 95% CI, 2.5–4.1; $P < 0.001$). Nearly 80% of the patients with chronic pain responded well to the treatment, without any significant difference in the baseline PSs of the responder and non-responder groups. More than 70% of the participants expressed satisfaction with the therapy and reported improvements in mood, function, and sleep.

TABLE 3. Factors related to responsiveness and pain score reduction of four-frequency protocol of rPMS.

	Responder *n*/total *n* (%)	95% CI (%)	*P*-value	Pain score reduction (mean ± SD)	95% CI	*P*-value
Genders			.067			.229
Male	17/18 (94.4)	74.2, 99.0		-3.9 ± 2.4	-5.1, -2.7	< .001
Female	21/30 (70)	52.1, 83.3		-2.9 ± 2.9	-4.0, -1.8	< .001
Pain diagnoses			.661			.107
Chronic musculoskeletal pain	8/9 (88.9)	56.5, 98.0		-5.1 ± 3.7	-7.9, -2.3	.003
Chronic neuropathic pain	30/39 (76.9)	61.7, 87.4		-2.8 ± 2.3	-3.6, -2.1	< .001
Types of pain			.615			***.036***
Nociceptive pain	5/6 (83.3)	43.6, 97.0		-4.3 ± 3.9	-8.4, -0.3	.041
Neuropathic pain	30/39 (76.9)	61.7, 87.4		-2.9 ± 2.3	-3.6, -2.1	< .001
Mixed pain	3/3 (100)	43.9, 100		-6.7 ± 3.2	-14.7, 1.3	.070
Pain areas; Sites of stimulation, over the region			***.026***			***.009***
Upper extremity	8/8 (100)	67.6, 100		-3.6 ± 1.1	-4.5, -2.7	< .001
Body	1/2 (50)	9.5, 90.5		-0.5 ± 0.7	-6.9, 5.8	.500
Back	12/12 (100)	75.8, 100		-5.3 ± 2.9	-7.1, -3.4	< .001
Lower extremity	17/26 (65.4)	46.2, 80.6		-2.5 ± 2.6	-3.5, -1.4	< .001
Sites of stimulation, over the dermatome			.094			.174
Cervical (C)	13/13 (100)	77.2, 100		-4.2 ± 1.9	-5.3, -3.0	< .001
Thoracic (T)	2/3 (66.7)	20.8, 93.9		-1.0 ± 1.0	-3.4, 1.5	.225
Lumbar-sacral (L)	23/32 (71.9)	54.6, 84.4		-3.1 ± 3.0	-4.2, -2.0	< .001
Types of neuropathic pain			.343			.592
Peripheral neuropathic pain	25/34 (73.5)	56.9, 85.4		-2.8 ± 2.4	-3.7, -2.0	< .001
Central neuropathic pain	4/4 (100)	51.0, 100		-3.5 ± 1.9	-6.5, -0.5	.035
Types of peripheral neuropathic pain			.114			.581
Chronic neuropathic pain after peripheral nerve injury	7/7 (100)	64.6, 100		-3.4 ± 1.7	-5.0, -1.8	.002
Painful polyneuropathy	0/1 (0)	0, 79.3		0	N/A	N/A
Postherpetic neuralgia	1/2 (50)	9.5, 90.5		-2.0 ± 2.8	-27.4, 23.4	.5
Painful radiculopathy	17/24 (70.8)	50.8, 85.1		-2.8 ± 2.6	-3.9, -1.7	< .001
Types of central neuropathic pain						
Chronic central neuropathic pain associated with SCI	3/3 (100)	43.9, 100		-4.0 ± 2.0	-9.0, 1.0	.074
Other central neuropathic pain	1/1 (100)	20.7, 100		-2.0	N/A	N/A

Abbreviations: Mixed pain; combination of nociceptive and neuropathic pain, rPMS; repetitive peripheral magnetic stimulation, SCI; spinal cord injury

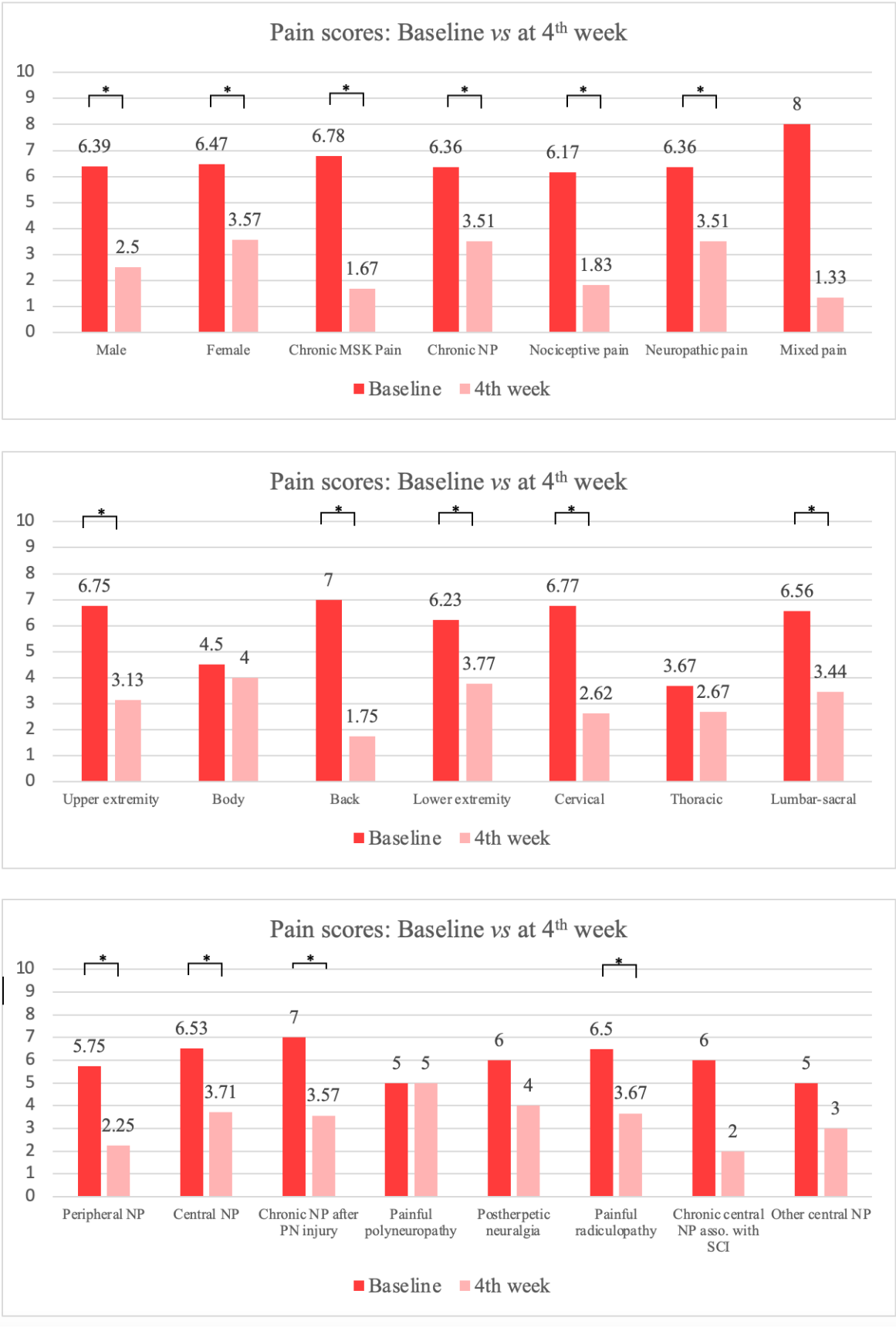

Fig 4. Pain score reduction for each factor after receiving the four-frequency protocol of rPMS.
Data are presented as means; *$P < 0.05$; mixed pain = combination of nociceptive and neuropathic pain; MSK, musculoskeletal; NP, neuropathic pain; PN, peripheral nerve; rPMS, repetitive peripheral magnetic stimulation; SCI, spinal cord injury

As for immediate effectiveness, the mean pain reduction was approximately 46% at the end of each session. Overall, 87.4% of the 174 treatment sessions were responsive to treatment.

Given the above results, the authors conclude that the FFP of rPMS can significantly reduce PSs for immediate effect and after 4 weeks of treatment.

The authors also analyzed factors potentially related to responsiveness to treatment and PS reduction from baseline. The FFP of rPMS may be useful for treating chronic musculoskeletal and neuropathic pain; some types of pain (neuropathic and nociceptive); and pain in the upper extremities, back, lower extremities, and cervical and lumbar dermatomes. As for neuropathic pain, the FFP may be beneficial for chronic peripheral neuropathic pain (chronic neuropathic pain after peripheral nerve injury and painful radiculopathy) and chronic central neuropathic pain.

Only 1 adverse event occurred among the 174 treatment sessions. After 1 session, a patient had worsened pain in the ankle (the same side as the rPMS). At the end of that particular treatment session, the PS rose from 6 to 10. The patient's pain was subsequently relieved by oral medication, resulting in the PS dropping from 10 to 4. This patient had good outcomes without any adverse effects for the other 3 treatment sessions undertaken. The cause of the adverse effects remains unclear. One possible mechanism might be the use of too high an intensity. However, this patient received the same protocol in all 4 sessions. Another possibility is that the coil was placed over the same area for a long time; nevertheless, there was no record. A third possibility is that the high-frequency stimulation increased the excitatory effects in the nervous system; still, there was no evidence of this occurring in any of the patient's 4 treatment sessions.

There is no clear conclusion about the mechanisms of action of rPMS. Some studies have proposed that PMS directly stimulates sensorimotor nerve fibers and indirectly stimulates mechanoreceptors of muscle fibers.[20-22] Another study reported that PMS over spinal roots and muscles decreased spasticity.[23] PMS might have some supraspinal mechanisms. It has been reported that when PMS was applied over an affected peripheral area, there was an increase in regional cerebral blood flow (shown by a PET scan) and increased homeostasis of cortical excitability. Therefore, PMS could potentially influence cerebral activation and neuroplasticity.[24-26]

This study used an rPMS protocol consisting of 4 frequencies (10, 20, 30, and 40 Hz) of magnetic stimulation. This protocol was selected because it can be used for pain diagnosis, many types of pain, and many pain areas. The 4 frequencies would stimulate diverse types of muscle cells and neurons, thereby producing different therapeutic effects. Because the protocol uses a frequency exceeding 1 Hz, the inhibitory effects (weakness and numbness) are not of concern. The treatment protocol may be easy for physicians who use rPMS to treat chronic pain in that it can be applied to almost all patients.

In some pain diseases (such as painful polyneuropathy and postherpetic neuralgia), the studied rPMS protocol did not produce good outcomes. This may be because the sample size was too small. Alternatively, these pain conditions may respond to frequencies below 10 Hz or over 40 Hz. Changing the frequency of the stimulation might provide a better result.

During the authors' 2-year experience of using the FFP, some variations in therapeutic effects were observed: some cases had very satisfactory outcomes, whereas others demonstrated poor results. This retrospective study may guide further practice and research for some types of chronic pain treatment and the selection of cases suited to this protocol. It would need to be modified for the types of pain that did not show good responsiveness.

Comparison with other studies

Many studies have shown that rPMS is advantageous for many medical conditions. Khedr et al, found promising results, with a 90% reduction in chronic neuropathic pain from traumatic brachial plexopathy.[6] An 84% reduction in chronic neuropathic pain from post-trauma (neuroma; nerve entrapment) was reported by Leung et al.[7] Pujol et al, observed that PMS reduced pain severity by 59% in subacute musculoskeletal injuries.[8] In a study on chronic myofascial pain syndrome, Smania et al, showed that PMS provided an improvement that lasted longer than transcutaneous electrical nerve stimulation.[9,10] Lo et al demonstrated a 62.3% reduction in lumbosacral spondylotic pain,[11] while Massé-Alarie et al reported a 46% reduction in chronic low back pain.[12,13] Lim et al, found a 57% reduction in acute low back pain.[27]

In the current investigation, pain levels declined by approximately 50% to 100%, depending on the type of pain diagnosed. The main difference between this study and previous research was the PMS protocol used. A variety of frequencies, number of pulses, and areas where stimulation is applied can be used by PMS. Unlike the present work, most earlier studies only used 1 frequency (0.5, 10, 15, or 20 Hz).[6-13] In addition, different equipment models used to produce PMS and different types of PMS coil may affect therapeutic effects by generating different magnetic fields. Furthermore, the present study evaluated more pain diagnosis types and more kinds of neuropathic pain than other studies.

Limitations

The primary limitation of this research was its retrospective design. This risked the introduction of biases when evaluating effectiveness, such as a selection bias (good candidate selection; no randomization), placebo effects, natural regression, and co-intervention (no control group; no blinding). Some data related to quality-of-life improvements, patient satisfaction, long-term efficacy and duration of pain were also missing in the present work. Moreover, the investigation lacked precise and validated tools for evaluating the quality-of-life and satisfaction outcomes. In addition, there were too few participants to analyze the factors associated with rPMS effectiveness.

Prospective randomized controlled trials should be conducted to investigate the FFP of rPMS for application to specific conditions. The current work can be used as a guide for such studies.

CONCLUSION

The FFP of rPMS for patients with chronic pain significantly reduced pain intensity in terms of immediate effectiveness and after 4 weeks of therapy. Nearly 80% of the patients had a satisfactory treatment response. The FFP effectively reduces chronic musculoskeletal and neuropathic pain (peripheral and central), increases the quality of life, and improves patient satisfaction with minimal adverse effects.

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Conflict-of-interest statement

The authors have no conflicts of interest to declare.

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Chronic Myeloid Leukemia (CML) at National Referral Hospital in Indonesia

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ABSTRACT

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome and BCR-ABL fusion oncogene. CML is one of the illnesses that may be treated using Tyrosine Kinase Inhibitors (TKIs), a type of targeted therapy. Since TKIs are the standard of therapy, long-term survival of CML has improved compared to chemotherapy and interferon-alpha. For the first-line treatment for CML, there are four commercially available TKIs that serve as an integral part of the disease management. However, there are many challenges in diagnosing, treating, and monitoring patients with chronic phase CML in Indonesia. This study highlights the epidemiology data of chronic phase CML patients, particularly at Dr. Cipto Mangunkusumo General Hospital, an Indonesian national referral hospital, and how to diagnose, select first-line TKIs, and monitor the response of treatment after TKIs administration.

Keywords: Chronic phase chronic myeloid leukemia; epidemiology; diagnosis; treatment; monitoring (Siriraj Med J 2022; 74: 530-536)

INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia (Ph) chromosome. The BCR-ABL fusion gene is produced by a reciprocal translocation between the ABL region of chromosome 9 and the breakpoint cluster region (BCR) section of chromosome 22 [t(9;22)(q34;q11)].[1,2] Cell proliferation, cytoskeletal disorganization, decreased cell apoptosis, enhanced mitogenic signaling, decreased cell differentiation, decreased cell adhesion, and increased cell motility are all caused by the BCR-ABL gene, which codes for transcripts with strong tyrosine kinase activity.[3,4]

Most CML patients present asymptomatic cases and are diagnosed in the early chronic phase. However, most patients in Indonesia and other Asia are symptomatic and diagnosed in the late chronic phase.[3] In Asian countries, CML tends to affect younger people than in Western countries.[5] The diagnosis is usually established by conventional cytogenetics and Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of BCR-ABL.[2]

Treatment of CML has changed drastically, and in the 1980s, Busulfan, allogenic bone marrow transplantation, and interferon-alpha were used as therapy for CML. After that, hydroxyurea was used as standard therapy of CML,

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and in the 2000s, the first-generation TKI, Imatinib, was used as the first-line therapy.[6] There are four commercially available TKIs as first-line therapy: Imatinib, Dasatinib, Nilotinib, and Bosutinib.[7] The most appropriate first-line therapy is selected based on the patient's characteristics and the availability in each nation or healthcare facility. Currently, only Imatinib, Nilotinib, and Ponatinib are available in Indonesia.

Dr. Cipto Mangunkusumo General Hospital is a national referral hospital that receives referrals from all provinces. This study determines CML's epidemiology, establishes the diagnosis of chronic phase CML, treats and monitors treatment response, and compares the findings to other countries.

Epidemiology

The proportion of CML is about 15% of all adult leukemia cases.[2] In the USA, the median age of diagnosis is 67 years, and between 60 to 65 years in Europe.[1,2] CML is less common in Asia than in Western countries, and it tends to strike at a younger age.[5,8] The median age in China, Hongkong, India, Philippines, Singapore, South Korea, Thailand, and Malaysia is between 36-55 years.[8-10] These countries showed a higher occurrence in males than females.[8,10] Indonesia has a similar situation, with a median age of 34-35 years (mean 36 years) and a male to female ratio of 1.5:1.[9] At Dr. Cipto Mangunkusumo General Hospital, the mean (SD) age of diagnosis is 39 (13) years old.[11] A previous study conducted between 2003 and 2008 revealed comparable findings, with the median age of diagnosis being 37 years and a male to female ratio of 1.2:1.[12] Based on these data, the epidemiology of CML patients at Dr. Cipto Mangunkusumo General Hospital and Indonesia is similar to Asia.

CML is a triphasic disease consisting of chronic, accelerated, and blast crisis phases. Patients in the chronic phase are frequently asymptomatic, and symptoms are mainly attributable to anemia and splenomegaly. The most common symptoms are fatigue, unexplained weight loss, left upper quadrant abdominal discomfort or pain, and early satiety. In the chronic phase, bleeding manifestations or priapism are infrequent, although splenomegaly is often observed on physical examination (40-50%).[2] Severe leukocytosis with a shift to the left, «myelocyte bulge» (more myelocytes than mature metamyelocytes), blast <2%, basophilia, eosinophilia, and increased platelet count (thrombocytopenia only in advance cases) are common laboratory results.[13] The World Health Organization defines accelerated phase CML as having one or more of the following characteristics: persistent or increasing white blood cells (WBC) >10x10^9 cells/L, persistent or increasing splenomegaly, persistent thrombocytosis or thrombocytopenia unresponsive to therapy, >20% basophils in peripheral blood, 10-19% blast in peripheral blood or bone marrow, and additional clonal chromosome abnormalities.[14] Meanwhile, CML is characterized as being in the blast phase when there is more than 20% blast in the peripheral blood or bone marrow or extramedullary involvement (excluding liver and spleen).[2]

The majority (90-95%) of CML patients are diagnosed in chronic phase CML (CP-CML)[3], and approximately 50% in the USA and Europe are asymptomatic.[2,3] CML is usually detected during a routine physical examination or blood tests.[3] In the study conducted by Tadjoedin, 72.7% of CML patients at Dr. Cipto Mangunkusumo General Hospital are classified as chronic phase, 23.9% accelerated phase and 3.4% blast crisis phase.[15] Most patients (83.3%) at Dr. Cipto Mangunkusumo General Hospital came with symptoms such as fatigue, night sweating, abdominal discomfort, and abdominal mass. Splenomegaly was detected in 82% of CML patients[11], and uncommon signs such as priapism and hyperleukocytosis were discovered owing to leukemic cell aggregation in the corpus cavernosum and the dorsal vein of the penis.[16] The majority of patients with chronic phase CML are symptomatic, and the proportion of splenomegaly is higher than in America and Europe. Laboratory also showed similar results from Western countries, which are leukocytosis with basophilia, immature granulocytes (promyelocyte, myelocyte, metamyelocyte), few blasts, mild anemia, and thrombocytosis.[11]

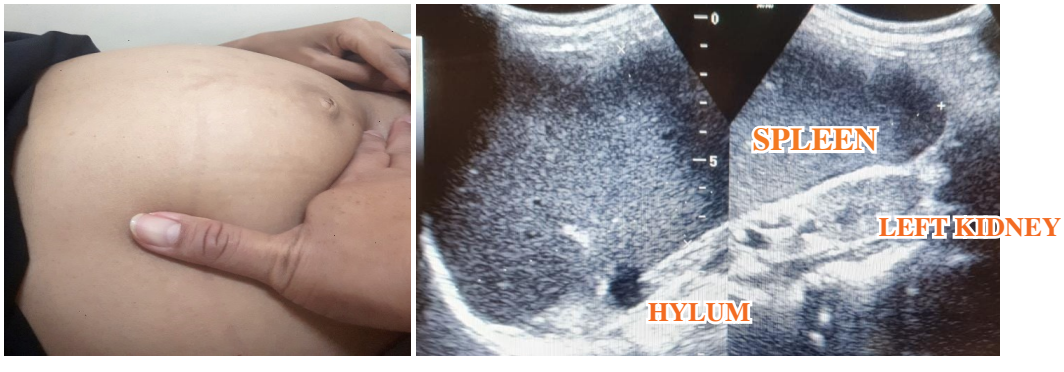

Fig 1. The percentage of splenomegaly in chronic phase CML patients at Dr. Cipto Mangunkusumo General Hospital was 82%. Splenomegaly can be detected clinically by palpation (left) or by bedside ultrasound (right).

Diagnosis

CML is suspected when there is unexplained leukocytosis, which is validated by bone marrow aspiration and biopsy and qualitative RT-PCR on peripheral blood cells. Bone marrow aspiration and biopsy samples are sent for cytogenetics and morphology examination. Morphology examination is essential to distinguish CML phases: chronic phase, accelerated phase, and blastic crisis phase.[7,17] Furthermore, qualitative RT-PCR is required to identify the BCR-ABL transcripts while monitoring therapeutic response.[7] Fluorescent in situ hybridization (FISH) is needed when Ph-chromosome is undetected in cytogenetics evaluation.[2,7]

At Dr. Cipto Mangunkusumo General Hospital, bone marrow aspiration was routinely performed for morphology and conventional cytogenetics evaluation. The sample was sent to Dharmais Hospital, the National Cancer Centre, or a private laboratory for qRT-PCR. In addition, the Philadelphia chromosome was evaluated using cytogenetic karyotyping. BCR-ABL transcripts are measured by multiplex reverse transcriptase-polymerase chain reaction (RT-PCR).

In addition to confirming the diagnosis, the risk of every CML patient before treatment was calculated. The three most common prognostic scores are Sokal, Hasford/Euro, and EUTOS Long-Term Survival (ELTS), as depicted in Table 1. Sokal score was introduced in 1984 during the chemotherapy era, while Hasford/Euro score came during the interferon-alpha era and ELTS score during the TKI era. Sokal and Hasford scores calculate overall survival probabilities, disease progression and predict therapeutic response. Meanwhile, the ELTS score calculates the probabilities of death due to CML.[18] All prognostic scores classify CML patients into low, intermediate, and high-risk profiles. Sokal and ELTS scores were calculated based on the patient's age, spleen size, platelet count, and blast percentage in peripheral blood. In addition to the variables above, data on eosinophil and basophil are needed to calculate the Hasford score.[1] According to Tadjoedin, CML patients at Dr. Cipto Mangunkusumo General Hospital, are divided into three groups: low risk (39.8%), intermediate-risk (22.7%), and high risk (37.5%) Sokal score.[15] For patients with intermediate to high risk, the most contributing factors are splenomegaly, followed by thrombocytosis. The risk stratification according to these scores, along with disease duration, history of treatment with hydroxyurea, and the phase of CML correlates with the response to therapy with TKI, particularly Imatinib.[15]

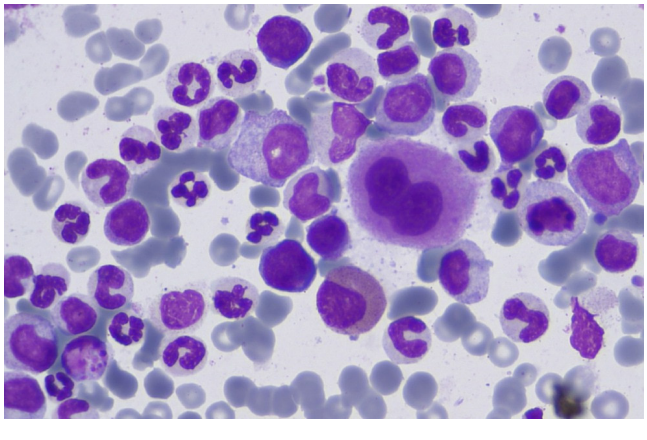

Fig 2. Bone marrow morphology of patients with chronic phase CML showed dwarf megakaryocytes, mature granulocytes (segments and bands), immature granulocytes (promyelocytes, myelocytes, metamyelocytes), and a few blasts.

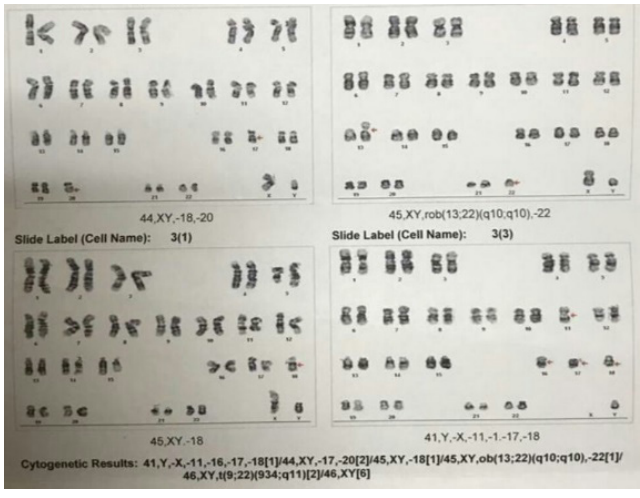

Fig 3. Conventional cytogenetics of a patient with chronic phase CML who progressed into accelerated phase after first-line treatment of Imatinib which showed complex karyotype abnormalities including Philadelphia chromosome.

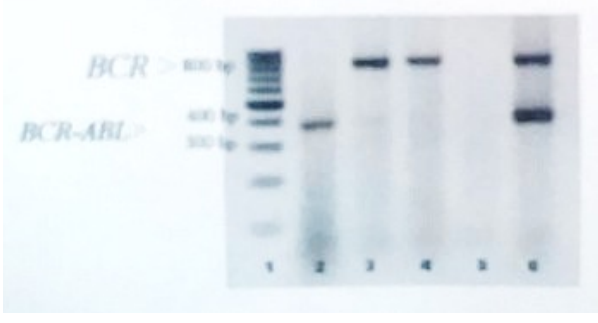

Fig 4. Multiplex RT-PCR for BCR-ABL

Treatment

There are many revolutionary changes in CML treatment before Tyrosine Kinase Inhibitors (TKIs) therapy. In 1960, busulfan was used as a CML therapy, followed by hydroxyurea, which is superior to busulfan. Then in 1980, interferon-alfa became the standard therapy for CP-CML. During 1990, allogenic hematopoietic stem

TABLE 1. Comparison of Sokal, Hasford/Euro, and ELTS Scores.

	Sokal	Hasford/Euro	ELTS
Factors	Age, spleen size, platelet count, blast percentage	Age, spleen size, platelet count, blast percentage, basophils percentage, eosinophils percentage	Age, spleen size, platelet count, blast percentage
Formula	Exp 0.0116 × (age-43.4) + 0.0345 × (spleen-7.51) + 0.1880 × [(platelet count/700)^2 - 0.563] + 0.0887 × (blasts - 2.10)	(0.6666 × age [0 when age <50 years; 1, otherwise] + 0.0420 × spleen + 0.0584 × blasts + 0.0413 × eosinophils + 0.2039 × basophils [0 when basophils <3%; 1, otherwise] + 1.0956 × platelet count [0 when platelets <1,500 × 10^9 /L; 1, otherwise]) × 1,000	0.0025 × (age/10)^3 + 0.0615 × spleen + 0.1052 × blasts + 0.4104 × (platelet count/1000)$^{-0.5}$
Risk	Low risk: <0.8 Intermediate risk: 0.8–1.2 High risk: >1.2	Low risk: ≤780 Intermediate risk: 781–1,480 High risk: >1,480	Low risk: ≤1.5680 Intermediate risk: 1.5680–2.2185 High risk: >2.2185

cell transplantation became the first-line therapy for CP-CML patients below 50 years old, while interferon-alpha (IFN-α) is indicated for those who are contraindicated to transplantation. In the meantime, in 1986, BCR-ABL oncoprotein was discovered, resulting in TKI targeted therapy. Firstly, Imatinib was used only as therapy for IFN-α resistant patients. However, in 2000, Imatinib 400 mg/day was designated as the first-line therapy for CP-CML after the International Randomized Study of Interferon and STI 571 (IRIS) revealed that Imatinib outperformed IFN-α in terms of cytogenetic response, event-free survival, progression-free survival, and overall survival.[6]

The United States Food and Drug administration (FDA) and European Medicines Agency (EMA) have authorized four TKIs as first-line therapy: one first-generation TKI (Imatinib) and three second-generation TKIs (Dasatinib, Nilotinib, and Bosutinib). In South Korea, Radotinib, the fifth TKI, has been approved[7] and TKIs are effective as CP-CML therapy. However, second-generation TKIs are associated with lesser disease progression and faster cytogenetic and molecular responses. There are no differences in terms of overall survival[1], and based on data from phase 3 study RERISE, Radotinib results in earlier and more profound molecular responses than Imatinib.[19] Ponatinib, a third-generation TKI, may be therapy for those with BCR-ABL mutation or resistance to ≥2 TKIs.[7] Selecting first-line treatment for patient CML should be based on the patient's age, risk score, comorbidities, response to therapy, side effects, and availability. Disease progression is more common in those with intermediate to high-risk Sokal or Euro scores, therefore, second-generation TKIs are preferred. Second-generation TKIs are also preferred for younger patients, specifically females, due to a faster response that may allow therapy discontinuation for fertility purposes.[1] Imatinib is recommended for older patients, specifically those with comorbidities, as the drug is safer in terms of adverse effects, specifically in patients with cardiovascular disease. Nilotinib usage is contraindicated in those with cardiovascular or metabolic disorders. Meanwhile, Dasatinib is contraindicated in patients with lung disease. Bosutinib should not be chosen as first-line therapy for hepatic or gastrointestinal disease patients.[7,20] Consumption of food with high-fat content and nilotinib should be avoided because of the effect on drug bioavailability.[20]

In the last decade, the therapy of CML has developed significantly. Before 1980, busulfan is the only available agent for the therapy of CML in Indonesia. Around 1987-1988, allogenic bone marrow transplantation (BMT) was introduced as CML therapy at Dr. Cipto Mangunkusumo General Hospital, Jakarta, with interferon-alpha. Hydroxyurea became available in Indonesia in

1989-1990 and was used as a CML therapy, and in February 2002, first-generation TKI Imatinib mesylate was approved by the Indonesian FDA (Badan Pengawasan Obat dan Makanan/BPOM). In 2003, The Glivec® International Patient Assistance Program (GIPAP) helped patients with chronic phase CML access imatinib by covering Imatinib's cost. It was replaced by Novartis™ Oncology Access (NOA) in 2008, and Indonesia National Health Insurance has covered Imatinib fully since 2009. Second generation TKI, Nilotinib, got approval by the BPOM in 2007, and in 2013, nilotinib was approved by BPOM and fully covered by Indonesian National Health Insurance. Ponatinib gets approved by BPOM in 2019, but Indonesia National Health Insurance does not cover it. Currently, the first-line therapy for CML is Imatinib, with nilotinib as second-line therapy. Nilotinib may be considered initial therapy for those with intermediate to high-risk profiles or younger patients, specifically females, who plan to get pregnant. Before TKI, hydroxyurea was the standard therapy of CML. There were 73.9% CML patients at Dr. Cipto Mangunkusumo General Hospital who received hydroxyurea before Imatinib, with 27.3% for more than 6 months.[15] Recent studies showed an association between administration hydroxyurea for > 6 months with the inability to achieve significant molecular response (Major Molecular Response/MMR).[21]

Monitoring

A good outcome depends not only on first-line therapy but also on monitoring the response to treatment, ensuring that the milestones are met, and intervening quickly when intolerance or resistance develops.[20,22] According to European LeukemiaNet (ELN) 2020, before obtaining a complete hematological response, blood cell and differential count monitoring every two weeks is essential.[7] Patient is classified as reaching complete hematological response (CHR) when WBC count <10 x 10^9/L, no immature granulocytes, basophils <5%, platelet count<450 x 10^9/L, and no sign and symptoms with the non-palpable spleen.[1,2] Quantitative BCR-ABL (IS) has to be conducted every 3 months, even after the MMR is achieved, to monitor the therapy's molecular response.[1,7] Molecular response of therapy classified to early [BCR–ABL (IS) ≤ 10% on the 3rd and 6th month], major molecular response (BCR–ABL<0,1% or reduction ≥ 3–log mRNA BCR–ABL from baseline), and deep molecular response [BCR-ABL (IS) ≤ 0.01%].[1] Furthermore, achievement of CHR on 3rd, 6th, and 12th month is associated with MMR on 18th month.[15] CML therapy monitoring milestones are based on BCR-ABL transcripts (IS) at 3, 6, and 12 months, where it is classified as ideal (maintain current treatment), warning (close monitoring and consider changing treatment), or failure (change treatment).[7] Adherence to treatment also plays an important role in therapy outcome.[23]

At Dr. Cipto Mangunkusumo General Hospital, CHR was achieved by 74% of CP-CML patients in the 3rd month.[12] After completing CHR in the 3rd month, monitoring by qRT-PCR is conducted every 6 months. However, it is not covered by Indonesia National Health Insurance, thus, patients should pay for it themselves.

For those with treatment failure, evaluation of BCR-ABL mutation is recommended.[24] Mutation on the BCR-ABL kinase domain is associated with resistance to therapy, disease progression, and poor prognosis. T315I mutation is associated with resistance to Imatinib,

TABLE 2. The milestone of therapy based on BCR-ABL transcripts (IS).[7]

	Optimal	Warning	Failure
Baseline	NA	High-risk additional chromosome abnormalities, high-risk ELTS score	NA
3 months	≤ 10%	> 10%	>10%, confirmed within 1-3 months
6 months	≤ 1%	> 1-10%	> 10%
12 months	≤ 0.1%	> 0.1-1%	> 1%
Any time	≤ 0.1%	> 0.1-1%, loss of ≤ 0.1% (MMR)	> 1%, resistance mutations, high risk additional chromosome abnormalities

Adapted from: Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-84.

Dasatinib, Nilotinib, and Bosutinib. T315A, F317L/I/V/C, and V299L resistant to Dasatinib. F359C/V and Y253H are resistant to nilotinib, while E255K/V, F359C/V, Y235H, and T315I mutations are linked to disease progression and recurrence.[1] According to a 2015 study, the following BCR-ABL mutations were discovered: N231Q, M35IT, E509G, c.661 662insG with 1555 1557insG, V506S, 1152C->T, and Y253H. Those with BCR-ABL mutations had an intermediate to high Sokal risk and did not produce a significant molecular response by the 18th month, therefore, BCR-ABL mutation plays a crucial role in disease progression.[15]

Overall survival of CP-CML treated with TKI from IRIS, DASISION, ENESTnd, TOPS, CML IV, and SWOG study varies between 83%-95%.[1] Unfortunately, CP-CML patients' overall survival at Dr. Cipto Mangunkusumo General Hospital is lower, which is 66%.[12] The decreased OS was due to the preponderance of patients arriving in the late chronic phase, with the majority presenting with splenomegaly and a greater Sokal risk.

CML in The Era of COVID-19

Dr. Cipto Mangunkusumo General Hospital requires patients with chronic phase CML who regularly attend the hematology-medical oncology clinic to monitor their body temperature, wear a mask, and schedule a previous online appointment to minimize crowding. Furthermore, before admitting chronic phase CML to the ward, Dr. Cipto Mangunkusumo General Hospital requires nasopharynx and oropharynx swabs for SARS-CoV-2 PCR test. The General Hospital also obligates vaccination to every medical staff who gives medical services.

There are several reported publications on the CML in the pandemic Era. Generally, patients with hematological malignancies are at increased risk due to immunosuppression and/or comorbidities. However, data from the UK showed that most patients with CML who are infected with SARS-CoV-2 had mild disease and recovered.[25] Another case series from Turkey also showed complete recovery of COVID-19 in CML patients, regardless of their Sokal skore.[26] Although these patients might have increased risk for complications of COVID-19, it is hypothesized that TKIs have antiviral effects by blocking viral entry through off-target Abl kinase inhibitor.[25] Currently, there is no sufficient data to conclude the findings. Therefore, American Society of Hematology does not recommend alteration in CML treatment in those who contracted COVID-19., except in severe cases in which the decision should be made on case-by-case basis.

CONCLUSION

Patients with chronic phase CML in our study tend to be younger than in the West, but equivalent to other Asian countries. Most are symptomatic with high percentage of splenomegaly, leading to intermediate to high-risk Sokal score and lower CHR and MMR.

Imatinib is the first line TKI for patients with chronic phase CML since next-generation TKIs are not widely available in Indonesia. Nilotinib is preserved for those with high Sokal scores, no comorbidities, and women who want to conceive in the nearest future. Monitoring of molecular response should be conducted every 6 months, however this is not covered by our National Health Insurance.

Dr. Cipto Mangunkusumo General Hospital has crucial preventative measures to limit the spread of COVID-19, including immunization of designated personnel and screening of COVID-19 in CML patients. Currently, there is no sufficient data to support the hypothesis that CML patients are at increased or less risk during this pandemic.

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- Osteoporosis and hip fracture
- Acute psychosis management
- DM through the lifespan
- Atopic diseases
- CPR

Challenges and workshops

- Prehospital critical care
- Emergency CT
- Dermatology
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