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Original Article **Open Access**

G6PD Enzyme Activity in Newborns and Children: Reference Values by the Quantitative Colorimetric Method and a Comparison with the Fluorescent Spot Test

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ABSTRACT

OBJECTIVE This study aimed to establish G6PD enzyme activity reference levels in newborns and children by the quantitative colorimetric method and to compare the results with the fluorescent spot test.

METHODS Leftover blood samples from newborns and children that were sent for G6PD measurement and tested by the fluorescent spot test at the Pediatric Laboratory, Faculty of Medicine, Chiang Mai University were further tested by the quantitative colorimetric method. The values were analyzed according to age group and the two methods were compared.

RESULTS There were 111 newborns (76 males, mean age 3.9±3.5 days) and 182 children (81 males, mean age 7.4±4.2 years). The mean G6PD enzyme activity levels in normal male and female newborns using the colorimetric method were 12.7±2.9 and 13.2±2.0 IU/g Hb, and in normal male and female children were 10.7±4.0 and 11.3±3.2 IU/g Hb, respectively. By the fluorescent spot test, 33 (11.3%), 7 (2.4%) and 253 (86.3%) samples were classified as G6PD deficient, intermediate-deficient and normal G6PD status, respectively. The sensitivity and specificity by the fluorescent spot test of males were 93.3, 98.4% and of female were 45.0, 99.1%, respectively.

CONCLUSIONS G6PD enzyme activity reference levels in newborns and children by a colorimetric method were established. The fluorescent spot test shows a good performance in males, but a lower performance in intermediate-deficient females. Therefore, females should be tested by the colorimetric method.

KEYWORDS colorimetric method, G6PD, Glucose-6-phosphate dehydrogenase, fluorescent spot test, G6PD enzyme activity, newborns, children

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) is an essential enzyme in the pentose phosphate pathway (PPP)(1). G6PD deficiency is one of the most common inherited enzymopathies in malaria-endemic areas including Southeast Asia (2). G6PD deficiency is common in the Thai population, with a prevalence of 3-18% in males (3). The condition is an X-linked disorder with more than 400 identified variant enzymes (4). Non-synonymous mutations in the gene can decrease enzyme activity or reduce the stability of the enzyme, resulting in different degrees of G6PD deficiency (1). G6PD enzyme is involved in the protection of erythrocytes from oxidative injury and a deficiency can result in mild to severe hemolysis (5). Symptomatic patients are mostly male and, less commonly, homozygous females. G6PD deficiency is the most common enzyme disorder that can cause neonatal hyperbilirubinemia, which can lead to kernicterus and spastic cerebral palsy or death. In older children and adults, G6PD deficiency can cause acute episodic hemolysis triggered

by exposure to oxidizing agents, e.g., those in specific drugs such as primaquine and other antimalarial drugs, and also in fava beans (5-7).

G6PD deficiency is diagnosed by a low G6PD enzyme level in enzyme assays. Qualitative tests such as the fluorescent spot test are simple to use and have diagnostic performance comparable to quantitative tests (8). However, the fluorescent spot test has a threshold ability to distinguish enzyme activity of around 30% of normal, which is sufficient to identify G6PD-deficient homozygous females and hemizygous males, but inadequate for heterozygous females with intermediate enzyme activities above 30% of normal but below a pre-defined considered safe threshold such as 70-80% of normal (9,10). Thus diagnosis of this higher threshold requires a quantitative test for G6PD activity.

Presently, there are many G6PD quantitative diagnostic tests available. An enzymatic colorimetric method is among the most frequently used quantitative measurement of G6PD enzyme activity in a whole blood specimen. The enzymatic colorimetric method has a high sensitivity for measuring NADPH which is a product in the G6PD-mediated pathway (11). This study aimed to determine the reference values for G6PD activity levels in newborns and children of both sexes using a quantitative colorimetric method, and to compare the fluorescent spot test and the colorimetric method.

METHODS

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University. Leftover blood samples obtained from newborns and children that had been sent for G6PD measurement and tested by a fluorescent spot test at the Pediatric Laboratory Faculty of Medicine, Chiang Mai University, were further tested using a quantitative colorimetric method. The whole blood samples were collected in EDTA tubes and were either immediately tested or were kept in a refrigerator at 4°C until tested. All samples were tested within 48 hours. G6PD enzyme activity levels were measured by two methods: the R&D Diagnostics® G6PD fluorescent spot test (R&D Diagnostics, Athens, Greece) and the Standard™ G6PD quantitative colorimetric test (SD Biosensor, Gyeonggi-do, Republic of Korea). G6PD values were analyzed by gender and age group and the two methods were compared using a quantitative method as the gold standard.

The fluorescent spot test was performed according to the manufacturer's recommendations using either a dried blood spot or whole blood. In brief, 5 µL of whole blood was mixed in a microtube with 100 µL of reagents containing glucose-6-phosphate, NADP, oxidized glutathione, saponin, and tris(hydroxymethyl)-aminomethane in dilution buffer. The normal control and sample tests were left at room temperature for ten minutes, after which 10 µL of the mixture was transferred onto filter paper. Deficiency controls were transferred to a filter paper immediately. The dried blood spots were examined under ultraviolet light. The normal controls showed strong fluorescence and the deficient controls showed very weak or no fluorescence. The fluorescence intensity of the tested samples were graded independently by two trained laboratory staff. In cases of discrepancy in grading, the test results were judged by a third trained staff member. Samples with weak to moderate fluorescence were graded as an intermediate deficiency.

The colorimetric test was performed according to the manufacturer's recommendations using a G6PD code chip. In brief, the test device was inserted into the slot in the G6PD analyzer. Ten µL of whole blood was mixed with an extraction buffer containing glucose-6-phosphate, NADP, 5-bromo-4-chloro-3-indoyl-phosphate (BCIP), and nitroblue tetrazolium (NBT). Then 10 µL of the mixture was applied to the specimen application hole of the test device. The G6PD level was read from the analyzer's screen after two minutes. G6PD normal and deficient controls were tested along with each lot of reagents. The measuring ranges of the tests were: total Hb 4-25 g/dL and G6PD 0-20 U/g Hb. Interpretation of the test results was done following WHO guidelines. The adjusted male median of G6PD activity was used as a reference of normal activity. The adjusted male median of G6PD activity in newborns and children was calculated by excluding results from males with severe G6PD deficiency (activity

less than 10% of normal) (9,10,12). In males, red cell G6PD activity less than 30% of the adjusted male median was regarded as G6PD deficient. Any males who had red cell G6PD activity of 30% or more of the adjusted male median were regarded as G6PD normal. In females with red cell G6PD activity, less than 30% of the adjusted male median was regarded as G6PD deficient. Any females who had red cell G6PD activity of 80% or more of the adjusted male median were regarded as G6PD normal. Red cell G6PD activity between 30% and 80% of the adjusted male median was regarded as intermediate deficiency.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 IBM Corp, 2013 (Armonk, NY, USA). The G6PD levels were analyzed by gender and age group The continuous variables were analyzed using descriptive statistics: mean and standard deviation for normally-distributed variables and median and interquartile range (IQR) for non-normally-distributed variables. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the fluorescent spot test were also calculated.

RESULTS

Blood samples from 111 newborns (76 males, mean age 3.9±3.5 days) and 182 children (81 males, mean age 7.4±4.2 years) were analyzed. G6PD enzyme activity levels in newborns and children by sex and proposed cut-off values for deficient, intermediate, and normal G6PD activity are shown in Table 1. Table 2 shows G6PD enzyme activity levels measured by the colorimetric test classified using WHO guideline recommended cutoff values. The mean normal levels in male and female newborns were 12.7±2.9 and 13.2±2.0 IU/g Hb, and in male and female children were 10.7±4.0 and 11.3±3.2 IU/g Hb, respectively. The distribution of samples from newborns and children by G6PD enzyme activity level is shown in Figure 1. By the colorimetric method, 31 (10.6%) and 40 (13.6%) samples were classified as G6PD deficient and intermediate-deficient. The fluorescent spot test showed 33 (11.3%) and 7 (2.4%) as G6PD deficient and intermediate-deficient, respectively. The classification of G6PD status by the colorimetric method and the fluorescent spot test is shown in Table 3. The sensitivity, specificity, accuracy, positive and negative predictive values by the fluorescent spot test in each age group are shown in Table 3.

DISCUSSION

There are several measurement methods available for G6PD assay. Some methods are more suited for population studies and others are more suited for individual case management decision-making (10). The reference method for the quantification of G6PD enzyme activity is spectrophotometry, which is based on the colorimetric detection of NADPH (1,12,13).

Table 1. G6PD enzyme activity levels in newborns and children by sex and proposed cutoff values for deficient, intermediate, and normal G6PD activity

G6PD enzyme activity level (IU/g Hb)	Male newborns (N=76)	Adjusted male newborns (N=73)	Female newborns (N=35)	Male children (N=81)	Adjusted male children (N=80)	Female children (N=101)
Median (IQR)	11.8 (5.0-13.8)	12.0 (7.1-13.9)	12.1 (9.7-14.5)	9.2 (6.9-13.2)	9.4 (7.1-13.2)	8.6 (6.6-11.6)
Deficient (< 30% of adjusted male median)	-	≤ 3.6	≤ 3.6	-	≤ 2.8	≤ 2.8
Intermediate (30-80% of adjusted male median)	-	-	3.7-9.6	-	-	2.9-7.5
Normal (> 30% of adjusted male median in males) (> 80% of adjusted male median in females)	-	≥ 3.7	≥ 9.7	-	≥ 2.9	≥ 7.6

Table 2. Glucose-6-phosphate dehydrogenase enzyme activity levels as measured by colorimetric test and classified by the proposed cutoff values

	Glucose-6-phosphate dehydrogenase enzyme activity level (IU/g of Hb)							
	Male				Female			
	N	Mean±SD	Min	Max	N	Mean±SD	Min	Max
Newborn								
Normal	58	12.7±2.9	4.4	> 20.0	27	13.2± 2.0	9.7	16.9
Intermediate	-	-	-	-	7	6.9±1.1	5.5	8.7
Deficient	18	2.0±1.0	0	3.6	1	1.8	-	-
Children								
Normal	72	10.7±4.0	3.0	19.8	65	11.3±3.2	7.6	19.9
Intermediate	-	-	-	-	33	5.8 ± 1.3	3.0	7.5
Deficient	9	1.4±0.3	0.9	2.0	3	2.5	2.5	2.6

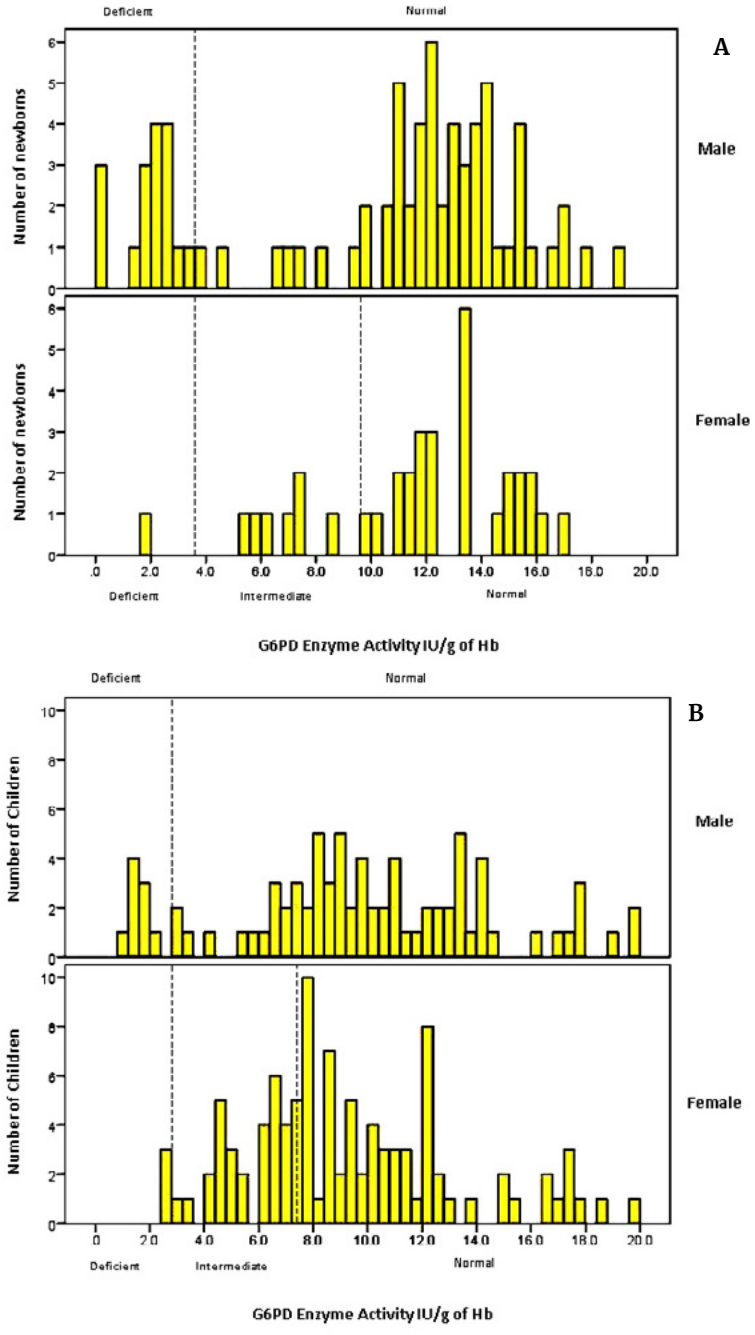

Figure 1. Distribution of samples from newborns (A) and children (B) by G6PD enzyme activity level

Table 3. Comparison of Glucose-6-phosphate dehydrogenase enzyme activity levels as measured by fluorescent spot test and the colorimetric test

	Colorimetric test			
Fluorescent spot test	**Deficient**	**Intermediate**	**Normal**	**Total**
Newborn				
Deficient	17	0	2	19
Intermediate	0	1	0	1
Normal	2	6	83	91
Total	19	7	85	111
Children				
Deficient	11	0	3	14
Intermediate	0	6	0	6
Normal	1	27	134	162
Total	12	33	137	182
Male				
Deficient	28	-	2	30
Intermediate	-	-	-	-
Normal	2	-	125	127
Total	30	-	127	157
Female				
Deficient	3	0	0	3
Intermediate	1	5	1	7
Normal	2	9	115	126
Total	6	14	116	136

Newborn: sensitivity 69.2%, specificity 97.6%, accuracy 91.0%, PPV 90.0%, NPV 91.2%
Children: sensitivity 37.8%, specificity 97.8%, accuracy 83.0%, PPV 85.0%, NPV 82.7%
Male: sensitivity 93.3%, specificity 98.4%, accuracy 97.4%, PPV 93.3%, NPV 98.4%
Female: sensitivity 45.0%, specificity 99.1%, accuracy 91.2%, PPV 90.0%, NPV 91.3%

It is essential to provide reference and cutoff values for each equipment platform and reagent. Also, the G6PD enzyme activity level for different age groups needs to be established for each method as G6PD levels in newborns and children are reported to be higher than in adults (14,15). Newborns with G6PD deficiency are at risk of hyperbilirubinemia, which can progress to kernicterus. G6PD enzyme activity reference levels in newborns and children were established in this study. The normal values of all groups were higher than the reported oriental adult reference values determined using a colorimetric method: 8.92±2.65, 8.99±2.29 U/g Hb in males and females, respectively (16).

In males, G6PD status is classified as either normal or deficient. The distribution pattern of G6PD enzyme levels is typically in two groups; however, in our study, the pattern of distribution was not clear. There were some male newborns and children with G6PD enzyme levels in the intermediate deficiency range of females. This may be caused by the falsely elevated G6PD levels associated with reticulocytosis during acute hemolysis or by previous blood transfusions (14,15,17-24). G6PD levels in females are classified as normal, intermediate deficiency and deficiency. In this study, the G6PD levels in females were distributed normally (25,26). The results show that fluorescent spot test can be used to diagnose G6PD deficiency in males, but the efficiency was low in females with intermediate deficiency. Limitations of this study include that the clinical information and reticulocyte count were not available. Additionally, the WHO methemoglobin reduction assay and molecular characterization of G6PD gene was not done.

Both the sensitivity and specificity of the fluorescent spot test to diagnose G6PD deficiency were high in males. However, the test showed low performance in discriminating intermediate deficiency in females. The children group had a higher percentage of females than the newborn group; as a result, the overall sensitivity was lower. Use of a quantitative method is suggested for diagnostic testing for G6PD intermediate deficiency in females. The risks

of hemolysis in females with intermediate deficiency when exposed to medications are largely uncertain. Knowledge of enzyme levels can help guiding decisions regarding whether medications can be safely given (27).

CONCLUSION

G6PD enzyme activity reference levels in newborns and children as measured by the colorimetric method were established. G6PD enzyme activity is age-dependent, with higher levels in newborns than in children as measured by the colorimetric method. As males usually have either normal or deficient activity, qualitative tests perform well in males. However, qualitative tests have lower performance in heterozygous females with intermediate deficiency (27). For that reason, this study suggests that females should be tested by the colorimetric quantitative method.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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Original Article **Open Access**

High-dose Proton Pump Inhibitor Versus Standard-dose Proton Pump Inhibitor in PPI-based Triple Therapy for *Helicobacter pylori* Eradication in Lampang Hospital: A randomized Controlled Trial

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ABSTRACT

OBJECTIVE The study aimed to compare the eradication rates with high-dose proton pump inhibitor (PPI) and standard-dose PPI in PPI-based triple therapy as first-line treatment for *H. pylori* eradication.

METHODS This prospective, open label, randomized controlled trial. A total of 150 patients infected with *H. pylori* diagnosed by rapid urease test were randomly assigned to one of 2 groups. The first group was treated with standard dose PPI-based triple therapy (omeprazole 20 mg bid, amoxicillin 1000 mg bid, and clarithromycin 500 mg bid) for 14 days and the second with high dose PPI-based triple therapy (omeprazole 40 mg bid, amoxicillin 1,000 mg bid, and clarithromycin 500 mg bid) also for 14 days. *H. pylori* eradication was evaluated using a urea breath test. Patient compliance and side effects were also recorded.

RESULTS In all, 75 patients were assigned each group. The *H. pylori* eradication rate in the high-dose PPI based triple therapy group was 92% by intention-to-treat (ITT) analysis and 93.05% by per-protocol (PP) analysis, compared with the standard-dose PPI based triple therapy group values of 84% and 85.92% ($p < 0.001$ and 0.032), respectively. Side effects were mild in both groups with no significant differences between groups.

CONCLUSIONS High-dose PPI based triple therapy provides a higher eradication rate of *H. pylori* infection than standard-dose PPI based triple therapy for first-line treatment with no difference in side effects.

KEYWORDS High-dose PPI based triple therapy, *Helicobacter pylori* eradication, Lampang Hospital

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacterium, measuring 0.6×3.5 microns that can be passed from person to person through direct contact with saliva, vomit or fecal matter. *H. pylori* can also be spread through contaminated food or water. *H. pylori* colonizes the human stomach and is a causative agent of various gastroduodenal diseases, including gastritis, gastric ulcer, duodenal ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. In 1994, *H. pylori* was categorized as a class I (definite) carcinogen by the International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO) indicating that eradication of *H. pylori* could reduce the risk of gastric cancer (1).

H. pylori infection is highly prevalent worldwide; more than half the world's population is infected (2). In Thailand, the prevalence of *H. pylori* infection is 45.9%, mostly in the north

and northeast regions of the country where the rates are 46.9% and 60.0%, respectively. The prevalence rates of *H. pylori* infection in the central and south regions of Thailand are 39% and 14.4%, respectively (3).

According to the Thai Consensus on *H. pylori* treatment 2015, the first-line regimen is standard PPI-based triple therapy including proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole for 10-14 days. The reported eradication rate of *H. pylori* with this regimen was 85% (4). An alternative first-line regimen is sequential therapy including PPI and amoxicillin for the first 5 days and PPI, clarithromycin, and metronidazole for the following 5 days. The eradication rate of *H. pylori* with the sequential regimen was 90% (5,6). Another alternative first-line regimen is concomitant therapy which includes PPI, amoxicillin, clarithromycin, and metronidazole for 10 days. The eradication rate of *H. pylori* with the concomitant regimen was 96.4% (7).

The current rate of successful eradication with a clarithromycin-containing triple therapy regimen is lower than 80% in many Southeast Asian countries, including Thailand. Factors affecting the eradication rate are antibiotic resistance of *H. pylori*, variation in *CYP2C19* genotypes among individual patients, differences in drug regimens, and the degree of patient compliance (8,9). Many studies have been conducted on modifying regimens to increase efficacy of *H. pylori* eradication (10,11). In spite of those efforts, the current first-line regimens are still the standard PPI-based triple therapy, sequential therapy, and concomitant therapy. Although the sequential therapy is more effective in eradication of *H. pylori* than the standard triple therapy, the sequential therapy can be negatively affected by compliance problems, e.g., some patients were confused about following this regimen. Concomitant therapy, taking clarithromycin with metronidazole has more side effects than the standard triple therapy, so that regimen is used more often in general hospitals than the standard PPI-based triple therapy because the side effects can be more easily mitigated in a hospital setting.

This study endeavored to evaluate a potentially more effective PPI-based triple therapy with the limitation of the kinds of proton pump inhibitors and antibiotics available in a general hospital and could not being able to detect *CYP2C19* genotypes. Many studies have suggested that sustained control of intragastric pH at 6 or above increases the bactericidal efficacy of oral antibiotics (12,13). Based on the knowledge that decreasing stomach acidity increases the efficacy of antibiotics, we used a high dose proton pump inhibitor (omeprazole 80 mg/day) instead of the standard dose proton pump inhibitor (omeprazole 40 mg/day) in PPI-based triple therapy. This increase is supported by studies which have reported that high dose PPI (omeprazole 80 mg/day) has no side effects (14,15). This study did not, however, increase the dose of antibiotics known to frequently cause side effects. This study compared high dose PPI (omeprazole 80 mg/day) with standard dose PPI (omeprazole 40 mg/day) in PPI-based triple therapy in terms of *H. pylori* eradication rate and side effects.

METHODS

Study design and participants

This prospective, open labeled, randomized controlled trial study was conducted in Lampang Hospital from April to June 2021. Our protocol was approved by Lampang Hospital Ethics Committee in Human Research. This trial was retrospectively registered with the Thai Clinical Trial Registry (TCTR20210829002). Adult patients (age > 18 years) with *H. pylori* infection who had not received prior eradication therapy were eligible for enrollment. The diagnosis of *H. pylori* infection was based on positive results of the rapid urease test. Subjects with any one of the following criteria were excluded from the study: [1] history of gastric cancer or gastrectomy, [2] severe concurrent disease or malignancy, [3] pregnant or lactating, [4] alcohol abuse or drug addiction, [5] previous allergic reaction to study drugs, [6] a history of taking PPI, bismuth or antibiotics within the previous 4 weeks, and [7] subjects who declined to participate. Signed informed consent was obtained from all participants. If

subjects requested to withdraw from the study for any reason or if they had serious side effects from study drugs, e.g., anaphylaxis, hypotension, or chest discomfort, their participation in the study was terminated immediately.

Randomization and interventions

Eligible patients were randomized to receive either standard dose PPI-based triple therapy (omeprazole 20 mg bid, amoxicillin 1000 mg bid, and clarithromycin 500 mg bid) for 14 days or high dose PPI-based triple therapy (omeprazole 40 mg bid, amoxicillin 1,000 mg bid, and clarithromycin 500 mg bid) for 14 days. Randomization was performed in blocks of four using computer generation and the process was concealed from investigators until the interventions were assigned. Patients were instructed to adhere to the drug regimen and were advised of the possible side effects. Baseline characteristics (gender, age, underlying diseases, and endoscopic findings) were recorded. Eradication rate was assessed six weeks after completion of the course of therapy by performing the urea breath test (UBT). Successful eradication was defined as negative UBT. Compliance and side effects were evaluated by self-reporting and direct interviews at the end of the treatment. Good drug compliance was defined as drug consumption > 80% of the total dosage.

Outcomes

The primary end point of the study was the eradication rate, which was assessed by intention-to-treat (ITT) and per-protocol (PP) analyses. All randomized patients were included in the ITT analysis. Patients who did not return for the follow up urea breath test were considered treatment failures. Patients who failed to take at least 80% of their prescribed drugs or were lost to follow up were excluded from the PP analysis. The secondary endpoints were side effects of the study drugs.

Statistical analysis

To calculate the sample size, we hypothesized that the eradication rate of the standard dose PPI-based triple therapy was 80% and that the high dose PPI-based triple therapy would achieve a 95% eradication rate (a 15% difference). Our sample size estimate was 75 individuals for each group (a total of 150), given a power of 80% and a confidence level of 95%.

Statistical differences in eradication rates among the different regimens were assessed using the chi-square test. Demographic data and frequencies of adverse reactions were compared using chi-square test or Fisher's exact test as appropriate. $P < 0.05$ were considered to be statistically significant. The statistical analyses were performed using Stata/SE 10.1.

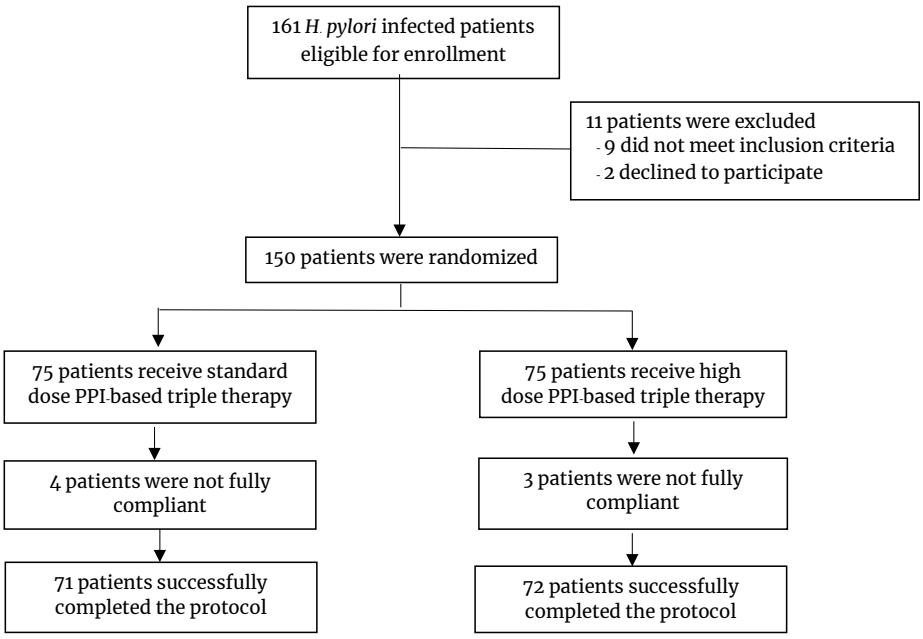

Figure 1. Flow chart of patients during the study

RESULTS

Baseline characteristics of patients

From April to June 2021, 161 patients with *H. pylori* infection from Lampang Hospital were evaluated. Of those patients, 150 were enrolled and randomized to receive one of two regimens. Seventy-five patients were assigned to receive standard dose PPI-based triple therapy and 75 patients received high dose PPI-based triple therapy. The flow chart of patients included in the study is displayed in Figure 1. Baseline characteristics of patients in the two treatment groups are summarized in Table 1. No differences were observed between the two groups in terms of baseline characteristics of patients. Most of patients were female (58.7% in the standard-dose PPI group and 61.3% in the high-dose PPI group). The most frequent endoscopic finding was gastritis (84% in the standard-dose PPI group and 82.67% in the high-dose PPI group). All patients received follow-up treatment. Almost all patients showed good compliance (94.67% in the standard-dose PPI group and 96% in the high-dose PPI group).

Eradication rates of *H. pylori* infection

The eradication rates by intention-to-treat (ITT) and per-protocol (PP) analysis are shown in Table 2. In the standard dose PPI-based triple therapy group, ITT and PP analyses of the eradication rates were 84% and 85.92 %, respectively;the eradication rates in the high dose PPI-based triple therapy group were 92% by ITT analysis and 93.05% by PP analysis. The eradication rates were higher in the high-dose PPI group than in the standard-dose PPI group by both ITT analysis and PP analysis ($p < 0.001$ and 0.032, respectively).

Side effects of the study drugs

Side effects, including bitter taste, diarrhea, nausea, headache, and dizziness were all mild and did not significantly differ between the two groups (Table 3). Bitter taste was the most commonly reported side effect in both groups (68% in the standard-dose PPI group vs. 72% in the high-dose PPI group; $p = 0.722$).

DISCUSSION

The results of this study showed the efficacy of the *H. pylori* eradication of high dose-PPI based triple therapy was higher than that of the standard dose-PPI based triple therapy with no difference in side effects. Advantages of the high dose regimen include that it is available in general hospitals, patients reported

Table 1. Baseline characteristics of subjects in the two treatment groups

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Male gender, n (%)	31 (41.3)	29 (38.7)	0.868
Age, mean	54.51 ± 14.94	53.88 ± 14.63	0.796
Underlying disease			
- DM, n (%)	8 (10.67)	13 (17.33)	0.347
- HT, n (%)	19 (25.33)	28 (37.33)	0.159
- DLP, n (%)	13 (17.33)	15 (20.00)	0.834
- IHD, n (%)	4 (5.33)	2 (2.67)	0.681
- Old CVA, n (%)	5 (6.67)	2 (2.67)	0.442
- CKD, n (%)	2 (2.67)	1 (1.33)	1.000
- Cirrhosis, n (%)	7 (9.33)	2 (2.67)	0.166
Endoscopic finding			
- Gastritis, n (%)	63 (84.00)	62 (82.67)	
- Duodenitis, n (%)	0 (0)	1 (1.33)	0.731
- Gastric ulcer, n (%)	10 (13.33)	8 (10.67)	
- Duodenal ulcer, n (%)	2 (2.67)	4 (5.33)	
Good compliance, n (%)	71 (94.67)	72 (96.00)	1.000
Follow-up, n (%)	75 (100.00)	75 (100.00)	1.000

Table 2. Efficacy of standard dose and high dose PPI-based triple therapy for *Helicobacter pylori* eradication

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Intention to treat (ITT)	63/75 (84.00)	69/75 (92.00)	<0.001
Per protocol (PP)	61/71 (85.92)	67/72 (93.05)	0.032

Table 3. Side effects of standard dose and high dose PPI-based triple therapy

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Bitter taste, n (%)	51 (68.00)	54 (72.00)	0.722
Diarrhea, n (%)	3 (4.00)	4 (5.33)	1.000
Nausea, n (%)	10 (13.33)	8 (10.67)	0.802
Headache, n (%)	2 (2.67)	3 (4.00)	1.000
Dizziness, n (%)	3 (4.00)	3 (4.00)	1.000
Skin rash, n (%)	0 (0.00)	0 (0.00)	-

ease in taking medication as prescribed and only mild side effects. Previous studies have suggested that sustained control of intragastric pH at 6 or above increases the bactericidal efficacy of oral antibiotics (12,13). We assumed that high dose PPI could reduce acidity in the stomach and thus increase bactericidal efficacy of the antibiotics. The current rate of *H. pylori* eradication using a clarithromycin-containing triple therapy regimen is lower than 80% in many studies, but our study found that the *H. pylori* eradication rate of standard-dose PPI based triple therapy was 84%. That difference may have resulted from the low prevalence of clarithromycin resistance among our patients (8,9).

The results of this study showed the eradication rate of *H. pylori* with high-dose PPI based triple therapy was 92% and more than 84% for standard-dose PPI based triple therapy. We could not directly compare the eradication rates of *H. pylori* observed in this study with sequential therapy and concomitant therapy reported in other studies (5-7). The advantages of standard triple therapy include being more efficacious than sequential therapy, that patients find taking the concomitant therapy medication to be easier and that there is a lower risk of side effects than with multiple antibiotics.

We found only mild side effects of the study drugs, including bitter taste, diarrhea, nausea, headache, and dizziness. The most common side effect was bitter taste, which most likely stemmed from clarithromycin. In the standard treatment, we used high dose PPI in some patients such those with Zollinger-Ellison syndrome. Some studies have reported that high dose PPI (omeprazole 80 mg/day) produced no side effects (14,15), indicating that high dose PPI can be used safely.

Strengths of this study included being a randomized controlled trial and that it was conducted in a general hospital following ordinary practices. A limitation of this study is that we did not test *CYP2C19* genotypes and clarithromycin resistance which constitute the main causes of failure to eradicate *H. pylori*. Because we studied subjects in the same hospital, we assumed that no significant difference in *CYP2C19* genotypes and clarithromycin resistance existed between the two groups. The fact of studying in a single hospital constituted a limitation, as well, because of restricted diversity of *CYP2C19* genotypes and clarithromycin resistance. Another limitation is that we did not monitor the intragastric pH of our subjects. We assumed that an open-label design for our study would not affect the results because we checked the compliance of all subjects and assessed eradication rates by performing the standard urea breath test. Further studies are recommended to test for the effect of different *CYP2C19* genotypes and to explore the prevalence of clarithromycin resistance.

In conclusion, high-dose PPI based triple therapy achieves a higher eradication rate of *H.*

pylori infection than standard-dose PPI based triple therapy for first-line treatment with no difference in side effects.

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Incidence of Lung Cancer in Chronic Obstructive Pulmonary Disease Patients: Prognostic Factors and Survival Analysis

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ABSTRACT

OBJECTIVE To estimate the incidence of lung cancer in chronic obstructive pulmonary disease (COPD) patients, to identify the associated prognostic factors and to conduct a survival analysis.

METHODS A retrospective cohort study was conducted between 1 June 2017 and 30 November 2020 with continued follow-up for an additional six months at the COPD Clinic of Phrae Hospital. Patients diagnosed with COPD and registered at the COPD Clinic who were age over 40 years and had a normal chest X-ray (CXR) within the previous year were enrolled. Patients diagnosed with or having a history of lung cancer, incomplete annual CXR or a follow-up period of less than six months were excluded.

RESULTS A total of 316 COPD patients who met the inclusion criteria were analyzed. Seven COPD patients were newly diagnosed with lung cancer during the 3.5-year study period. The incidence rate of lung cancer in COPD patients was 0.69% per person-year. Smoking was a significant prognostic factor for lung cancer in the COPD patients. The mortality rate was significantly higher in patients with lung cancer. The mortality rate in COPD patients who developed lung cancer was 24.5% per person-year, higher than the 1.68% per person-year for patients who did not develop lung cancer.

CONCLUSIONS The incidence rate of lung cancer in COPD patients is higher than in the general population and the mortality rate in COPD patients with lung cancer is higher than those without lung cancer. Annual CXR to detect lung cancer should be performed as part of routine lung cancer screening for COPD patients. Because CXR has lower sensitivity than low-dose computed tomography (LDCT) for detecting lung cancer in the early stage, this study found the incidence of lung cancer is slightly lower than previous reports that using LDCT. Moreover, CXR is simple to use, readily available and inexpensive.

KEYWORDS COPD, lung cancer, incidence rate of lung cancer, annual chest x-ray (CXR)

INTRODUCTION

Lung cancer and chronic obstructive pulmonary disease (COPD) are relatively common in clinical practice. Lung cancer and COPD have similar risk factors and share some symptomatology (1-3). A previous study reported that COPD is common in patients with lung cancer; however, the incidence of lung cancer in patients with COPD is still unclear (4).

The most common risk factor for lung cancer and COPD is smoking (2). Smoking is also one of the prognostic factors for lung cancer in COPD patients. The respective risk of developing lung cancer among male and female smokers vs. nonsmokers is 17.2% and 11.6% vs. 1.3% and 1.4%, respectively (5). Pathobiology of lung cancer development involves the molecular aberrations in oncogenes and tumour

suppressor genes (6). Lung cancers normally initiate from the basal epithelial cells. There are two types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (7). NSCLC constitutes about 85% of cases, comprising 40% adenocarcinoma, 30% squamous cell carcinoma, and 5-10% large cell carcinoma. SCLC constitutes about 15% of lung cancer and is made up of smaller, undifferentiated cells that are fast growing and can spread quickly (8). COPD is one of the risk factors for lung carcinoma, especially for squamous cell carcinoma. Smokers with airflow obstruction are five times as likely to have lung cancer than people with normal lung function (9). Young et al. reported that COPD patients have twice the risk for lung cancer than non-COPD patients (10).

A 2019 study estimated the worldwide mean prevalence of COPD at 13.1% (10.2-15.6%; 95%CI) (11). In 2010, the number of COPD patients were estimated to be about 384 million and the global prevalence of COPD was 11.7% (8.4%-15.0%; 95% CI) (12). Annual deaths from COPD were about 3 million (13). The prevalence of COPD is expected to rise in the next 40 years and the annual deaths from COPD and related conditions are predicted to reach more than 5.4 million by 2060 (14,15). The Burden of Obstructive Lung Disease (BOLD) program reported that the overall prevalence of COPD was 10.1%, 11.8% for men and 8.5% for women and the prevalence among the never-smoked was 3-11% (16). The prevalence of COPD in those age over 40 years in 12 public health regions in Thailand (excluding Bangkok) in 2019, 2020 and 2021 were 1,032.04, 976.76 and 888.40 per 100,000, respectively. The public health region 1, which includes Phrae province had the highest prevalence of 12 public health regions. The prevalence of COPD in those over 40 year in Phrae province in 2019, 2020 and 2021 was 1,341.36, 1,273.71 and 1,038.68 per 100,000, respectively, higher than mean prevalence for the 12 public health regions combined (17).

In 2020, lung cancer was the second most common cancer in the word (11.7%), with new cases estimated at about 2.3 million (11.7%). Lung cancer was the leading cause of cancer death, about 1.8 million cancer-related deaths (18%); deaths from lung cancer is projected to reach 2.45 million worldwide by 2030. Lung cancer was the most frequent cancer in men (14.3%) and the foremost cause of cancer death in men (21.5%) in 2020. It was also the third most common cancer in women (8.4%) and the second most common cause of cancer death in women (13.7%). The five-year survival rate for all types of lung cancer in middle-income countries is about 19%, which is lower than other cancers such as the colon (71%), breast (85%) and prostate (98.9%) cancers (18,19). The incidence of lung cancer worldwide in the general population in 2020 was about 39 per 100,000 in males and 18.2 per 100,000 in females (11). The global incidence rate of lung cancer in both sexes has been reported about 0.06-0.12% per person-year (20,21). In Thailand, lung cancer was the second most common cancer in males and the fourth most common cancer in females in 2016-2018. The mean annual incidence rate of lung cancer in Thailand and in the northern region of the country during 2016-2018 was 22.8 and 33.1 per 100,000 in males, 11.5 and 19.9 per 100,000 in females, respectively (22). The incidence rates of lung cancer in Phrae province in 2019, 2020 and 2021 were 26.7, 20.2 and 21.6 per 100,000/year, respectively in individuals with age over 40 years (about 0.02% per person-year) (17). Previous studies have reported the incidence rate of lung cancer in COPD patients to be about 0.8-1.7% per person-year which is higher than in the general population (23,24). A recent study in Japan reported the incidence of lung cancer in COPD patients who had an annual chest computed tomography (CT) scan was about 1.85% per person-year (25). The incidence of lung cancer in COPD patients in Thailand remains uncertain and there has been no published estimate of the incidence of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital.

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) has issued recommendations for selection of groups for lung cancer screening. The Guidelines recommend lung cancer screening using low-dose computed tomography (LDCT) for individuals with high-risk factors including current and former smokers aged 55 to 74 years with a 30 or more pack-year history of smoking

tobacco, those who quit smoking less than 15 years and individuals aged 50 years or older with a history of smoking 20 or more pack-year who also have at least one additional risk factor (other than second-hand smoke). Additional risk factors include history of lung cancer or lung disease, a family history of lung cancer, exposure to radon, and occupational exposure to carcinogens (26). These guidelines are based on the ability of LDCT to detect early stage lung cancer and to improve mortality outcomes.

Most previous guidelines did not recommend CXR for routine lung cancer screening (27), although some studies have suggested that routine annual CXR screening of high-risk patients can detect a significant number of lung cancer cases. Nevertheless, no studies of mortality outcome improvement from lung cancer screening with CXR have been published (28). LDCT is still recommended for lung cancer screening in high risk population due to the reduction of lung cancer mortality, but LDCT also gives false-positive results leading to unnecessary tests and invasive procedures (29). LDCT has higher sensitivity for detecting lung cancer in early stage, improve mortality outcomes and has been shown to be cost-effective in many countries in Europe, the United States and Canada. However, in other countries, e.g., Australia, which use The National Lung Screening Trial (NLST) criteria, lung cancer screening with LDCT did not demonstrate the cost effectiveness (30). A 2019 study showed the annual lung cancer screening by CXR resulted in higher benefits for the exclusion of lung cancer in repeat patients more than first time patients (31). CXR is simple to use, readily available, and inexpensive, making it suitable for low to middle income countries such as Thailand. This study aimed to estimate the incidence of lung cancer in COPD patients, to identify the associated prognostic factors, to conduct a survival analysis and to determine the benefits of annual CXR screening for lung cancer in COPD patients in Thailand.

METHODS

Population

This study was conducted at the COPD Clinic of the Medicine Unit, Phrae Hospital, in northern Thailand. The retrospective cohort study was conducted between June 1, 2017 and November 30, 2020 for study period with six months continued follow-up period to June 1, 2021. Patients who had registered with the COPD clinic before the start of the study, were age over 40 years, and had no prior CXR evidence of lung cancer were enrolled. Annual CXR during study were required to be officially reported by a radiologist. Patients diagnosed with lung cancer and those having a history of lung cancer were excluded. Patients who did not complete an annual CXR during study and those who had a short duration follow-up period less than six months were also excluded. Data were collected from the hospital database and medical records.

Study protocol

At the enrollment time, the information of COPD patients was recorded including age, sex, weight, BMI, smoking status, family history of lung cancer, comorbidities including diabetes (DM), hypertension (HT), ischemic heart disease (IHD), dyslipidemia (DLP), cerebrovascular accident (CVA), chronic kidney disease (CKD), pulmonary tuberculosis, bronchiectasis, other cancers, duration of COPD diagnosis, FEV1% (Forced expiratory volume in one second) post-bronchodilator, FEV1/FVC (Forced Vital Capacity) post-bronchodilator, CAT (COPD assessment test) score, MMRC (Modified Medical Research Council) dyspnea scale, 6MWT (Six Minute Walk Test), COPD group (A, B, C, and D) and COPD grade (GOLD 1, GOLD 2, GOLD 3 and GOLD 4) which were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (32), laboratory test results including WBC (white blood cell) count, eosinophil count, GFR (glomerular filtration rate), CXR and chest CT scan findings (if available).

During the study period, the following data was recorded included annual CXR findings, exacerbation per person-year, inhaler medication used during the study including LABA (long acting beta2 agonist), LAMA (long acting muscarinic antagonist), LABA/ICS (combination of long acting beta2 agonist plus inhaled corticosteroids), LABA/LAMA (combination of long acting beta2 agonist plus long acting muscarinic antagonist), date and duration of lung cancer diagnosis with histopathological confirmation and lung cancer staging including

NSCLC classification using the TNM classification (33,34) stages IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA and IVB and clinical staging of SCLC into limited and extensive stage (35,36), and treatment and management for COPD patients who developed lung cancer.

End of study data, including number and date of patient deaths, follow-up status at the end of the study and length of follow-up period were also recorded.

This study protocol was approved by the Institutional Ethics Committee of Phrae Hospital.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 23 was used for descriptive data analysis. Categorical data are reported as frequency and percentage, numeric data are reported as mean and standard deviation (SD). Comparison between groups was done using the Student's t-test, the chi-square test, and Fisher's exact test. Univariate and multivariate logistic regression analysis of prognostic factors and lung cancer development are reported as relative risk (RR) and 95% confidence interval (95%CI). The survival curve was calculated using the Kaplan-Meier method.

RESULTS

A total of 345 COPD patients who were existing cases and who were registered in the COPD Clinic before 1 June 2017, with age over 40 years and no prior CXR evidence of lung cancer were initially enrolled. One patient was excluded due to a history of lung cancer. During the study period between 1 June 2017 and 30 November 2020, 19 patients were excluded due to missing complete annual CXR and 9 patients were excluded due to a short follow-up period of less than 6 months. Finally, 316 COPD patients were analyzed and follow-up was continued for 6 months until 1 June 2021 (Figure 1).

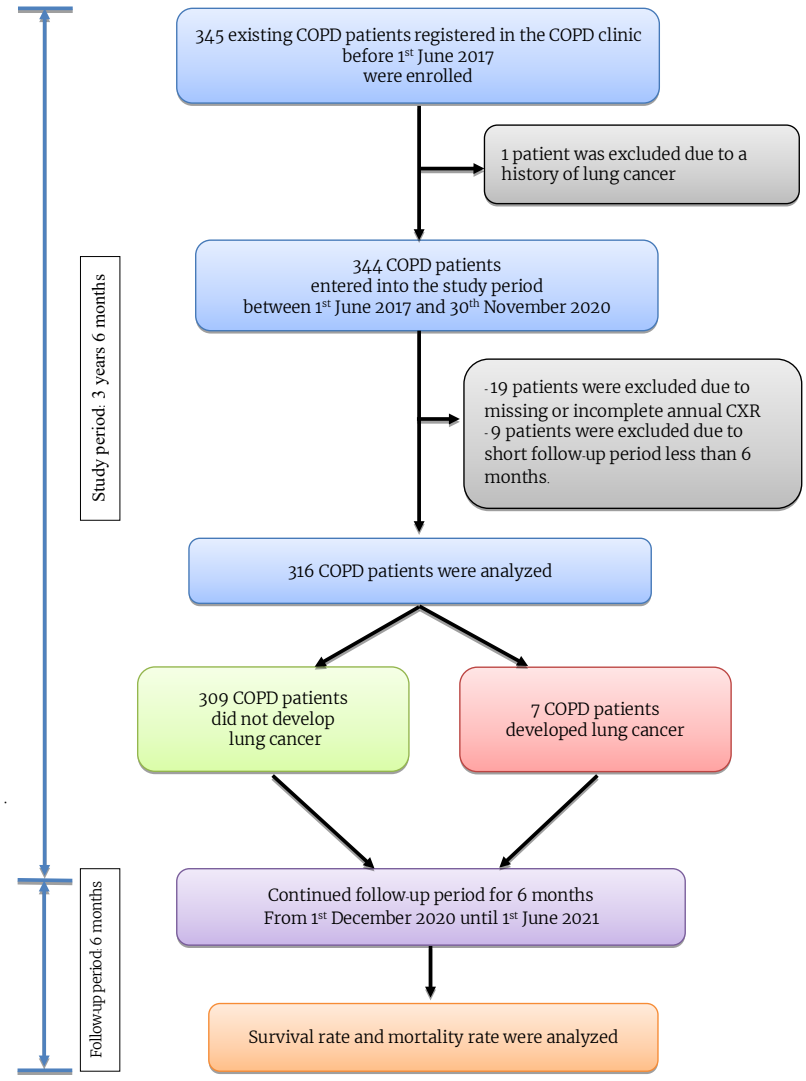

Figure 1. Study flow of COPD patients entered into the study

Table 1. Baseline clinical characteristics of COPD patients in the study and comparison between the lung cancer and without lung cancer groups

Characteristic	Total N=316	Lung cancer group N=7	Without lung cancer group N=309	*p*-value
Age (year, mean±SD)	71.61±10.19	70.86±8.81	71.63±10.25	0.843
Min 44, max 96				
Sex, n (%)				
Male	248 (78.48)	5 (71.42)	243 (78.64)	0.657
Female	68 (21.52)	2 (28.58)	66 (21.36)	
BMI (mean±SD)	20.59±4.64	18.97±4.41	20.63±4.65	0.350
Family history of lung cancer, n (%)	14 (4.43)	1 (14.29)	13 (4.21)	0.274
Smoking status, n (%)				
Nonsmoker	131 (41.46)	0 (0.00)	131 (42.39)	0.044*
Smoker	185 (58.54)	7 (100.00)	178 (57.61)	
- Past smoker	183 (57.91)	7(100.00)	176 (56.96)	1.000
- Current smoker	2 (0.63)	0 (0.00)	2 (0.65)	
Comorbidities, n (%)				
Diabetes mellitus (DM)	30 (9.49)	0 (0.00)	30 (9.71)	1.000
Hypertension (HT)	86(27.22)	3 (42.86)	83 (26.86)	0.395
Ischemic heart disease	19 (6.01)	0 (0.00)	19 (6.15)	1.000
Dyslipidemia	5 (1.58)	0 (0.00)	5 (1.62)	0.995
Cerebrovascular accident	4 (1.27)	0 (0.00)	4 (1.30)	1.000
Chronic kidney disease	4 (1.27)	1 (14.29)	3 (0.97)	0.086
Pulmonary tuberculosis	31 (9.81)	1 (14.29)	30 (9.71)	0.530
Bronchiectasis	4 (1.27)	0 (0.00)	4 (1.30)	1.000
Other cancers	7 (2.22)	0 (0.00)	7 (2.27)	1.000
COPD duration before study (year, mean±SD)	5.61±2.73	3.57±0.79	5.66 ±2.73	0.045*
FEV1 (%), (mean±SD)	62.09±23.38	55.29±17.52	62.25 ± 23.49	0.437
Post-bronchodilator				
FEV1/FVC (mean±SD)	0.58±0.12	0.61±0.11	0.58±0.12	0.542
Post-bronchodilator				
CAT score (mean±SD)	13.52±6.81	14.14±8.39	13.50±6.78	0.806
MMRC (mean±SD)	1.6±0.86	1.86±1.07	1.6±0.86	0.429
6MWT (metre, mean±SD)	275.92±116.20	230.00±165.44	276.48±115.84	0.492
COPD group, n (%)				
A	10 (3.17)	0 (0.00)	10 (3.23)	0.749
B	55 (17.40)	2 (28.57)	53 (17.15)	
C	73 (23.10)	2 (28.57)	71 (22.98)	
D	178 (55.33)	3 (42.86)	175 (56.63)	
GOLD grade, n (%)				
GOLD 1	80 (25.31)	1 (14.28)	79 (25.57)	0.400
GOLD 2	123 (38.92)	2(28.57)	121 (39.16)	
GOLD 3	92 (29.11)	4 (57.14)	88 (28.48)	
GOLD 4	21 (6.65)	0(0.00)	21 (6.80)	
Hemoglobin (g/dL)	12.59±2.29	11.46±2.85	12.61±2.28	0.188
Hematocrit (%), n (%)	38.27±6.58	34.70±7.88	38.35±6.54	0.148
WBC (/µL) (mean±SD)	10,163.77±5338.23	14,000.00±6954.85	10,076.86±5278.26	0.054
Eosinophil (/µL) (mean±SD)	539.11±629.41	243.14± 327.16	545.82±633.27	0.209
GFR (mL/min/1.73 mm^2) (mean±SD)	76.64±22.30	72.06±29.23	74.70±22.18	0.757

BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD assessment test (0-40); MMRC, modified Medical Research Council dyspnea scale (0-4); 6MWT, Six Minute Walk Test; WBC, white blood cell; GFR, glomerular filtration rate

Note: - The classification of COPD Groups A-D by symptoms (MMRC and CAT) and risk of exacerbation history, based on GOLD guideline (32)

- The classification of airflow limitation severity in COPD; GOLD 1=mild (FEV1 ≥ 80% predicted), GOLD 2=moderate (50% ≤ FEV1 < 80% predicted), GOLD 3=severe (30% ≤ FEV1< 50% predicted), GOLD 4 = very severe (FEV1< 30% predicted), based on GOLD guideline (32)

The baseline characteristics of 316 enrollees are showed in Table 1. There were 248 males (78.5%) and 68 females (21.5%). The mean age of the patients was 71.6±10.2 years. The mean duration for COPD was 5.6±2.7 years. Baseline CXR reports showed old pulmonary TB scar, bronchiectasis and emphysema in 31 (9.81%), 4 (1.27%) and 64 (20.25%) of the COPD patients, respectively. Most of the COPD patients were in GOLD group D (55.33%) and GOLD grade 2 (38.92%). Seven COPD patients were newly diagnosed with lung cancer during the 3.5 years study period. The incidence rate of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital was 0.69% per person-year. Most of COPD patients in the lung cancer group were classified in COPD group D (42.9%) and GOLD grade 3 (57.1%).

Baseline clinical characteristic of patients with and without lung cancer were similar in the two groups (Table 1), including age, sex, weight, BMI, family history of lung cancer, comorbidities (DM, HT, IHD, DLP, CVA, CKD, pulmonary tuberculosis, bronchiectasis, other cancers), FEV1(%) post-bronchodilator, FEV1/FVC post-bronchodilator, CAT score, MMRC dyspnea scale, 6MWT, COPD group (A, B, C, and D) and COPD grade (GOLD 1, GOLD 2, GOLD 3 and GOLD 4), laboratory testing results including WBC count, eosinophil count and GFR. This study found that smoking was a significant prognostic factor for lung cancer in COPD patients (p-value 0.044). However, there was no statistically significant correlation in the incidence of developing lung cancer between current smoker and past smoker COPD patients. There were 131 COPD patients (41.46%) who were nonsmokers, 65 of whom (49.62%) were second-hand smokers, 42 (32.06%) were occupationally exposed to particulate matter, 14 (10.69%) were exposed to indoor air pollution from cooking with biomass and 10 (7.63%) had a history of chronic bronchitis and respiratory infection. Duration for COPD diagnosis prior to the study was significantly lower in patients with lung cancer (p = 0.045) but the age of COPD onset was higher in the lung cancer group.

Table 2 shows clinical characteristics of COPD patients during the study, including comparison between the lung cancer and without lung cancer groups. Inhaler medications used during the study, including LABA, LAMA, LABA/ICS and LABA/LAMA were similar in both groups. Exacerbation rate was not statistically significantly different between the groups. Patients in the without cancer group were followed-up significantly longer than the lung cancer group (p = 0.002). The follow-up period in patients without lung cancer was statistically significant longer than those with lung cancer (p = 0.042), because some patients in lung cancer group were loss to follow-up and some patients died

Table 2. Clinical characteristics of COPD patients during the study and comparison between the lung cancer and without lung cancer groups

Characteristic	Total (N=316)	Lung cancer group (N=7)	Without lung cancer group (N=309)	p-value
LABA used during study, n (%)	8 (2.53)	1 (14.28)	7 (2.27)	0.166
LAMA used during study, n (%)	199 (62.97)	5 (71.43)	194 (62.78)	1.000
LABA/ICS used during study, n (%)	276 (87.34)	5 (71.43)	271 (87.70)	0.218
LABA/LAMA used during study, n (%)	34 (10.76)	1 (14.28)	33 (10.68)	0.553
Exacerbation during study (person/year)	0.83	0.46	0.83	0.620
Follow-up status at the end of study, n (%)				
Follow-up	229 (72.46)	1 (14.28)	228 (73.79)	0.002*
Loss follow-up	61 (19.30)	2 (28.57)	59 (19.09)	0.624
Referred	3 (0.95)	0 (0.00)	3 (0.97)	1.000
Death, n (%)	23 (7.28)	4 (57.14)	19 (6.15)	0.001*
Follow-up period (day, mean±SD)	1320.96±279.33	851.57±494.05	1,331.59±264.43	0.042*

LABA, long acting beta2 agonist; LAMA, long acting muscarinic antagonist; LABA/ICS, combination of long acting beta2 agonist plus inhaled corticosteroids; LABA/LAMA, combination of long acting beta2 agonist plus long acting muscarinic antagonist

Table 3. COPD patients who developed lung cancer in the study

Case number	COPD GOLD Group/Grade	COPD duration before study (days)	Days before lung cancer diagnosis	Follow-up period (days)	Diagnosis and treatment	Status at the end of study
1 71-yr Male	B GOLD 2	173	98	1,461	NSCLC stage IA (T1bN0M0) underwent LUL lobectomy: pathology report showed adenocarcinoma	Under follow-up
2 87-yr Female	D GOLD 3	93	293	688	RUL mass suspected lung cancer stage IIIA(T3N1M0), denied for further investigation, palliative care treatment	Died (cancer-related) 20th Apr 2019
3 66-yr Female	D GOLD 3	79	438	560	Lung cancer stage IVA with adrenal gland metastasis, denied for further investigation, palliative care treatment	Died (cancer-related) 13th Dec 2018
4 68-yr Male	C GOLD 3	607	185	299	NSCLC stage IIIB, pathology report showed poorly differentiated squamous cell carcinoma (T4N2M0), treated with chemotherapy	Lost to follow-up Last visit 27th Mar 2018
5 61-yr Male	C GOLD 1	271	1,114	1,272	NSCLC stage IVB, pathology report showed squamous cell carcinoma with bone and right adrenal gland metastasis (T3N3M1c), treated with chemotherapy	Died (cancer-related) 24th Nov 2020
6 73-yr Female	B GOLD 2	369	233	341	SCLC extensive stage,treated with complete course chemotherapy and radiation	Lost to follow-up Last visit 8th May 2018
7 70-yr Male	D GOLD 3	148	805	1,340	Lung cancer stage IVA (T2aN2M1a), denied for further investigation, treated with palliative care treatment	Died (cancer-related) 31th Jan 2021

during study.

Table 3 shows details of the 7 COPD patients in the lung cancer group: 2 (28.6%) were in COPD group B, 2 (28.6%) in COPD group C, and 3 (42.9%) in COPD group D. None of the COPD patients in COPD group A were diagnosed with lung cancer. The mean duration of COPD before the study was 248.57±188.09 days. The mean time to lung cancer diagnosis was 452±372.65 days. Four (57.1%), one (14.3%), one (14.3%), and one (14.3%) patient (s) were diagnosed with lung cancer during the first, second, third year of study, and after third year of the study, respectively. The mean follow-up period was 851 ± 494.05 days. The final pathology report revealed 4 patients (57.1%) had lung cancer: 3 had NSCLC (42.9%) (1 adenocarcinoma and 2 squamous cell carcinoma), and 1 patient had SCLC (14.3%). Patients in the NSCLC group were classified as stage IA, IIIB and stage IVB with one patient in each stage and the one patient in the SCLC group was classified as extensive stage. Three COPD patients in the lung cancer group were clinically diagnosed (no pathology report) as they elected for palliative care and no further investigation. Five patients (71.44%) were symptomatic cases, while 2 patients (28.57%) were asymptomatic at the time of lung cancer diagnosis. Three patients (42.9%) died during study period and one (14.3%) died during the follow-up period.

The univariate and multivariate logistic analysis of COPD patients who developed lung cancer is shown in Table 4. Smoking was a statistically significant prognostic factor for lung cancer development (p = 0.044). However, the correlation between smoking and lung cancer could not be analyzed for RR as all COPD patients in the lung cancer group were smokers.

Finally, the survival rate and mortality rate were analyzed. Twenty-three patients (7.3%) died during the study period and follow-up period, 4 (57.1%) were patients with lung cancer and 19 (6.2%) were patients without lung cancer. Three patients with lung cancer died during the study period and 1 patient died during the follow-up period. Eight patients without lung cancer died during the study period and 11 patients died during the follow-up period. The overall mortality rate for the study period and follow-up period combined was statistically significantly higher in patients in the lung cancer group compared with patients without lung cancer (p = 0.001, Table 2). The mortality rate in COPD patients who developed lung cancer was 24.5 % per person-year which is higher than for those who did not develop lung cancer (1.68% per person-year). The survival curve was determined according to the Kaplan-Meier method, compared COPD patients who developed lung cancer and those who did not develop lung cancer in Figure 2. The survival rate was significantly lower in COPD patients who developed lung cancer compared with those who did not develop lung cancer. The crude analysis hazard ratio (HR) for death in COPD patients with lung cancer compared to those without lung cancer was 25.5 (8.51-76.6;95%CI) and in the adjusted analysis, the HR for death in COPD patients with lung cancer compared to those without lung cancer adjusted for age, sex, and smoking status was 16.3 (5.2-51.1;95%CI).

DISCUSSION

Lung cancer and COPD are relatively common health problems. Both lung cancer and COPD have similar symptoms, i.e., cough, dyspnea, fatigue, and weight loss (1). Since the symptoms overlap with those of other respiratory conditions, misdiagnosis of the condition can occur until the cancer reaches an advanced stage, leading to an increase in high mortality outcomes (37). Some studies have reported on the benefits of annual CXR for lung cancer screening (31,38). This study aimed to estimate the incidence of lung cancer in COPD patients who were followed-up in a COPD Clinic and who received an annual CXR.

The incidence rate of lung cancer in COPD patients at the COPD Clinic of Phrae Hospital, was 0.69% per person-year, which is slightly lower than previous reports (0.8-1.7% per person-year worldwide) (23,24). However, that incidence rate is still higher than the general population. This study found that smoking was a significant prognostic factor for lung cancer in COPD patients (p = 0.044). This finding illustrates that COPD patients who have a history of smoking are more likely to develop lung cancer than nonsmokers.

Table 4. Univariate and multivariate logistic analysis for COPD patients who developed lung cancer

Univariate analysis	Lung cancer group (N=7)	Without lung cancer group (N=309)	RR	95%CI	*p*-value
Age, year n (%)					
< 65	2 (28.57)	97 (31.40)	0.877	0.173-4.441	1.000
≥ 65	5 (71.43)	212 (68.60)			
BMI, n (%)					
< 18.5	3 (42.86)	116 (37.54)	1.242	0.383-5.452	1.000
≥ 18.5	4 (57.14)	193 (62.45)			
Comorbidities, n (%)					
With comorbidities,	5 (71.43)	138 (44.66)	0.331	0.065-1.679	0.251
No comorbidities	2 (28.57)	171 (55.34)			
GOLD grade, n (%)					
GOLD 2 (vs GOLD 1)	2 (28.57)	121 (39.16)	0.769	0.071-8.339	1.000
GOLD 3 (vs GOLD 1)	4 (57.14)	88 (28.48)	0.288	0.033-2.520	0.374
GOLD 4 (vs GOLD 1)	0 (0.00)	21 (6.80)	0.988	0.963-1.012	1.000
GOLD group, n (%)					
Group B (vs Group A)	2 (28.57)	53 (17.15)	1.038	0.986-1.092	1.000
Group C (vs Group A)	2 (28.57)	71 (22.98)	1.028	0.989-1.069	1.000
Group D (vs Group A)	3 (42.86)	175 (56.63)	1.017	0.998-1.037	1.000
MMRC score, n (%)					
< 2	2 (28.57)	186 (60.19)	0.272	0.054-1.382	0.124
≥ 2	5 (71.43)	123 (39.81)			
CAT score, n (%)					
< 10	2 (28.57)	102 (33.01)	0.815	0.161-4.132	1.000
≥ 10	5 (71.43)	207 (66.99)			
Smoking status, n (%)					
Smoker	7 (100.00)	178 (57.61)	-	-	0.044*
Nonsmoker	0 (0.00)	131 (42.39)			
Eosinophil (/μL), n (%)					
< 300	5 (71.43)	141 (45.63)	2.911	0.573-14.781	0.255
≥ 300	2 (28.57)	168 (54.37)			
Multivariate analysis			**RR**	**95%CI**	***p*-value**
Age					
≥ 65 (vs < 65)			1.136	0.229-5.640	0.876
BMI					
< 18.5 (vs ≥ 18.5)			1.291	0.295-5.664	0.734
Sex					
Male vs female			0.577	0.118-2.815	0.497
FEV1 (%) post-bronchodilator					
< 50 (vs ≥ 50)			1.989	0.450-8.800	0.365
CAT score					
≥ 10 (vs < 10)			1.023	0.197-5.319	0.979

Previous reviews have reported that lung cancer is a frequent comorbidity in COPD patients. COPD patients are 6.35 times more likely to develop lung cancer than the general population (4). A previous study reported the risk ratio for lung cancer in COPD patients was higher than for other comorbidities, i.e., hyperension, diabetes, or chronic kidney disease. Nevertheless, the prevalence of lung cancer is quite low compared to that of other comorbidities. The current study found the common comorbidities in COPD patients were hypertension (27.2%), pulmonary TB (9.8%), diabetes (9.5%) and ischemic heart disease (6.0%). Prior research has revealed that the age and sex adjustment odds ratio for lung cancer development in COPD patients is quite high (OR = 8.538,7.597-9.595; 95% CI) compared to hypertension (1.60,1.57-1.62; 95% CI) or diabetes (1.55,1.52-1.57; 95% CI) (39). That in this study no statistically sig-

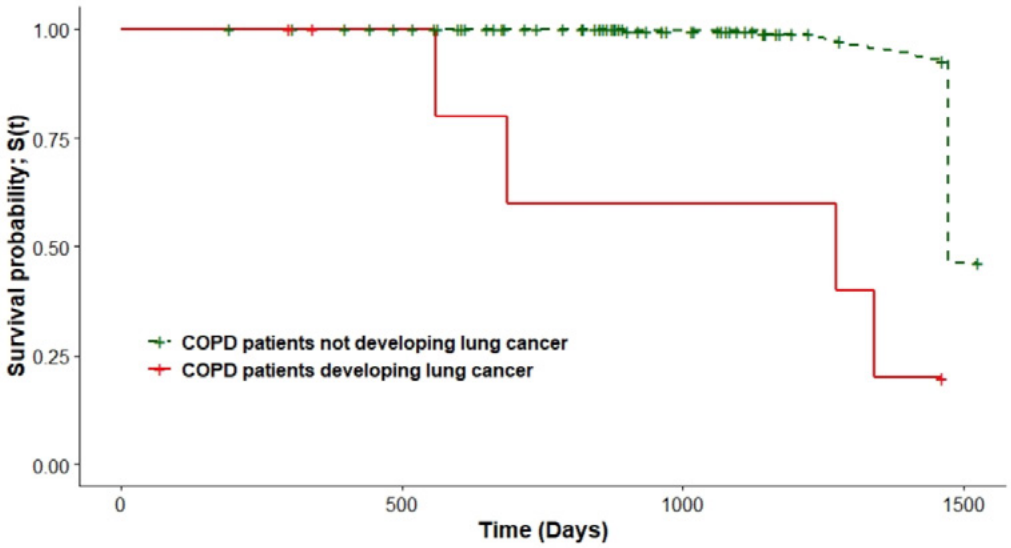

Figure 2. Survival curve using the Kaplan-Meier method to compare between COPD patients who developed lung cancer and those who did not develop lung cancer

nificant relationship between comorbidities and the development of lung cancer was found may be due to the small number of patients in the lung cancer group.

From the demographic data of COPD patients in this study according to the GOLD classification, most of the COPD patients were in GOLD groups C and D which have a greater severity than groups A and B, and most of them were classified in GOLD 2 and GOLD 3. Most of the COPD patients who had lung cancer were in COPD group D (42.9%) and GOLD grade 3 (57.14%). Although, the severity of COPD in terms of GOLD group and grade in this study was not associated with lung cancer, the severity of airflow limitation (GOLD grade 3 and 4) was higher in the lung cancer group but the different was not statistically significant.

For most COPD patients in the lung cancer group, their lung cancer was detected in the first year of study (57.1%). However, only one patient (14.3%) had stage I lung cancer while six (85.7%) had advanced stage lung cancer. These findings indicate that the lung cancer of some of the COPD patients was detected only at an advanced stage despite having undergone routine annual CXR follow-up. This could be because they were asymptomatic in the early phase and the natural course of some types of histopathological lung cancer is later becomes aggressive and spreads quickly, leading to delayed diagnosis of first stage lung cancer. The results showed about 42.9% of COPD patients had NSCLC and 14.3% had SCLC, which is similar to previous studies. In the NSCLC group, the most histopathology cell type was squamous cell carcinoma (66.7%) which is similar to a previous study that reported squamous cell carcinoma was a major cell type in COPD related lung cancer (9).

This study demonstrated that most COPD patients who entered the study had good compliance as 72.5% of them remained in follow-up throughout study. Patients in the without lung cancer group remained in follow-up significantly longer than those in the lung cancer group. About 28.6% of patients in the lung cancer group were lost to follow-up during the study period. Exploration of the details of patients with lung cancer who were lost to follow-up revealed that all of them had an advanced stage of lung cancer; one had stage IIIB NSCLC and was lost to follow-up during chemotherapy and another had extensive stage SCLC and was lost to follow-up after a complete course chemotherapy and radiation.

The survival curve revealed a significant decrease in survival rate among COPD patients with lung cancer (Table 2 and Figure 2). The mortality rate in COPD patients who developed lung cancer was more than ten time higher than those who did not develop lung cancer (24.5% per person-year vs 1.68% per person-year, respectively).

A limitation of this study was that it was not possible to investigate potential prognostic factors for developing lung cancer other than smoking. That may, in part be due to the large difference in number of patients with lung cancer and those without lung cancer, a reflection of the low incidence rate of lung cancer development in the COPD population. If a longer study period and follow-up period are included in future research, additional potential prognostic factors could be investigated. Another limitation was that the study protocol used CXR instead of LDCT for lung cancer screening, leading to a lower incidence of lung cancer compared with previous studies that used LDCT, detecting early stage lung cancer only 1 patient (14.28%). Because CXR is less sensitive than LDCT in detecting lung cancer in early stage, this study found the incidence of lung cancer to be slightly lower than in previous reports. However, CXR is simple to use, readily available, and in expensive, which is suitable for the economic status of Thailand. Finally, there were 3 patients (0.42%) in lung cancer group who had no histopathological confirmation although the clinical symptoms and radiological reports, including CXR and CT scan of chest and abdomen, showed the most likely diagnosis was primary lung cancer rather than other extrapulmonary malignancy with distant pulmonary metastasis.

In clinical practice, routine yearly CXR should be recommended for all COPD patients because of the benefits, easy availability, and low cost in clinical practice (38,40). Although LDCT has greater sensitivity for detecting lung cancer in the early stage, improved mortality outcomes in many countries indicate the cost-effectiveness that method (30). However, LDCT is not practical for use in Thailand except for COPD patients who have been evaluated as being in the high risk group for lung cancer. With those patients, it can be helpful for differentiating cancer from other respiratory disease that can be found in COPD patients, e.g., pulmonary tuberculosis, pulmonary fibrosis, pulmonary fungal infection, and bronchiectasis (32,41).

CONCLUSION

The incidence rate of lung cancer in COPD patients is higher than in the general population and the mortality rate in COPD patients with lung cancer is higher than in patients without lung cancer. An annual CXR should be performed as part of routine lung cancer screening for COPD patients to detect lung cancer. Because CXR has lower sensitivity than LDCT in detecting lung cancer in the early stage, the incidence of lung cancer is slightly lower than previous reports using LDCT. In clinical practice, CXR is simple to use, readily available and inexpensive.

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CONFLICTS OF INTEREST

The author declares no potential conflicts of interest.

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The Prevalence of Pneumonia in Children under 15 Years of Age Who Have Air Bronchogram Sign on Chest Computed Tomography Studies

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ABSTRACT

OBJECTIVE The aim of the study was to investigate the prevalence of pneumonia in the presence of air bronchogram on chest computed tomography (CT) according to pediatrician's concerning about the presence of air bronchogram in favor of pneumonia in children under 15 years of age.

METHODS A total of 371 children under 15 years of age who had air bronchogram on chest CT studies from January 2015 to December 2019 in Siriraj Hospital were included, of which 182 cases had been diagnosed with pneumonia. CT analysis was conducted, including identification of the location of air bronchograms, consolidation, atelectasis, interstitial infiltration, ground glass opacity (GGO), pleural effusion, bronchiectasis, lymphadenopathy, cardiomegaly, lung abscess and nodules and findings were determined by consensus of an experienced pediatric radiologist and an in-training resident.

RESULTS The prevalence of pneumonia in this group was 49.1% and that of atelectasis was 68.2%. Air bronchograms in consolidation, especially at the right lower lobe, were more likely associated with pneumonia. Air bronchograms in atelectasis were more likely associated with non-pneumonia conditions. Air bronchogram sign in consolidation combined with GGO, pleural effusion or bronchiectasis in union pattern were associated with an increased incidence of pneumonia of 69.2%, 67.1% and 74.6%, respectively.

CONCLUSIONS The presence of air bronchograms is not specific for pneumonia. Air bronchograms were found more frequently in atelectasis than in pneumonia (68.2% vs. 49.1%). Although air bronchogram in consolidation should raise concerns for lesions in both pneumonia and non-pneumonia cases, the combination of air bronchogram in consolidation with additional GGO, pleural effusion and bronchiectasis is associated with an increased likelihood of pneumonia.

KEYWORDS air bronchogram, atelectasis, chest computed tomography, ground glass opacity, interstitial infiltration, pneumonia

INTRODUCTION

Pneumonia is one of the major causes of death in the Thai population, especially among pediatric patients (1). The World Health Organization (WHO) reported that pneumonia accounted for nearly 400,000 deaths annually and more than 60 deaths per 100,000 people in 2012-2013. Among children younger than 5 years, pneumonia accounted for 10-25% of the total mortality (1). In 2016, the Thai Department of Disease Control, Ministry of Public Health reported that during the period 2006-2015, there was an increase in the mortality rate, especially in children less than 4 years of age (2). This is an indication that the correct diagnosis of pneumonia and exclusion of other medical

mimics are crucial to determining appropriate treatment.

In practice, the diagnosis of pneumonia relies primarily on history taking and physical examination. Chest radiographs are generally used only to confirm a diagnosis and as baselines for pre-treatment evaluations. Chest CT scans are normally performed only in selected pediatric cases which do not improve after appropriate treatment with antibiotic drugs or which are suspected of having complications such as lung abscess. It is important to be aware of possible complications in immunocompromised patients, who are prone to develop severe diseases (3,4).

The air bronchogram sign was first described by Fleischner and was named by Felson (5) as a means to distinguish pulmonary parenchymal lesions from extrapulmonary lesions such as pleural effusion. Fleischner (5) stated that airless lung tissue surrounding normal open airways could produce a radiographic effect. The consolidation processes in alveoli with airway preservation results in the appearance of the air bronchogram sign. Traditionally, the air bronchogram sign was used to identify alveolar diseases. The sign is defined as air-containing distal bronchi and/or bronchioles within the alveolar infiltrated area (6).

A review of the literature showed that the air bronchogram can be found in many conditions, including pneumonia which was the focus of this study, causing the pathology in the alveoli. Air bronchograms are found in pneumonia that occur in alveoli which is known as alveolar pneumonia. However, they are also found in interstitia (contiguous fluid-filled spaces between alveoli), including interstitial pneumonia. They can potentially lead to compressive atelectasis and can cause crowding of tissue around open airways (7,8).

The presence of air bronchograms in pediatric patients has been considered as an indication of pneumonia, although controversial. However, a review of the literature on adult populations shows that air bronchograms are found not only in pneumonia, but also in other diseases or conditions, e.g., atelectasis, pulmonary hemorrhage, pulmonary alveolar proteinosis, bronchioloalveolar cell carcinoma, alveolar sarcoidosis and lymphoma (7,8). This study sought to determine if air bronchograms on chest CT scans documented in OPD cards can be an indication of diseases or conditions other than pneumonia in children.

A review of the relevant literature found no publications on the prevalence of pneumonia in pediatric patients under 15 years of age who had air bronchograms on chest CT studies. This study was conducted to explore the prevalence of pneumonia in pediatric patients under 15 with air bronchograms and other signs on chest CT scans. We anticipated that the results of our study could provide information on the prevalence of air bronchograms and whether the presence of air bronchograms favors a diagnosis of pneumonia. The study was also intended to enhance pediatrician's awareness of pneumonia and other mimic conditions in combination with various imaging features and clinical contexts to help achieve correct diagnoses and proper treatments.

METHODS

Ethical approval for this study was obtained from Siriraj Institutional Review Board (SiRB), Code Number 905/2562 (IRB4).

Patient selection

This retrospective cohort study enrolled 0-15 year old patients in Siriraj Hospital who had had chest CT or chest CTA studies from January 2015 to December 2019. All had undergone 64-slice chest CT scans using standard machines. In cases of repeated studies, the earliest study was selected. Chest CT studies which appeared to be without air bronchograms, e.g., asymptomatic cases and annual follow-ups of non-respiratory diseases were also excluded.

CT protocols

All studies were performed using a 64 row multi-slice helical CT scanner system (LightSpeed VCT, Discovery CT 750 HD and Optimal CT660, GE Healthcare, Cleveland, OH, USA; SOMATOM Definition Dual Source, Siemens, Munich, Germany. All images were stored in PACS digital formats. CT parameters were adjusted for age and body weight according to the Siriraj pediatric body CT zone protocol using

a tube voltage of 80-120 kV, tube current of 100-224 mA, matrix of 512×512 mm, rotation time of 0.5 seconds, pitch of 0.984 in chest CT studies and 1.375 in chest CTA studies, layer thickness of 5 mm, reconstruction thickness of 1.25 mm, and a reconstruction interval of 0.625 mm. About 1.0-1.5 mL/kg of nonionic iodinated contrast agent was injected in contrast-enhanced studies.

Imaging analysis

All patients were analyzed using retrospective reviews of CT chest studies for the air bronchogram sign by consensus of an experienced pediatric radiologist and an in-training 3rd year resident who were blinded to the report findings and diagnosis, and knew only clinical presentations, underlying diseases and/or chest trauma history.

The gold standard for diagnosis of pneumonia is clinical presentation and radiographic findings of consolidation. However, the sputum results are also used, not for diagnostic purposes but for determining appropriate treatment with adequate antibiotics. Some patients also had chest CT studies due to severe diseases. Those patients are described as 'severe cases' in this study.

There are many other radiographic signs of potential concern which need to be evaluated together in cases of pneumonia, e.g., infiltration and consolidation. In addition, frequently found complications such as bronchiectasis and/or pleural effusion can also occur (6). For that reason, the chest CT image analyses in this study included the location of the air bronchogram, consolidation, atelectasis, interstitial infiltration, ground glass opacity (GGO), pleural effusion, bronchiectasis, lymphadenopathy, cardiomegaly, lung abscess and nodules.

To differentiate air bronchogram signs in consolidation and in atelectasis evaluated by CT findings, contrast study is helpful. The air bronchogram sign in atelectasis represents a lung volume loss with enhancement, while in consolidation it does not. However, in the patients who did not receive intravenous contrast media, the air bronchogram sign in atelectasis was interpreted based on the evidence of lung volume loss which could be differentiated from consolidation. In cases where the lesions were unclear, we reached at a consensus of the most likely diagnosis. Following that, the definite diagnosis in each case was retrospectively reviewed using an electronic record summary.

Statistical analysis

Statistical analysis was performed using SPSS software (version 17, IBM Corp, Chicago, IL, USA).

The descriptive statistics of the patients under 15 years of age with air bronchogram are given in percentages and 95% confidence intervals (CI) to represent prevalence. Quantitative age group variables are shown as median (25th and 75th percentiles).

Comparison of baseline characteristics between groups of quantitative variables was done using the Independent T-test or the Mann Whitney U test, and for group variables using the Chi-squared test. Crude Odds ratio (95% CI) was analyzed by univariate analysis using simple logistic regression. *P*-values < 0.05 were considered statistically significant. Further analysis of the significant univariate parameters using adjusted odds ratio (95% CI) and *p*-value was performed using multiple logistic regression.

RESULTS

Patient characteristics

A total of 2,030 patients under 15 years of age who underwent chest CT studies in Siriraj Hospital were included in this study. After exclusion of repeated studies of the same patient, 821 studies remained. After exclusion of chest CT studies that appeared to lack an air bronchogram based on screening of clinical presentations as described above, a total of 621 patients were enrolled for evaluation of whether air bronchogram signs were present or not. After a case-by-case evaluation and with the consensus of an experienced pediatric radiologist and an in-training 3rd year resident, a total of 371 patients showing evidence of the presence of air bronchograms were included in the study (Figure 1). All study findings were similarly arrived at by consensus.

A total of 182 patients with air bronchogram signs were diagnosed with pneumonia. The

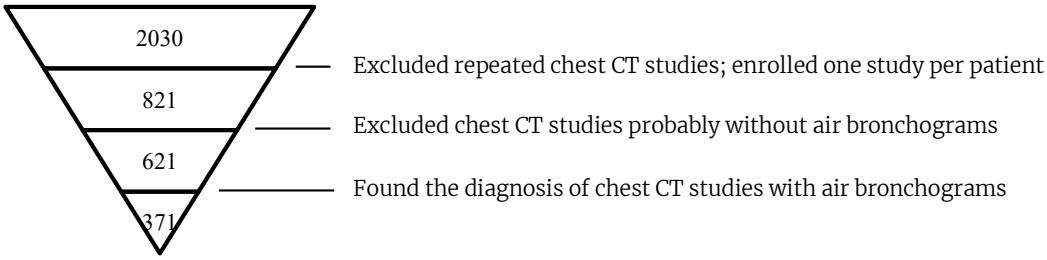

Figure 1. Patient selection algorithm

median age of patients with air bronchogram signs was 3 years (range P25-P75:1-10 year olds) (Table 1). Multivariate analysis found no significant differences in age between patients with and without pneumonia (Table 2). However, an analysis of age alone found the median age of patients with air bronchogram signs who were diagnosed pneumonia was 5.5 years (range P25-P75: 1-12 years), while for those without pneumonia the median was 2 years (range P25-P75: 0.6-9 years). The male to female ratio in the selected patients was 182/189 with no significant difference in gender among the included cases.

There was no difference between CT scans with contrast and those without contrast or between the first study and follow-up studies in the evaluation of whether air bronchograms were present in consolidation or atelectasis (Table 1).

Imaging features of the air bronchogram sign and diagnosis

The prevalence of pneumonia in our study was 49.1% and 95%CI (44.0, 54.1) which was less than that of atelectasis at 68.2% and 95%CI (63.3, 72.7). The prevalence of pulmonary hemorrhage was 2.7% and 95%CI (1.5, 4.9). The prevalence of lung abscess was 4.9% and 95%CI (3.1, 7.5). The prevalence of carcinoma was 1.3% and 95%CI (0.6, 3.1). The prevalence of other diseases was 31.3% and 95%CI (26.8, 36.2). A case-by-case inspection review found that there was a high diversity of other diseases, most being consistent with a co-diagnosis of pneumonia and/or atelectasis (Table 3).

Statistical analysis showed that only leukemia/lymphoma significantly increased the risk of developing pneumonia ($p < 0.05$) (Tables 1 and 2). Most of these had cases received induction chemotherapy at the time of diagnosis.

Cases could have more than one lesion and location. Considering the location of air bronchograms in consolidation, we found that most cases had a lesion in one location, median (P25, P75) of 1 (0, 2). In the pneumonia group, most patients also had a lesion/location, median (P25, P75) of 1 (1, 2) while those in the non-pneumonia group had a median (P25, P75) of 0 (0, 0) consolidation lesions which was statistically significant. The location of the air bronchograms in atelectasis showed that most cases had a lesion in one location, median (P25, P75) of 1 (0, 2). Most cases in the pneumonia group had a lesion/location at median (P25, P75) of 1 (0, 2) while in those in the non-pneumonia group had had two lesions/location, median (P25, P75) of 2 (1, 2) which was also statistically significant.

Knowing that consolidation was more likely related to pneumonia than to atelectasis, if CT findings showed consolidation associated with clinical dyspnea, the patient would be diagnosed with pneumonia and would receive proper antibiotic treatment. According to the CT findings, the air bronchogram sign in consolidation was significantly associated with pneumonia, while that in atelectasis was not (Table 2). The air bronchogram sign in consolidation was related to pneumonia in all lobes of the lungs. The air bronchogram sign in atelectasis was associated with non-pneumonia in both upper and both lower lobes. We also analyzed the association between the overall air bronchogram sign in consolidation and in atelectasis without reference to the lobes of the lungs. The air bronchogram sign in consolidation was found to be significantly associated with pneumonia but not with atelectasis (Table 1). Further multivariate analysis showed that only air bronchogram sign in consolidation at RLL was related to pneumonia (Table 2).

Table 1. Comparison of patients with air bronchogram sign in pneumonia and non-pneumonia groups

Baseline characteristics	All (n=371)	Pneumonia (n=182)	Non-Pneumonia (n=189)	*p*-value
Gender: male	182	96	108	0.395
Age: median (P25, P75)	3 (1,10)	5.5 (1,12)	2.0 (0.6,9.0)	< 0.001
Underlying disease* n (%)				
Congenital lung disease	28 (75.5)	16 (8.8)	12 (6.3)	0.373
Congenital heart disease	46 (12.4)	26 (14.3)	20 (10.6)	0.279
Primary lung cancer	1 (0.3)	0 (0.0)	1 (0.5)	1
Leukemia/Lymphoma	42 (11.3)	30 (16.5)	12 (6.3)	0.002
Lung metastasis	8 (21.6)	2 (1.1)	6 (3.2)	0.284
HIV	4 (10.8)	4 (2.2)	0 (0.0)	0.057
Pulmonary TB	10 (2.7)	7 (3.8)	3 (1.6)	0.213
Other underlying diseases	215 (58.0)	98 (53.8)	117 (61.9)	0.116
The first study in the selected period	340 (91.6)	166 (91.2)	174 (92.1)	0.766
CT with contrast	353 (95.1)	170 (93.4)	183 (96.8)	0.1215
Median of consolidated lesion/cases	1 (0,2)	1 (1,2)	0 (0,0)	< 0.001
Consolidation*	187 (50.4)	140 (76.9)	47 (24.9)	< 0.001
LUL	52 (14)	39 (21.4)	13 (6.9)	< 0.001
LLL	102 (27.5)	74 (40.7)	28 (14.8)	< 0.001
RUL	73 (19.7)	57 (31.3)	16 (8.5)	< 0.001
RML	40 (10.8)	34 (18.7)	6 (3.2)	< 0.001
RLL	104 (28.0)	84 (46.2)	20 (10.6)	< 0.001
Median of atelectatic lesion/cases	1 (0,2)	1 (0,2)	2 (1,2)	< 0.001
Atelectasis*	266 (71.7)	97 (53.3)	169 (89.4)	< 0.001
LUL	87 (23.5)	33 (18.1)	54 (28.6)	0.018
LLL	167 (45.0)	58 (31.9)	109 (57.7)	< 0.001
RUL	105 (28.3)	34 (18.7)	71 (37.6)	< 0.001
RML	32 (8.6)	17 (9.3)	15 (7.9)	0.63
RLL	159 (42.9)	59 (32.4)	100 (52.9)	< 0.001
Other CT findings*				
Interstitial infiltration	18 (4.9)	11 (6.0)	7 (3.7)	0.294
GGO	109 (29.4)	76 (41.8)	33 (17.5)	< 0.001
Pleural effusion	113 (30.5)	71 (39.0)	42 (22.2)	< 0.001
Bronchiectasis	38 (10.2)	31(17.0)	7 (3.7)	< 0.001
Lymphadenopathy	91 (24.5)	56 (30.8)	35 (18.5)	0.006
Cardiomegaly	31 (8.4)	17 (9.3)	14 (7.4)	0.501
Lung abscess	14 (3.8)	13 (7.1)	1 (0.5)	0.001
Nodule	48 (12.9)	34 (18.7)	14 (7.4)	0.001
Others	167 (45.0)	67 (36.8)	100 (52.9)	0.002

*One case could have more than one lesion location, CT finding and underlying disease.

Additionally, we grouped the subtypes of atelectasis into four groups: compressive, adhesive, obstructive and cicatrizing types. Of the total of 266 cases of atelectasis with air bronchogram, 246 cases (92.8%) were of the compressive type, while adhesive, obstructive and cicatrizing types were found in 7 (1.9%), 4 (1.1%), and 8 (2.2%) cases, respectively.

Among the other signs on chest CT studies, ground glass opacity, pleural effusion and bronchiectasis were significantly associated with pneumonia after odd ratio adjustment using multivariable analysis (Table 2).

In our series, patients who were diagnosed with pneumonia had a significantly higher chance of having air bronchogram in consolidation. In practice, pneumonia can have more than one finding. Hence, we combined the other significant findings and air bronchogram in consolidation to increase the sensitivity to detect pneumonia using prevalence as the parameter. The other significant CT findings consisted of GGO, pleural effusion and bronchiectasis. The results showed the prevalence of pneu-

Table 2. Comparison of patients with air bronchogram sign in pneumonia and non-pneumonia groups using multivariate analysis

Baseline characteristics	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.07 (1.03, 1.12)	0.001	1.00 (0.95, 1.07)	0.894
Leukemia/Lymphoma	2.91 (1.44 5.88)	0.003	2.99 (1.27,7.06)	0.012
Consolidation at LUL	3.69 (1.90, 7.18)	< 0.001	1.01 (0.42, 2.45)	0.982
Consolidation at LLL	3.94 (2.39, 6.49)	< 0.001	1.40 (0.70, 2.79)	0.338
Consolidation at RUL	4.93 (2.70, 8.99)	< 0.001	1.88 (0.84, 4.17)	0.123
Consolidation at RML	7.01 (2.86, 17.14)	< 0.001	1.88 (0.60, 5.86)	0.282
Consolidation at RLL	7.24 (4.19, 12.52)	< 0.001	5.43 (2.60, 11.35)	< 0.001
Atelectasis at LUL	0.55 (0.34, 0.91)	0.018	0.82 (0.41, 1.63)	0.5678
Atelectasis at LLL	0.34 (0.22, 0.53)	< 0.001	0.66 (0.37, 1.20)	0.174
Atelectasis at RUL	0.38 (0.24, 0.61)	< 0.001	0.48 (0.25, 0.93)	0.029
Atelectasis at RLL	0.43 (0.28, 0.65)	< 0.001	0.84 (0.47, 1.52)	0.562
Other CT findings				
GGO	3.39 (2.10, 5.46)	< 0.001	3.31 (1.82, 6.04)	< 0.001
Pleural effusion	2.24 (1.42, 3.53)	< 0.001	2.68 (1.45, 4.94)	0.002
Bronchiectasis	5.34 (2.29, 12.46)	< 0.001	5.39 (2.04, 14.22)	0.001
Lymphadenopathy	1.96 (1.21, 3.17)	0.007	0.94 (0.49, 1.80)	0.842
Lung abscess	14.46 (1.87, 111.72)	0.01	9.33 (0.98, 88.72)	0.052
Nodule	2.87 (1.48, 5.55)	0.002	2.19 (0.94, 5.10)	0.069
Others	0.52 (0.34, 0.79)	0.002	0.65 (0.15, 2.80)	0.563

Table 3. Prevalence of final diagnosis

Final diagnosis from the chart summaries by pediatrician*	Number (n=371)	Prevalence (%)	95%CI
Pneumonia	182	49.1	(44.0, 54.1)
Atelectasis	253	68.2	(63.3, 72.7)
Pulmonary hemorrhage	10	2.7	(1.5, 4.9)
Lung abscess	18	4.9	(3.1, 7.5)
Cancer	5	1.3	(0.6, 3.1)
Others	116	31.3	(26.8, 36.2)

monia was 69.2, 67.1 and 74.6%, respectively, which showed increase in prevalence as compared to the prevalence of pneumonia with air bronchogram was 49.1%. We interpreted this to mean that the incidence of patients under 15 years of age who had air bronchogram in consolidation or GGO on chest CT scans associated with pneumonia was 69.2%. The incidence in patients who had air bronchogram in consolidation or pleural effusion on chest CT scans associated with pneumonia was 67.1%. The incidence of patients who had air bronchogram in consolidation or bronchiectasis on chest CT scans associated with pneumonia was 74.6%.

DISCUSSION

An air bronchogram is defined as air-filled bronchi which appear as dark attenuation on CT images. It is visible due to the opacification of surrounding alveoli which appear gray or white. It is almost always caused by a pathologic alveolar process occurring in a secondary pulmonary lobule, in which lesions other than air fills the alveoli, e.g., water, blood, pus or cells (8).

There were no significant differences in gender, age, first studies and the contrast enhanced CT findings among patients with and without pneumonia (Table 2). However, analyzing only age independently found the median age of patients with air bronchogram signs diagnosed with pneumonia was 5.5 years while for those without pneumonia it was 2 years. Older patients might have had more lesions than the younger ones (Table 1).

Air bronchogram can be found in consolidation and/or atelectasis. Most consolidation lesions are found to represent pneumonia after correlation with evaluation of the clinical context. The morphology of consolidation and of atelectasis have been analyzed over the past decade. Consolidation shows high attenuation areas and poor enhancement of preserved lung

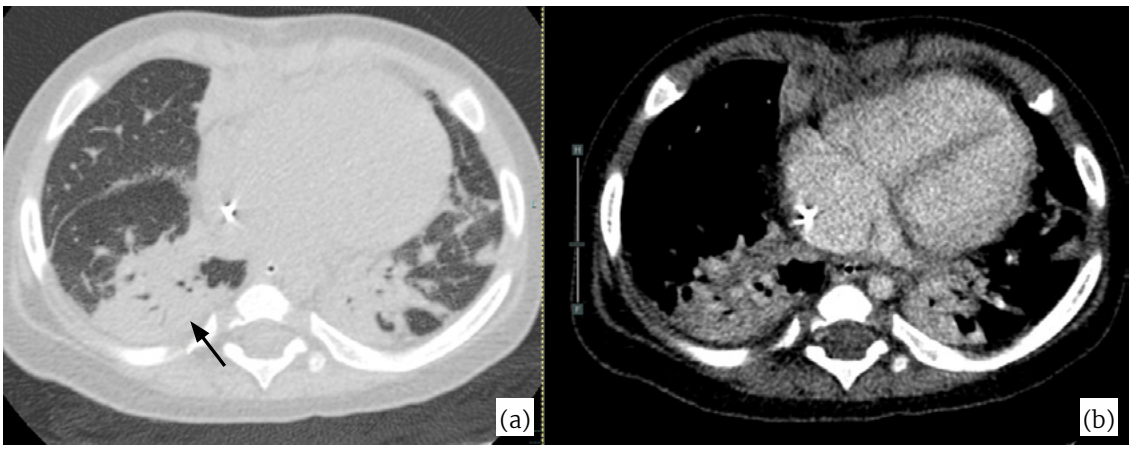

Figure 2. An 11-month-old girl with Down syndrome, ASD, VSD, PDA with subtotal correction presented with dyspnea. Her axial chest CT scan showed consolidation which was represented as a poor enhancing area (b) with preserved lung volume at both lower lobes. The air bronchogram (black arrow) (a) was also found in the consolidation at RLL. The final diagnosis was pneumonia.

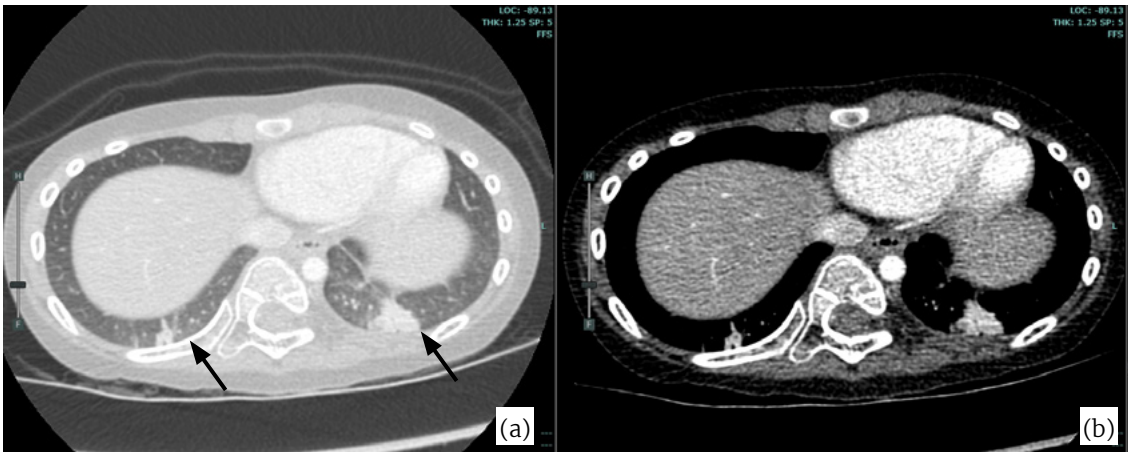

Figure 3. A 7-year-old boy with Lennox-Gastaut syndrome (LGS) presented with dyspnea. His axial chest CT scan showed wedged shaped homogeneous enhancement (b), representing atelectasis with air bronchogram signs (black arrows) (a) at both lower lobes.

volume (Figure 2) (8). Conversely, atelectasis has lesions with lung volume loss and homogeneous enhancement on chest CT studies (Figure 3). However, in our study there was no difference between CT scans with contrast and without contrast in the evaluation of whether air bronchogram was present in consolidation or in atelectasis. This could be due to the fact that in non-contrast studies we used associated findings such as lung volume loss to differentiate between consolidation and atelectasis.

In our study, we assessed the role of air bronchogram sign in the diagnosis of pneumonia and found a higher prevalence of air bronchogram with atelectasis than with pneumonia. Further serial case-by-case data analysis found patients who had chest CT scans mostly had dependent atelectasis at both lower lobes due to severe underlying diseases and long stays in bed during hospitalization. A limitation of CT chest scans in our study was that they were primarily performed only in the severe patients with dyspnea or unimproved pneumonia after appropriate antibiotic treatment. The long stays in bed during hospitalization explained the result that dependent atelectasis was found at both lower lobes. Our findings could be used to help determine the prevalence of air bronchogram sign in severe cases of pneumonia, but not in mild cases. In addition, pulmonary hemorrhage also presents with air bronchogram sign in traumatic lung injury cases with the same pathophysiology as pneumonia, called consolidation process. Lung abscess and lung cancer act as mass lesions that compress lung parenchyma, causing compressive atelectasis

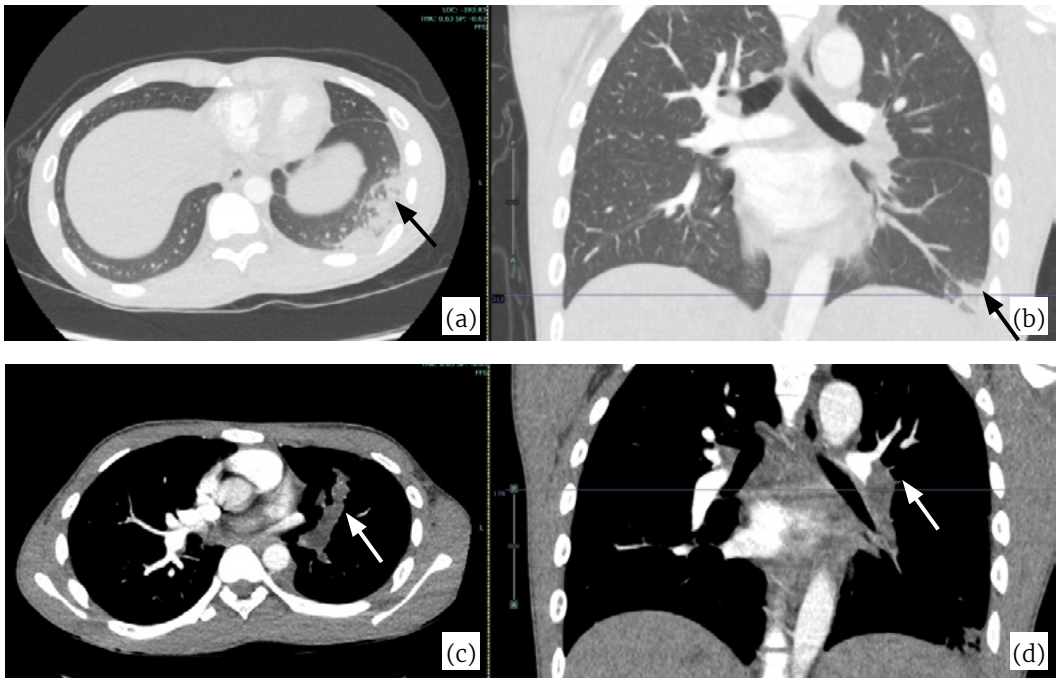

Figure 4. A 13-year-old boy, who presented with chondroblastic osteosarcoma at the left iliac bone with intravascular lung metastasis, developed progressive legs edema and dyspnea. The axial and coronal chest CT scan showed an air bronchogram in consolidation at the posterobasal segments of LLL (black arrow) (a, b), related to a resolving pulmonary infarction following a pulmonary embolism at the lingular segment and lateral basal segment of LLL. A massive tumor thrombus was seen in the left main pulmonary artery in axial and coronal views (white arrow) (c, d).

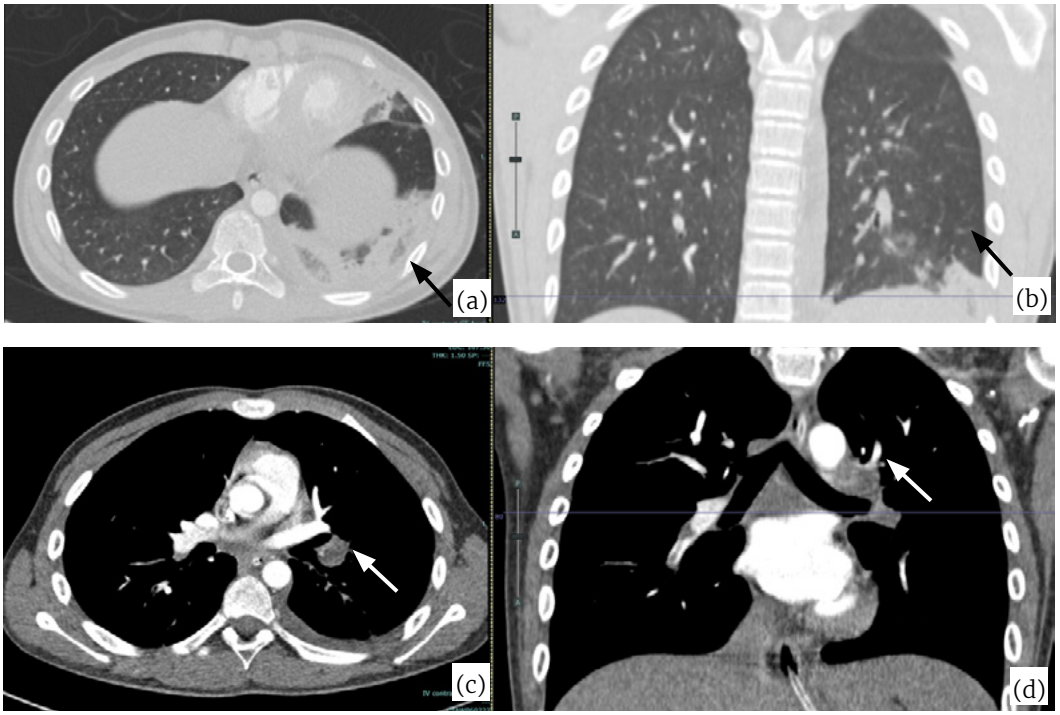

Figure 5. A 14-year-old boy with deep venous thrombosis of the left internal iliac artery developed progressive legs edema, dyspnea and hemoptysis. The axial and coronal chest CT scan showed air bronchogram in consolidation at the posterior basal segments of LLL (black arrows) (a, b), and a suspected infarction. The massive tumor thrombus was seen in the left main pulmonary artery in axial and coronal views (white arrow) (c, d).

which also appear as air bronchograms.

Other diagnoses with air bronchogram were found in 31.3% of cases (Table 1). Analysis of the crude data found a diversity of diagnoses. We chose two interesting cases (Figures 4 and 5) which had air bronchogram in consolidation

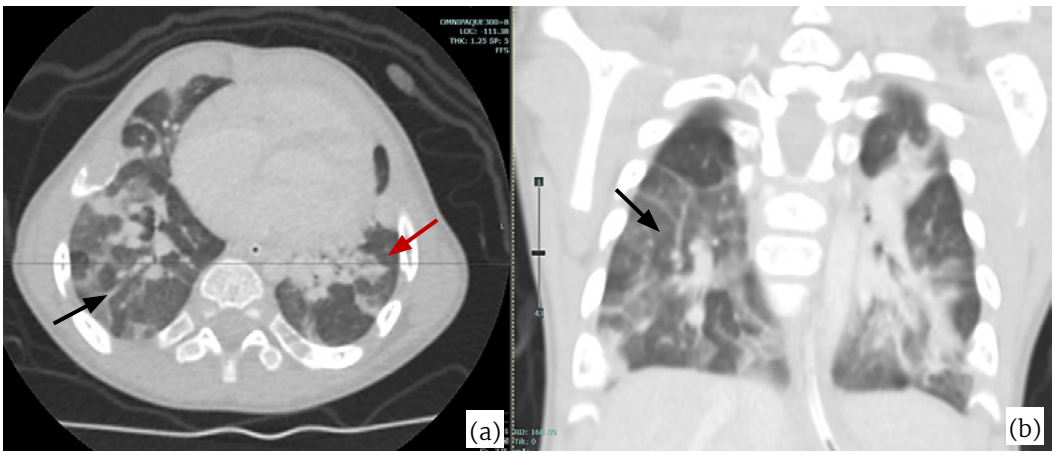

Figure 6. A 10-month-old male infant with oral-facial-digital syndrome and skeletal dysplasia, presented with recurrent pneumonia. His chest CT findings showed air bronchogram in consolidation (red arrow) at LLL with diffuse GGO (black arrows) at both lungs in axial and coronal views (a, b). The final diagnosis was pseudomonas aeruginosa and influenza pneumonia.

but were not diagnosed as pneumonia. The first patient was a 13-year-old boy who presented with chondroblastic osteosarcoma at the left iliac bone with intravascular lung metastasis who developed progressive leg edema and dyspnea. His CTPA showed progressive tumor thrombi at the left main pulmonary artery and lateral basal segmental branch of LLL and a resolving pulmonary infarction following a pulmonary embolism at the lateral basal segment of LLL. This lesion appeared as an air bronchogram in consolidation (Figure 4). The other case was a 14-year-old boy with deep venous thrombosis of the left internal iliac artery. He developed progressive leg edema, dyspnea and hemoptysis. His CTPA showed a filling defect at the left main pulmonary artery and all segmental branches of the upper, middle and lower lobes of the left pulmonary artery as well as the medial, anterior, lateral and posterior basal segmental branches of the right lower lobar artery, suggestive of acute pulmonary embolism and air bronchogram in consolidation at the posterior basal segment of LLL, and suspected infarction (Figure 5). This indicates that a lung infarction can manifest the appearance of air bronchogram.

Garcia et al (10) reported that pneumonia is common during induction chemotherapy for acute leukemia and is associated with increased morbidity, mortality, and health care resource utilization (9). Our study supported this result, i.e., the risk of pneumonia was significantly increased in the leukemia/lymphoma group with induction chemotherapy. Congenital heart and lung diseases did not increase the risk of developing severe pediatric pneumonia in our series. However, some underlying diseases, including primary lung cancer, lung metastasis, HIV and pulmonary tuberculosis, also showed no statistically significant correlation which could be due to the study's small sample size (Table 1).

Air bronchogram in consolidation was associated with an increased risk of pneumonia while there was no such association with atelectasis (Table 1). This indicates that air bronchogram in consolidation favors pneumonia more than in atelectasis. As we considered the location of the lesions, we found that air bronchogram in consolidation in the RLL significantly increased the risk of pneumonia (Table 2).

In theory, atelectasis with air bronchogram sign was primarily found in the compressive type (4). Our study also supported this association with a high prevalence of 92.8%. However, we are still concerned that adhesive, obstructive and cicatrizing atelectasis can also be associated with air bronchogram.

Other CT factors significantly associated with an enhanced risk of severe pneumonia in pediatric patients are GGO, pleural effusion and bronchiectasis (Table 2). However, some CT findings could not be well evaluated due to the small sample size, e.g., interstitial infiltration, cardiomegaly, lung abscess and nodules. Significant findings were identified in three

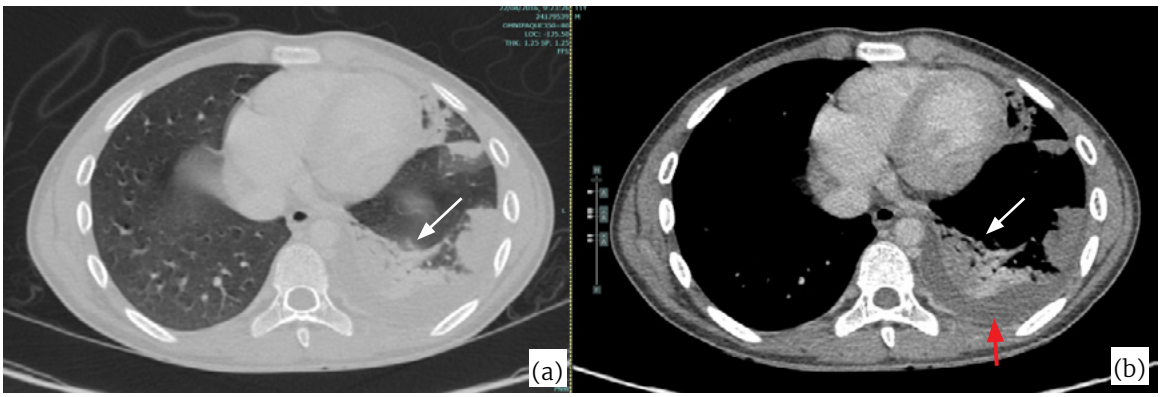

Figure 7. An 11-year-old boy with antiphospholipid syndrome, deep venous thrombosis and pulmonary embolism, presented with dyspnea. His axial chest CT study showed LLL atelectasis with patchy areas of faint enhancement (dashed white arrow) (b) which represented an air bronchogram in consolidation (solid white arrow) (a). The finding was suspected concomitant pneumonia. Left pleural effusion (red arrow) (b) was also demonstrated at LLL. The final diagnosis was pneumonia.

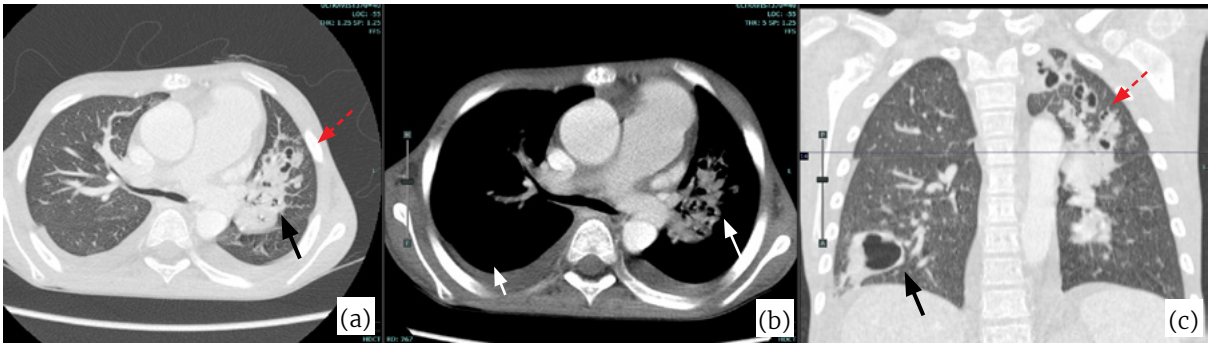

Figure 8. A 12-year-old boy with post-infectious glomerulonephritis causing RPGN presented with persistent LUL and RLL infiltration. The chest CT study revealed air bronchogram (solid black arrow) (a) in consolidation (solid white arrow) (b) which presented as a less enhanced area at LUL. The adjacent bronchiectasis with bronchial and bronchiolar wall thickening at LUL was also related to a superimposed infection in axial and coronal views (dashed red arrows) (a, c). A cavitary lesion with wall thickening at RLL (black arrow) (c) was also noted as infection. The final diagnosis was Nocardiosis and Aspergillosis pneumonia with bronchiectasis.

different cases as shown below (Figures 6, 7, 8). Following on the result that in all patients air bronchogram in consolidation favored a diagnosis of pneumonia, when we combined air bronchogram in consolidation with other significant CT findings, including GGO, pleural effusion and bronchiectasis in union pattern, the prevalence of pneumonia increased to 69.2, 67.1 and 74.6%, respectively. In comparison, the prevalence of pneumonia with air bronchogram alone was 49.1%. These results could be applied to clinical practice. Pediatricians should pay attention to these statistically significant signs to help confirm a diagnosis of pneumonia in severe cases.

There are some limitations in our study. First, CT studies are not regularly performed on out-patients or on patients with mild cases of pneumonia, so the prevalence of pneumonia in our study represents only severe cases. Second, some of the study groups were too small to evaluate statistical significance. Further studies are warranted.

In conclusion, chest CT findings can play a crucial role in the evaluation of air bronchogram signs in consolidation and atelectasis. The presence of an air bronchogram alone is not definitive for pneumonia. A higher prevalence of air bronchograms was found in atelectasis cases (68.2% in atelectasis vs. 49.1% in pneumonia). Although air bronchograms in consolidation favor a diagnosis of pneumonia, especially in RLL, air bronchogram sign should raise concern for lesions in both pneumonia and non-pneumonia. Consequently, air bronchogram in consolidation combined with GGO,

pleural effusion and/or bronchiectasis increases the likelihood of pneumonia. The results of the study should be focused on severe cases of pneumonia or immunocompromised patients who are suspected of having complications rather than on mild cases of pneumonia.

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Original Article **Open Access**

Normal Reference Range Values of Arterial Spin Labeling of Magnetic Resonance Imaging Brain Perfusion during Normal Maturation from Childhood through Adolescence to Adulthood

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ABSTRACT

OBJECTIVE The aim of this study was to evaluate cerebral blood flow using arterial spin labeling magnetic resonance imaging in normal healthy subjects from childhood through adolescence to adulthood.

METHODS A total of 38 normal, healthy subjects age between 8 and 32 were evaluated during the years 2018-2021 using arterial spin labeling magnetic resonance imaging.

RESULTS The average region of interest (ROI) of all brain regions combined in all subjects was 37.05 ± 11.94/100 g per minute. The difference in average ROI in all regions in males and females was not statistically significant. The differences in average ROI in each of the brain regions by age group was not statistically significant. The average ROI of all brain regions combined and in each of the regions were not statistically significantly correlated with age.

CONCLUSIONS During the transition from childhood through adolescence to adulthood, there is no correlation between age or gender and overall cerebral blood flow in all regions as measured by the arterial spin labeling (ASL) method.

KEYWORDS arterial spin labeling (ASL), cerebral blood flow, normal maturation

INTRODUCTION

Growth and development of brain parenchyma during the period from childhood through to adulthood is important for both for the structure and function of the human brain (1). One prior study reported that brain perfusion is related to normal development of the human brain, especially during from age 10 to 20 years (2).

Two advantages of using magnetic resonance imaging (MRI) rather than other imaging methods, e.g., computed tomography, x-ray scans, and ultrasound, are that with MRI there is no radiation and that it provides high image resolution. MRI is helpful for studying the structure of brain parenchyma. Metabolism cannot be measured directly by MRI, but cerebral perfusion and cerebral blood flow can be quantified and coupled to levels of cerebral oxygen and glucose consumption (3) which reflected brain's metabolism and neuronal function.

Generally, MRI-based perfusion techniques are usually involve imaging after administration of a paramagnetic contrast agent to dynamically track passage of a labeled bolus through the vasculature. However, the use of exogenous contrast injection is limited in patients with renal failure due to the associated risk of nephrogenic systemic fibrosis (4), as well as in children due to technical difficulties and ethical problems related to contrast agents.

Measurement of cerebral perfusion has become important tool in clinical evaluation of the brain. There are many methodologies available for cerebral perfusion evaluation. For example, dynamic susceptibility contrast (DSC)-MRI

measures perfusion by dynamic imaging of the passage of a contrast agent while arterial spin labeling (ASL) generates an image by magnetically labeling water molecules and using them as an endogenous tracer as they travel to an organ of interest.

ASL is a quantitative method for cerebral perfusion measurement which is used to evaluate cerebral blood flow (CBF) non-invasively by magnetically labeling inflowing blood without requiring a gadolinium-based tracer (5,6). A limitation of ASL is a very low signal-to-noise ratio (SNR) due to the fact that the inflowing labeled molecules comprise only about 1% of the static tissue signal which requires an increase in total scan time, making the technique sensitive to motion artifacts. ASL does, however, have the advantage of using an endogenous tracer by magnetically labeling water in arterial blood supply. ASL is a completely non-invasive and non-ionizing technique, making it safe for repeated measurements and providing increased patient comfort during measurement. The parameter measured with ASL is CBF, the delivery rate of oxygen and nutrients to the capillary bed. CBF is expressed as the volume of blood per volume of tissue per minute (mL/100 g/min). ASL is suitable for use in longitudinal and multicenter studies (7,8).

In recent years, the ASL technique has been more popular in clinically relevant research such as cerebrovascular disease, neurodegenerative disease and brain tumors. However, alteration in cerebral blood flow during human maturation could potentially affect disease interpretation. There have been few studies of ASL in Thailand. In this study, we investigated the ASL signal in terms of cerebral blood flow in healthy subjects aged between 8 and 32 years. In very young patients, a limitation of MRI is that it cannot be performed without use of sedation. However, sedation can interfere with cerebral blood flow interpretation. For example, previous studies have shown a significant increase in cerebral blood flow in halogen-sedated children compared with awake children. Other factors can also affect interpretation such as patient movement (9) that was not an issue in this study, however, as no sedation was used. Additionally, females have been found to have greater cerebral blood flow than males (10). In this study, the authors provided normal reference values of ASL using the MRI technique in healthy subjects of both genders aged between 8 and 32 years, for which reference values will be benefit for further clinical application.

METHODS

The study was approved by the ethics committee and informed consent was waived. Retrospective analysis of normal healthy subjects in Vajira Hospital between year 2018 to 2021 was conducted. The gender and age of subjects were recorded. Patients undergoing MRI study due to non-specific symptoms such as abnormal movement, precocious puberty or hormonal disturbance with no gross MRI abnormality, e.g., brain infarction, hemorrhage or abnormal mass lesion were included. Only non-sedated brain MRI subjects were included in this study.

MRI data acquisition

Cerebral blood flow was measured using arterial spin labeling, scanned by a 3.0 tesla MR system (Ingenia, Philips Medical System, Best, the Netherlands) with a 20-channel head coil. Pulse sequences used for analysis were 3D pCASL (pseudocontinuous arterial spin labeling) acquired with GRASE read-out, providing normalized images with a 4-pulse background suppression scheme with the following parameters: repetition time 4200 ms; echo time 12 ms; NEX 1; field of view 240 mm; matrix size 64x60; thickness 6 mm. Scanning time was 4.56 minutes. The label duration of this sequence was 2000 ms.

Postprocessing

The ASL images, which included mainly gray matter plus some included white matter, was segmented into major vascular territories. The four regions of interest (ROIs) were defined as the left and the right cortical vascular territories of the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA). Vascular territory ROIs were manually drawn by neuroradiologist based on anatomic landmarks on a signal ASL image using a standard Montreal Neurological Institute template.

Statistical analysis

Subject characteristics are reported as descriptive statistics. Continuous data is presented as mean ± standard deviation (SD). Categorical data are presented as number and percentage. All ROI reference values are reported as mean and standard deviation. The correlation between age and ROI values was analyzed using Pearson correlation coefficients. The unpaired t-test was used to evaluate the differences in ROI between males and females. One-way analysis of variance (ANOVA) was performed to assess the effect of age on ROI values. A *p*-value less than 0.05 was considered statistically significant. All analyses were conducted using PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the subjects are presented in Table 1. A total of 38 healthy subjects (15 males and 23 females) were studied, age between 8 and 32 years (mean ± standard deviation: 15.68 ± 7.16 years). The largest group of subjects were in age the group 8-16 years (60.5%).

The average ROI of all regions combined and all subjects was 37.05 ± 11.94/100 g per minute. The values for males was 36.51 ± 13.70/100 g per minute and for females was 37.40 ± 10.95/100 g per. The differences in average ROI of all regions combined between males and females was not statistically significant (p = 0.826) and there were no statistically significant differences between male and females in the ROI for any of the regions (Table 2).

The average ROI of all regions studied combined was 35.47 ± 11.85/100 g per minute in the age group 8-16 years, 38.30 ± 10.66/100 g per minute in the age group 17-24 years, and 41.19 ± 14.81/100 g per minute in the age group 25-32 years. There was no statistically significant difference in the average ROI of all regions combined among the age groups (p = 0.556).

Table 1. Demographic data

Variable	n = 38
Age (years): mean ± SD	15.68 ± 7.16
Age (years): n (%)	
8-16	23 (60.5%)
17-24	9 (23.7%)
25-32	6 (15.8%)
Sex: n (%)	
Male	15 (39.5%)
Female	23 (60.5%)

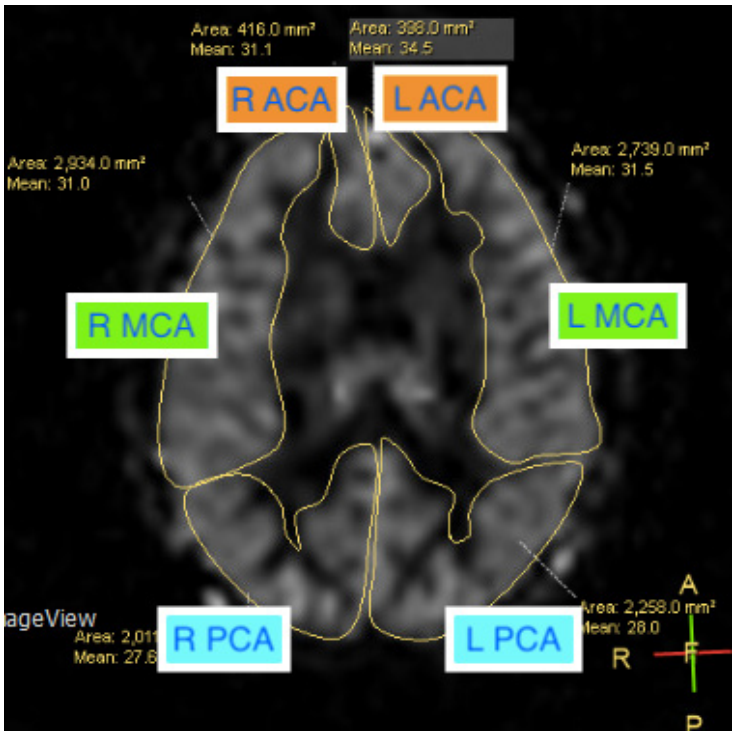

Figure 1. Example of an arterial spin labeling image segmentation based on the vascular flow territories for six vascular territories: anterior cerebral arteries, middle cerebral arteries, and posterior cerebral arteries on both the right and left sides

Table 2. Mean and standard deviation of ROI in males and females

Parameter	Total (n=38)	Male (n=15)	Female (n=23)	*p*-value[#]
All average ROI	37.05 ± 11.94	36.51 ± 13.70	37.40 ± 10.95	0.826
Average ROI ACA	40.31 ± 13.05	38.84 ± 14.97	41.28 ± 11.89	0.580
Average ROI MCA	36.00 ± 11.46	35.94 ± 13.08	36.04 ± 10.57	0.979
Average ROI PCA	34.83 ± 12.61	34.75 ± 14.49	34.88 ± 11.56	0.977

[#]Independent t-test

Table 3. Mean and standard deviation of ROI by age group

	Age 8-16 (n=23)	Age 17-24 (n=9)	Age 25-32 (n=6)	*p*-value
All average ROI	35.47 ± 11.85	38.30 ± 10.66	41.19 ± 14.81	0.556
Average ROI ACA	39.25 ± 14.37	40.94 ± 8.23	43.44 ± 14.99	0.781
Average ROI MCA	35.03 ± 12.02	36.68 ± 9.86	38.68 ± 12.90	0.779
Average ROI PCA	32.14 ± 10.00	37.29 ± 14.42	41.44 ± 17.50	0.223

Table 4. Correlation between age and ROI parameters

	Pearson correlation coefficients (r)	*p*-value
Average ROI ACA	0.042	0.801
Average ROI MCA	0.061	0.717
Average ROI PCA	0.257	0.119

The difference in average ROI in each of the regions between age groups was also not statistically significant (Table 3).

The average ROI of all regions combined and of each of the regions were not statistically significantly correlated with age (All: r = 0.125, ACA: r = 0.042, MCA: r = 0.061, PCA: r = 0.257) (Table 4).

DISCUSSION

Our study excluded elderly subjects because the aging process may affect cerebral blood flow. This study also excluded very young subjects because the necessary sedation would interfere with cerebral blood flow interpretation. The authors aimed to analyze specifically healthy adolescent subjects during the transition from childhood into adulthood.

Our CBF measurement of subjects with a mean age of 15.68 ± 7.16 years showed a mean CBF value of 37.05 ± 11.94 mL/100 g per minute, a lower CBF value than prior studies as described in Table 5. For instance, in a previous study with a mean age of 11 years, Hales et al. (11) reported a mean CBF value of 62 ± 4 mL/100 g per minute. A study with a mean age of 11 ± 3 years by Jane et al. (12) reported a mean CBF value of 65 ± 10 mL/100 g per minute. Another study with a mean age of 32 years by Wang et al. (13) measured a mean CBF value of 58 ± 12 mL/100 g per minute. Studies by Pollock et al. (14) showed a cerebral perfusion plateau between 4-11 years with rates of CBF greater than 90 mL/100 g per minute which then rapidly decreased after age 11, with rates of CSF in adolescents less than 90 mL/100 g per minute. Assessment of CBF is affected by the partial volume effect which is related to the voxel size of ASL and is several times that of 3D T1-weighted acquisitions. Different types of tissues have different perfusion characteristics, e.g., perfusion in white matter is less than in grey matter. A study by Vavilala et al. (15) found the normal average CBF in adult humans to be about 50 mL/100 g per minute, with lower values in white matter (about 20 mL/100 g per minute) and higher values in gray matter (about 80 mL/100 g per minute). Our study included both gray and white matter which may have resulted in lower CBF values than the

Table 5. Comparison of mean age and mean CBF of this study and prior studies

	Mean age (years)	Mean CBF ± SD (mL/100 g per min)
This study	15.68 ± 7.16	37.05 ± 11.94
Hales et al. (11)	11	62 ± 4
Jane et al. (12)	11 ± 3	65 ± 10
Wang et al. (13)	32	58 ± 12
Pollock et al. (14)	4-11 years - mean CBF > 90 >11 years - mean CBF < 90	

average CBF values reported in prior studies.

Variation of cerebral blood flow values can be influenced by factors such as differences in label duration time which can impact the CBF perfusion map. Another potential factor that may affected for data processing is that baseline hematocrit levels may different in different populations.

The authors evaluated CBF values in different age groups, 8-16, 17-24 and 25-32 years, and found negative correlation with age in all three. As well as CBF values in regional vascular territories, our results showed negative correlation with age in all regions of vascular territories combined which agrees with previous a study by Hales et al. (11). A previous study by Zhang et al. (16) showed age to be negatively correlated with CBF, but, after adjusting by global value, CBF was found to decrease with age in certain regions but to increase in others, suggesting that different analysis methods can affect the age-related CBF pattern.

The propose of this study is to provide a reference range of cerebral blood flow in normal healthy subjects which can be further used for comparison with pathologies that cause abnormal cerebral blood flow, e.g., cerebrovascular disease, dementia and cognitive disorder, tumor, vascular malformation, infections such as encephalitis and migraine-associated hyperperfusion.

There are several limitations to our study including the small sample size and that it was a single time period study. Future investigation is needed with larger sample sizes in both longitudinal and multicenter studies.

CONCLUSION

This study provides normal reference values of cerebral blood flow using arterial spin labeling magnetic resonance imaging in normal healthy subjects age from 8 to 32 years. During the transition from childhood through adolescence to adulthood, there is no correlation with age, gender or brain region in cerebral blood flow as measured using the ASL method. In the future, these data will aid evaluation of clinical conditions of patients with disorders affecting cerebral blood flow such as cerebrovascular disease, brain tumor or neurodegenerative disease. However, due to the small sample size in this study, the use of these results in clinical evaluations should be done with caution.

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None

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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Original Article **Open Access**

Health-Related Quality of Life and Disease-Specific Symptoms Among Persons with Thyroid Cancer After Surgery in Yunnan Province, the People's Republic of China

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ABSTRACT

OBJECTIVE To examine health-related quality of life (HRQOL), disease-specific symptoms, and relationships between HRQOL and disease-specific symptoms among thyroid cancer patients after surgery in Yunnan Province, the People's Republic of China.

METHODS Participants in this cross-sectional study included 333 persons with thyroid cancer after surgery receiving care at the First Affiliated Hospital of Kunming Medical University. The HRQOL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. The Thyroid Cancer Specific HRQOL questionnaire was used to measure the disease-specific symptoms.

RESULTS The mean global health score was 75.00 + 17.09. The mean score of role, social, physical, cognitive, and emotional function were 95.10±14.32, 92.67±16.12, 92.00±8.94, 82.83±16.15 and 81.11±16.47, respectively. The top three disease-specific symptoms experienced by thyroid cancer patients after surgery were psychological symptoms (18.74±17.16), problems with scars (17.77±24.18) and throat/mouth symptoms (17.07±16.64). There were statistically significant negative correlations between dimensions of disease-specific symptoms and dimensions of HRQOL.

CONCLUSIONS This study revealed negative relationships between HRQOL and disease-specific symptoms experienced by thyroid cancer patients after surgery. Health care providers caring for thyroid cancer patients, especially those in China, could use these findings as a basis for further enhancing the quality of care for patients with thyroid cancer after surgery.

KEYWORDS health-related quality of life, quality of life, symptoms, thyroid cancer

INTRODUCTION

The incidence of thyroid cancer is increasing worldwide (1). In the past decades, the incidence of thyroid cancer has continued to rise (2). It is the fourth most common type of cancer found among women in China (3). According to the American Thyroid Association Guidelines, surgery is the recommended treatment for thyroid cancer (4).

Shortly after surgery, risk assessment is normally adjusted based on surgical and pathological findings and a determination is made whether radioactive iodine (RAI) ablation and/or thyroid stimulating hormone (TSH) inhibition is required (5). The main adjuvant therapy after surgery is TSH suppression, which can significantly reduce recurrence and cancer-related mortality in patients with differentiated thyroid cancer (6,7). Patients receiving TSH

suppression therapy can experience fatigue, insomnia, flushes, anxiety, irritability, muscle weakness, sweating, and palpitations (8-10), and those receiving RAI therapy may experience salivary gland pain and xerostomia from sialoadenitis (10). Those symptoms may persist for an unpredictable period of time, which may significantly affect the patient's quality of life after surgery.

After surgery, the patient may also experience many disease-specific symptoms. Some patients may suffer from neuromuscular symptoms caused by hypoparathyroidism resulting from parathyroid injury or inadvertent resection during thyroid surgery (11). These symptoms are directly related to thyroid cancer surgery and may include muscle cramping, twitching and spasms, circumoral and acral numbness and paresthesias, laryngospasm and bronchospasm. In addition, patients may experience hoarseness because of recurrent laryngeal nerve injury (9). Patients can also experience pain and tightness in their neck because of scars left by surgery (12).

Postoperative thyroid cancer patients usually need long-term or even lifelong adjuvant therapy. Although adjuvant therapy prevents the recurrence of the disease, it can produce many undesirable symptoms. These symtoms may persist for an unpredictable period of time after surgery, and may make a significant difference in the patient's quality of life after surgery. Many studies have shown that long-term or lifelong adjuvant therapy and disease-specific symptoms after thyroid cancer surgery can affect patients' health-related quality of life (HRQOL) (8,12,13).

HRQOL is a term derived from the development of quality of life. In oncology, quality of life is often described as various aspects of health, such as physical symptoms, daily activity levels, psychological well-being, and social functioning (14). According to the European Organisation for Research and Treatment of Cancer (EORTC), HRQOL refers to the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical function, emotional function, social function, cognitive functions, role function and symptoms (15).

There have been only limited studies exploring HRQOL and disease-specific symptoms among thyroid cancer patients after surgery in China. Since HRQOL is subjective (15), perceptions of each individual are different, thus a subjective survey of patients in other countries cannot be generalized to the Chinese population. This study was conducted to examine HRQOL, disease-specific symptoms and the relationship between HRQOL and disease-specific symptoms among thyroid cancer patients after surgery in Yunnan province, the People's Republic of China.

OBJECTIVES

The aims of this study were to examine disease-specific symptoms, HRQOL, and the relationship between disease-specific symptoms and HRQOL among thyroid cancer patients after surgery in Kunming city, Yunnan province, the People's Republic of China.

METHODS

A cross-sectional study was conducted at the Thyroid Surgery Clinic of the First Affiliated Hospital of Kunming Medical University. A total of 2,000 adult thyroid cancer patients were receiving care after surgery at the Thyroid Surgery Clinic of the First Affiliated Hospital of Kunming Medical University. The number of participants was calculated using Yamane's formula with a 5.0% margin of error, yielding a sample size of 333. Inclusion criteria were thyroid cancer patients aged at least 18 years old and at least 1 month after thyroid surgery. A total of 333 participants were recruited between March and April 2020. None of the identified participants were excluded.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) Chinese version was used to assess HRQOL. It consists of five functional dimensions (physical, role, cognitive, emotional, and social), three symptom dimensions (fatigue, pain, and nausea and vomiting), global health, and six single items addressing various symptoms and perceived financial impact (16). Global health was scored on a seven-point Likert scale ranging from very poor to excellent. The rest of the items were scored on

a four-point Likert scale ranging from not at all to very much. Each item score was transformed into a scale score ranging from 0 to 100. A high score for functional dimensions represents a high level of functioning, a high score for global health represents a high level of QOL, and a high score for symptom scales/items represents a high number of symptomatic problems. The Thyroid Cancer Specific HRQOL questionnaire (THYCA-QOL) (17) Chinese version (18) was used to assess the disease-specific symptoms. It consisted of seven symptom dimensions (neuromuscular, voice, concentration, sympathetic, throat/mouth, psychological and sensory problems) and six single items (problems with scar, feeling chilly, tingling hands/feet, gaining weight, headaches, interest in sex) (18). Each item was scored on a four-point Likert scale, and then transformed into scale scores ranging from 0-100. A higher score on this scale means more symptoms with the exception of the dimension of interest in sex where a higher score indicates better sexual functioning. The reliability of the EORTC-QLQ-C30 Chinese version and the THYCA-QOL Chinese version in this study was tested with 15 thyroid cancer patients after surgery who met the same inclusion criteria as the study participants. Internal consistency was examined using Cronbach's α. The reliability of the EORTC QLQ-C30 Chinese version was 0.70-0.95, while the reliability of the THYCA-QOL- Chinese version was 0.82-1.00.

Data collection was conducted after receipt of ethical approval from the Research Ethics Committee of the Faculty of Nursing, Chiang Mai University (research ID 2020-043, study code 2020-EXP035), and permission for data collection from the First Affiliated Hospital of Kunming Medical University. The participants were placed in a relatively private and quiet environment while answering the questionnaires.

The data were analyzed using SPSS version 23. Categorical variables are given as percentages. Continous variables are presented as mean ± standard deviation. The difference of scores between gender groups and between duration of treatment groups were tested by independent t-test. The Pearson correlation (r value) was used to determine positive and negative correlations. All tests were considered statistically significant if $p < .05$.

RESULTS

The characteristics of the 333 participants are presented in Table 1. Most participants were female (86.2%). Their age ranged between 20 and 74 years old with a mean of 42.63. Most (92.8%) had received levothyroxine alone and more than half (62.8%) had received treatment for more than 1 year after surgery. Most did not have a comorbidity (69.4%).

Table 2 shows HRQOL as assessed by the EORTC-QOL-C30. The mean global health score was 75.00±17.09. On the five functional scales, emotional function had the lowest score (81.11±16.47). Regarding the symptom scales, fatigue (19.94±17.93), insomnia (19.94±26.88) and dyspnea (13.58±19.03) were the top three highest mean scores. The female group had higher mean score of nausea/vomiting than the male group. Patients who had received treatment for more than 1 year reported less pain than those who had received treatment for 1 year or less.

The disease-specific symptoms are presented in Table 3. Among the symptom scales, the

Table 1. Characteristics of the participants (n = 333)

Characteristics	Frequency (%)
Age (years)	
Mean±SD	42.63±11.16
Range	20-74
Gender	
Male	46 (13.8)
Female	287 (86.2)
Educational status	
Below associates degree	124 (37.2)
Associates degree	69 (20.7)
Bachelor degree	125 (37.5)
Master degree and above	15 (4.5)
Marital status	
Single	32 (9.6)
Married	285 (85.6)
Divorced/separated/widowed	16 (4.8)
Type of adjuvant treatment received	
Medication (levothyroxine)	309 (92.8)
Medication + Radioactive Iodine	24 (7.2)
Duration of treatment received	
< 1 year	124 (37.2)
> 1 year	209 (62.8)
Comorbidity	
No	231 (69.4)
Yes	102 (30.6)

Table 2. EORTC-QOL-C30 scores among thyroid cancer patients after surgery

EORTC-QOL-C30 score	Total group (n=333)	Gender		Duration of treatment	
		Male (n=46)	Female (n=287)	< 1 year (n=124)	> 1 year (n=129)
Global health[a]	75.00±17.09	74.28±14.68	75.11±17.47	74.35±17.17	75.37±17.08
Functioning scales[a]					
1. Role function	95.10±14.32	91.30±18.51	95.70±13.47	94.35±15.16	95.53±13.82
2. Social function	92.67±16.12	91.30±14.80	92.89±16.34	92.67±14.20	92.66±17.20
3. Physical function	92.00±8.94	93.62± 8.89	91.74± 8.94	90.83± 9.68	92.69± 8.42
4. Cognitive function	82.83±16.15	84.06±15.30	82.63±16.30	82.79±16.31	82.85±16.09
5. Emotional function	81.11±16.47	82.07±15.71	80.96±16.61	80.06±15.24	81.73±17.16
Symptom scales[b]					
1. Fatigue	19.94±17.93	18.59±18.00	20.16±17.94	22.04±18.15	18.70±17.73
2. Insomnia	19.94±26.88	16.81±19.46	20.44±27.88	21.50±27.28	19.01±26.68
3. Dyspnea	13.58±19.03	12.32±16.27	13.78±19.45	15.05±20.98	12.70±17.76
4. Pain	8.21±12.45	8.70±12.04	8.13±12.53	11.16±13.05	6.46±11.76**
5. Constipation	7.11±15.70	5.80±16.18	7.32±14.90	7.53±15.81	6.85±14.64
6. Financial difficulties	5.51±15.30	3.62±10.49	5.81±15.92	6.45±15.72	4.94±15.05
7. Appetite loss	4.50±12.80	2.90±9.50	4.76±13.24	5.91±13.47	3.67±12.33
8. Diarrhea	3.40±16.75	4.35±11.35	3.25±10.66	3.78±11.41	3.19±10.35
9. Nausea/vomiting	1.90±6.50	0.36±2.46	2.15±6.91**	1.97±6.61	1.86±6.45

[a]higher score indicates a higher level of health-related quality of life; [b]higher score indicates a higher level of problems
** $p < 0.01$

psychological scale had the highest score (18.74±17.16), and the concentration scale had the lowest score (10.46±16.00). Among single item symptoms, problems with scar had the highest score (17.77±24.18) and tingling hands/feet had the lowest score (9.31±17.07). Females had more sympathetic symptoms, problems with scar, and headaches than males. Patients who received treatment for more than 1 year reported less throat/mouth symptoms and headaches than those who received treatment for 1 year or less, although they did report greater weight gain.

The relationships between the dimensions of disease-specific symptoms and each dimension of HRQOL in patients with thyroid cancer after surgery are presented in Table 4. The three disease-specific symptoms that had the strongest negative relationship with physical function were neuromuscular (r=-.480, $p < 0.01$), psychological (r=-.393, $p < 0.01$) and sympathetic (r =-.365, $p < 0.01$). The three disease-specific symptoms that had the strongest negative relationship with role function were concentration (r=-.323, $p < 0.01$), voice (r=-.322, $p < 0.01$) and throat/mouth (r =-.301, $p < 0.01$). The three disease-specific symptoms that had the strongest negative relationship with emotional function were psychological (r=-.588, $p < 0.01$), concentration (r=-.460, $p < 0.01$) and feeling chilly (r=-.310, $p < 0.01$). The three disease-specific symptoms that had the strongest negative relationship with cognitive function were concentration (r=-.569, $p < 0.01$), psychological (r=-.465, $p < 0.01$) and neuromuscular (r=-.337, $p < 0.01$). The three disease-specific symptoms that had the strongest negative relationship with social function were concentration (r= -.483, $p < 0.01$), psychological (r=-.476, $p < 0.01$) and neuromuscular (r=-.325, $p < 0.01$). The three disease-specific symptoms that had the strongest negative relationship with global health were psychological (r= -.381, $p < 0.01$), neuromuscular (r= -.310, $p < 0.01$) and voice (r = - .291, $p < 0.01$).

DISCUSSION

The most seriously affected domain of HRQOL found in this study was global health status, followed by cognitive and emotional function (Table 2). The mean global health score in this study was comparable to the global health score of thyroid cancer patients after surgery reported in a German study (19). The score was also similar to global health in thyroid cancer patients reported in many previous

Table 3. Disease-specific symptoms among thyroid cancer patients after surgery

Disease-specific symptoms	Total group (n=333)	Gender		Duration of treatment	
		Male (n=46)	Female (n=287)	≤ 1 year (n=124)	> 1 year (n=129)
Symptom scales					
1. Psychological	18.74±17.16	15.88±16.05	19.20±17.31	19.49±17.42	18.30±17.02
2. Throat/mouth	17.07±16.64	18.58±18.90	16.83±16.27	21.29±17.82	14.57±15.40**
3. Neuromuscular	15.60±13.98	13.51±13.65	15.93±14.03	15.68±14.81	15.56±13.51
4. Sympathetic	13.57±17.26	7.39±11.94	14.56±17.78**	12.59±16.51	14.15±17.70
5. Sensory problem	13.56±15.15	11.23±13.17	13.94±15.43	11.83±14.84	14.59±15.28
6. Voice	11.91±17.97	15.94±20.77	11.27±17.43	14.38±20.75	10.45±15.97
7. Concentration	10.46±16.00	11.23±14.07	10.33±16.30	11.56±16.21	9.81±15.87
Single item symptom					
1. Problem with scar	17.77±24.18	12.32±16.27	18.64±25.12*	20.97±24.22	15.87±24.01
2. Feeling chilly	16.21±21.59	13.77±21.75	16.61±21.57	16.40±20.16	16.11±22.43
3. Gaining weight	15.51±22.62	10.87±21.14	16.26±22.79	11.83±20.47	17.70±23.58*
4. Headache	12.71±17.60	7.25±13.90	13.59±17.99**	16.23±18.76	10.68±16.59**
5. Tingling hands/feet	9.31±17.07	8.70±16.38	9.41±17.20	8.87±18.09	9.57±16.47
6. (Less) interest in sex[a]	27.93±20.47	37.68±21.78	26.36±19.85**	26.88±20.68	28.55±20.37

[a]Higher scores indicate better sexual functioning; *$p < 0.05$, **$p < 0.01$

Table 4. Relationship between disease-specific symptoms and HRQOL among thyroid cancer patients after surgery

Disease-specific symptoms	Physical function	Role function	Emotional function	Cognitive function	Social function	Global health
Neuromuscular	-.480*	-. 241*	-. 301*	-. 337*	-. 325*	-.310*
Voice	-. 287*	-. 322*	-. 248*	-. 302*	-. 307*	-. 291*
Concentration	-. 334*	-. 323*	-. 460*	-. 569*	-. 483*	-. 274*
Sympathetic	-. 365*	-. 190*	-. 255*	-. 330*	-. 288*	-. 237*
Throat/mouth	-. 360*	-. 301*	-. 259*	-. 255*	-. 277*	-. 288*
Psychological	-. 393*	-. 281*	-. 588*	-. 465*	-. 476*	-. 381*
Sensory problem	-. 149*	-. 043	-. 240*	-. 252	-. 155*	-. 232*
Problems with scar	. 019	-. 071*	-. 228*	-. 095	-. 214*	-. 128*
Feeling chilly	-. 311*	-. 148*	-. 310*	-. 284*	-. 220*	-. 208*
Tingling feet/hands	-. 311*	-. 148*	-. 156*	-. 232*	-. 250*	-. 195*
Gaining weight	-. 293*	-. 105	-. 137*	-. 066	-. 086	.024
Headache	-. 185*	-. 084*	-. 191*	-. 184*	-. 213*	-. 230*
Less interest in sex	. 177*	. 012	.049	.037	. 054	.077

HRQOL, health-related quality of life; *$p < 0.01$;

studies around the world, (8,13,20,21) including a study from China (22-24). Decreased global health in thyroid cancer patients compared to that of the general population has been documented (8,20). Thyroid cancer patients after thyroidectomy require long-term treatment. Many of them encounter fears, uncertainties and symptoms from surgery or treatments after surgery (25) which could contribute to a decline in global health.

Emotional function had the lowest score among the five HRQOL functional scales in this study (Table 2). This finding was similar to many previous studies in which emotional function score was reported as the lowest of the HRQOL dimensions (9,21,26). Emotional functions may be affected by symptoms experienced by the patient. The side effects and symptoms of all kinds of adjuvant therapy after surgery can aggravate the psychological burden of patients.

Fatigue and insomnia had the highest mean score of the symptoms dimension of HRQOL and seemed to be reported more among females than among males (Table 2), a result is similar to an earlier study (21). Fatigue and insomnia have been prominent symptoms found in patients with thyroid cancer after surgery,

not only in this study but also in previous studies from around the world (9,12,13,23,26-28). Fatigue is a common symptom in all types of cancer, and is associated with chemotherapy, radiation therapy and the treatment of primary disease processes (29). The same is true for patients after thyroid cancer surgery. Postoperative TSH suppression therapy in patients with thyroid cancer can lead to subclinical hyperthyroidism, resulting in high levels of fatigue (28). This could be a reason why the vast majority of studies on HRQOL in patients with thyroid cancer after surgery found high levels of fatigue.

Thyroid hormone dysfunction can not only cause fatigue but can also cause other symptoms such as irritability, insomnia and pain (9,17). Although all patients in this study received medication after surgery (Table 1), levothyroxine given to patients after thyroid surgery may not totally replicate their normal physiological hormone condition (8). Patients may have either hypothyroidism or hyperthyroidism during treatments, leading to the fatigue and sleep disturbances experienced by participants.

Among the disease-specific symptoms, psychological symptoms were the most common disease-specific symptoms experienced by participants in this study. These results are similar to findings from a study by Lan and colleagues (30), in which psychological symptoms were among the top three disease-specific symptoms experienced by thyroid cancer patients after surgery. Psychological symptoms included palpitations, tiredness, feeling restless or agitated and feeling anxious. Psychological symptoms experienced among thyroid cancer patients after surgery may arise from the treatment of thyroid cancer after a thyroidectomy. The TSH suppression therapy that the participants in this study received was an important treatment for avoiding recurring cancer among thyroid cancer patients (5), but it may cause palpitations, tiredness, irritability burden of the patients. TSH suppression medication can lead to hyperthyroidism, causing fatigue (31). Fatigue has been found to be associated with emotional aspects in patients with thyroid cancer receiving long-term treatment (26,28).

In addition, psychological symptoms in thyroid cancer patients after an operation may be a result of anxiety and discomfort related to concerns about the recurrence of their cancer (12,32). A previous study confirmed the existance of constant fear of recurrence among patients after thyroid cancer surgery (13). Although in Chinese culture people are reluctant to express their psychological problems to others, psychological symptoms can often be assessed by questionnaires or other research methods, which may lead to the prominent finding of psychological symptoms in this study.

The results from our study showed a difference in some symptoms between genders (Tables 2 and 3). We also noted that females tended to report more psychological symptoms and seemed to have lower emotional function than males. The difference in HRQOL and disease-specific symptoms between genders may perhaps be due to different sex-dependent reactions to the cancer and different sex-dependent coping strategies (33). The higher problem with scar in females than in males may be a result of female concerns regarding body image (30). With respect to limitations of our cross-sectional study, we noted that patients receiving treatment for more than 1 year seemed to experience fewer symptoms than those receiving treatment for 1 year or less. A possible reason for the decrease in symptoms over time could be accommodation to the treatment and the illness by the thyroid cancer patients. However, changes in symptoms over time warrants further investigation in longtitudinal studies.

In terms of the relationship between disease-specific symptoms and HRQOL, the overall results showed that each dimension of disease-specific symptoms was negatively correlated with the 5 functional dimensions and the global health dimension of HRQOL. This suggests that the more disease-specific symptoms patients experienced after thyroid cancer surgery, the lower their HRQOL levels. There has been only one study published which investigated the relationship between disease-specific symptoms and HRQOL in patients after thyroid cancer surgery (8). The results from this current study are similar to that study.

The results showed a significant negative correlation between neuromuscular symptoms and all dimensions of HRQOL and global health (Table 4). These results indicate that the more neuromuscular disease-specific symptoms a patient experienced, the lower their HRQOL. As mentioned in the literature review, problems caused by neuromuscular symptoms may be due to parathyroid injury (11). This includes the possibility that the patient may develop muscle cramping, twitching and spasms. Although most of these symptoms are temporary and some patients may recover quickly, the condition can take at least a year to fully resolve (34).

Voice specific-symptoms had the strongest negative correlation with role function (r=-.322, $p < 0.010$) and social function (r=-.307, $p < 0.010$) (Table 4). This could be due to hoarseness and inability to speak due to voice problems directly affecting the role and social functioning of the patient.

There was a significant negative correlation between concentration symptoms and cognitive function (r =-. 569, $p < 0.010$), social function (r = -.483, $p < 0.010$), and emotional function (r =-.460, $p < 0.010$) (Table 4). Reduced concentration in patients may lead to incomplete or faulty cognitive function (35). Concentration problems could also cause both difficulty in thinking and attention problems, which may affect family life and social activities as well as aggravate the patient's nervousness and anxiety (36). Concentration problems could stem from TSH suppression therapy following thyroid cancer surgery which the patient has to undergo for a long period of time and possibly for life (25).

Additionally, throat and mouth symptoms showed a significant negative correlation with physical function (r=-. 360, $p < 0.010$) and role function (r=-. 301, $p < 0.010$) (Table 4). Disease-specific symptoms such as dry mouth, difficulty swallowing and a foreign body sensation in the throat limited the ability to engage in some physical activities, as well as interfering with work, daily activities and leisure hobbies.

Finally, psychological symptoms had the highest correlation with HRQOL (Table 4). The more psychological symptoms, the worse the physical, role, emotional, cognitive and social functions. There was also a significant negative correlation between psychological symptoms and global health. Many studies have reported on psychological problems of patients after thyroid cancer surgery (12,23,37-40), the same as patients after thyroid cancer surgery in this study. Since psychological symptoms are correlated with HRQOL, support for patients with postoperative psychological problems is an essential part of postoperative follow-up.

CONCLUSION

This study revealed the existence of HRQOL and disease-specific symptoms experienced by thyroid cancer patients after surgery. There are negative relationships between disease-specific symptoms and HRQOL. Health care providers caring for thyroid cancer patients, especially those in China, could use these findings as a basis for working to further enhance the quality of care of thyroid cancer patients after surgery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Case Report

Successful Treatment of Generalized Pustular Psoriasis Triggered during Pregnancy with Secukinumab: A Case Report

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ABSTRACT

Secukinumab is one of the biologic drugs targeting interleukin-17 (IL-17) which is highly effective in the treatment of generalized pustular psoriasis (GPP). However, there is only limited data regarding treatment with GPP during pregnancy because of the rarity of the disease as well as ethical issues. This study describes the successful treatment with secukinumab of a 10 weeks pregnant women with recurrent GPP.

KEYWORDS generalized pustular psoriasis, pregnancy, interleukin-17, secukinumab

INTRODUCTION

Generalized pustular psoriasis (GPP) is characterized by an abrupt onset of widespread sterile pustules with systemic symptoms, especially fever (1). Pregnancy is one of the important triggering factors (2) making management decisions both problematic and challenging. Owing to the rarity of the disease as well as to ethical issues, there is a lack of data from large, controlled studies in humans regarding the efficacy and safety of GPP treatment during pregnancy. We herein report the successful treatment of GPP flare during pregnancy with secukinumab, a biologic drug targeting interleukin-17 (IL-17).

CASE REPORT

A 27-year-old Thai woman had been diagnosed with GPP since she was 18 years old. Her symptoms were well controlled with methotrexate treatment until a flare of the disease was precipitated by an unplanned pregnancy at the age of 25. At that time, her gestational age (GA) was 10 weeks. Dermatologic examination revealed multiple tiny non-follicular pustules on an erythematous base coalesced into lakes of pus, predominately on the trunk (Fig. 1a), groin and both upper extremities (Fig. 1b). Other physical findings and basic laboratory investigations, including a complete electrolyte panel, were unremarkable. After a rigorous discussion regarding the risks and benefits of the treatment options, methotrexate was then withheld and a combination of secukinumab with a topical steroid was administered and bed rest was advised. The pustular eruptions were notably improved by the first week after a 300 mg secukinumab subcutaneous injection

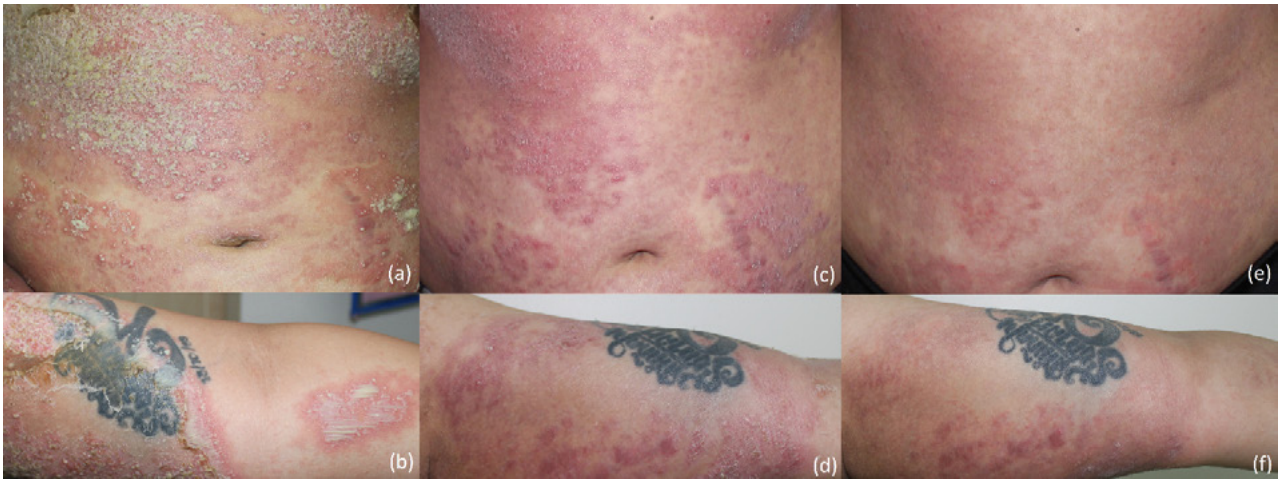

Figure 1. Clinical course and treatment response. Generalized pustular psoriasis eruption on the trunk (a) and left arm (b) before secukinumab injection (c), (d) Initial response 1 week after 300 mg dose of secukinumab. The pustular lesions were almost cleared, remaining as flat erythematous plaques (e), (f) Clinical resolution after 2 weeks of secukinumab treatment. Only residual erythematous patches were noted

(Fig. 1c-d). For financial reasons, two additional weekly doses of 150 mg secukinumab were administered instead of the standard dose of 300 mg weekly. By the end of the second week, the rash was almost completely cleared (Fig. 1e-f); therefore, the treatment was then discontinued. Unfortunately, the disease recurred at a GA of 35 weeks. Weekly doses of 150 mg secukinumab were then administered for three weeks, followed by oral ciclosporin (3 mg/kg/day), with a satisfactory response. The patient eventually delivered a full-term healthy boy with a body weight of 2,720 gm. Breastfeeding was not allowed during the postpartum period due to the ciclosporin treatment.

DISCUSSION

In the past, systemic corticosteroids and ciclosporin were the optimal treatments of GPP during pregnancy; however, regarding potential long-term adverse effects in severe and refractory cases limited their use (3,4). Recently, there has been growing evidence of the efficacy of targeted therapies for GPP, including IL-17 inhibitors (5). These novel biologics, known as pregnancy category B drugs, are considered safe for use during pregnancy (6). In light of these efficacy and safety profiles, we considered using secukinumab in the present case. To date, there have been only a few reports of secukinumab therapy for GPP during pregnancy (7,8), but, impressively, all of them have reported a dramatic and prompt positive response, with the pustular eruptions almost completely cleared within two weeks after the first injection, a result which is concordant with that of our case, even with a lower-dose prescription. Regarding the safety profile in terms of fetal health, one case reported a successful delivery of healthy baby (4), whereas another stated that the intrauterine death was presumed to be from long-standing uncontrolled GPP (8). The healthy offspring in the current case supports the non-teratogenic effect of secukinumab, albeit administered only during the first trimester. More evidence to confirm the efficacy and safety of secukinumab in GPP during pregnancy is needed.

CONCLUSIONS

This case study indicates that secukinumab (anti-IL-17 Ab) can be a highly effective and safe treatment for GPP during pregnancy. In refractory cases, the more rapid the initiation of treatment, the less serious the patient's complications.

ABBREVIATIONS

GA: Gestational age
GPP: Generalized pustular psoriasis
IL-17: Interleukin-17

DECLARATIONS

Ethics approval: This study was reviewed by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (study code: MED-2564-08061).

Photographic Consents and Consent to Participate: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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