Case Report

Case Report of SLE Patients with Cryptococcosis in Nongkhai Hospital

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Background: Cryptococcal infection, especially cryptococcal meningitis, is the most common cause of central nervous system (CNS) infection with a high mortality rate in patients with systemic lupus erythematosus (SLE). The clinical features of cryptococcal meningitis may be non-specific, which may lead to miss or delay diagnosis and treatment.

Objective: To collect the case series of SLE patients with cryptococcosis treated in Nongkhai Hospital between 2013 and 2021 and compared it with other studies.

Materials and Methods: The medical records of SLE patients (ICD-10 M320-M329) with cryptococcal infection (ICD-10 B450-B459) treated in Nongkhai Hospital between 2013 and 2021 were reviewed and collected onto a medical record form. The following information were obtained, gender, occupation, age at SLE diagnosis, age of onset, duration of disease, comorbid or risks, previous infection, SLE disease activity, glucocorticoids, and immunosuppressors administered before or at infection diagnosis, cryptococcosis clinical manifestations, laboratory data, Cerebrospinal fluid (CSF) findings, antifungal agents used, and outcomes.

Results: Six hundred thirty-six patients with SLE were identified and six patients developed cryptococcosis. Five patients had cryptococcal meningitis and one patient had cryptococcocemia. Fever and headache were the symptoms of all patients. CSF cryptococcal antigen was positive in five patients. Antifungal therapy was initiated as soon as the diagnosis was confirmed in all patients. Five patients (83.3%) recovered completely, and one patient was against the advice.

Conclusion: The present study suggested that SLE patients presenting with fever and headache along with a history of moderate to high dose steroids and immunosuppressants administration should always be suspected of cryptococcal infection and cryptococcal meningitis. Meanwhile, CSF cryptococcal antigens are the effective screening tools to establish an early diagnosis. Accordingly, early appropriate treatment is crucial for a favorable outcome.

Keywords: Cryptococcal infection; Cryptococcosis; Cryptococcal meningitis; SLE; Lupus

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Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production of pathogenic autoantibodies, leading to uncontrolled inflammatory response, heterogeneous signs and symptoms, unpredictable course, and flares[1,2]. Despite increased awareness and improved management in the last two decades, infections remain a major cause of morbidity, mortality, and hospitalization in patients with SLE[2-6]. The Euro Lupus Cohort Study as well as other studies found that approximately 50% of hospitalized SLE patients have infections throughout the disease. The mortality rate from SLE was five times higher than the general population. Thirty-six percent of SLE patients developed an infection during follow-up, and approximately 30% of deaths were related to infections during the five-year-follow-up[6-8]. Furthermore, infections in SLE patients can be difficult to distinguish from disease flare-ups while immunosuppressive drugs can change the clinical manifestation of infection. Together, these latter factors may lead to delay diagnosis[8]. Cryptococcal infection (cryptococcosis) is caused by *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*), which are responsible for a broad range of infections involving the central nervous system (CNS), lung, blood, skin, skeletal system, and prostate. However, pulmonary and CNS diseases are the most common presentations of cryptococcosis, with cryptococcal meningitis being the most frequent and serious manifestation. Cryptococcal meningitis

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Table 1. Baseline characteristics of SLE patients with cryptococcosis in Nongkhai Hospital

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Male	Female	Female	Female	Female
Occupation	Students	Employee	Students	Students	Students	Students
Age at SLE diagnosis (year)	19	42	16	22	17	17
Age of onset (year)	20	43	18	23	19	21
Duration of disease (year)	1	1	2	1	2	4
Antinuclear antibody (ANA)	1:320 Homogeneous	1:1,280 Homogeneous, coarse speckle	1:1,280 Homogeneous	1:5,120 Coarse speckle	1:320 Homogeneous	1:1,280 Coarse speckle
Anti-double strand DNA (anti-ds DNA)	NA	Positive	NA	Positive	Negative	Positive
Comorbid/risks	None	Primary pulmonary hypertension, fatty liver	None	Chronic hepatitis B viral infection	Acute hepatitis E, fatty liver, dyslipidemia	Hypertension, dyslipidemia
Previous infection	Urinary tract infection, pneumocystis pneumonia, pulmonary TB	Salmonella group D septicemia	No	*Streptococcal pneumoniae* septicemia, necrotizing fasciitis at left thigh	*Escherichia coli* septicemia	Abscess at left knee
Prednisolone (mg/day)	30	30	30	10	20	20
Immunosuppressive drugs	No	No	AZA	MMF	No	MMF
Hydroxychloroquine	Yes	Yes	Yes	Yes	Yes	Yes

SLE=systemic lupus erythematosus; TB=tuberculosis; NA=not available

is the most common cause of CNS infection with a high mortality rate in patients with SLE. The clinical features of cryptococcal meningitis may be non-specific, which may lead to a missed or delayed diagnosis and treatment[9-21]. Because of the above reasons, the authors collected case series of SLE patients with cryptococcosis, which is a rare condition difficult to diagnose with a high morbidity and mortality rate, in Nongkhai Hospital between 2013 and 2021 and compared those with other studies. The physicians may apply the results of the present study for diagnostic and treatment planning in Nongkhai Hospital.

Materials and Methods

The present case report was a retrospective study. The medical records of SLE patients (ICD-10 M320-M329) with cryptococcal infection (ICD-10 B450-B459) treated in Nongkhai Hospital between 2013 and 2021 were reviewed and collected onto a medical record form. The following information were obtained and included gender, occupation, age at SLE diagnosis, age of onset, duration of disease, comorbid or risks, previous infection, SLE disease activity, glucocorticoids, and immunosuppressors administered before or at infection diagnosis, cryptococcosis clinical manifestations, laboratory data, Cerebrospinal fluid (CSF) findings, antifungal agents used, and outcomes. Cryptococcocemia was defined as serum cryptococcal antigen positive or fungal hemoculture positive for *C. neoformans* or *C. gattii*. Cryptococcal meningitis was defined as CSF cryptococcal antigen positive or CSF culture positive for *C. neoformans* or *C. gattii*.

Results

Between 2013 and 2021, 636 patients with SLE were identified. Of the 636 patients, six patients developed cryptococcosis. Five patients were female (83.3%), with a mean age (standard deviation) of 22.2 years (4.1) at SLE diagnosis, and 24.2 years (3.8) at the time of cryptococcosis, with a mean disease duration of 1.8 years (0.5). Most of them were students. Only two patients had no underlying diseases. Five of the six patients (83.3%) had previous infections including bacterial, fungal, and mycobacterial infections. All these patients were receiving hydroxychloroquine (HCQ) and prednisone with a mean dose of 23.3 (3.3) mg/day before the onset of cryptococcal infection. There was concomitant use of immunosuppressants in three patients, including azathioprine (AZA) and mycophenolate mofetil (MMF). Characteristics of patients with cryptococcosis are shown in Table 1.

In the present study, five patients had cryptococcal meningitis and one patient had cryptococcocemia. The symptoms of all the patients included fever and headache, followed by altered mental status, nausea, vomiting, blurred vision, and seizure. On neurological

Table 2. Clinical symptoms and laboratory data of SLE patients with cryptococcal infection

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Onset of symptoms (day)	14	3	2	2	3	3
Signs & symptoms						
Fever	Yes	Yes	Yes	Yes	Yes	Yes
Headache	Yes	Yes	Yes	Yes	Yes	Yes
Nausea/vomiting	Yes	Yes	No	Yes	No	Yes
Blurred vision	No	Yes	No	Yes	No	No
Alteration of consciousness	Yes	No	No	No	Yes	Yes
Seizure	No	No	No	No	Yes	No
BT (°C)	37.0	37.9	37.9	37.8	38.3	38.6
Stiff neck	Negative	Negative	Negative	Negative	Positive	Positive
Papilledema	No	No	No	Yes	No	No
Cranial nerve VI palsy	No	No	No	Yes	No	No
CSF examination						
Open pressure	NA	22	NA	40	15	23
WBCs (cells/mm^3)	NA	376	NA	50	21	1
PMN/L%	NA/NA	5/94	NA/NA	52/48	67/33	0/0
Protein (g/L)	NA	140	NA	115	173	37
Glucose (mg/dL)	NA	20	NA	15	26	81
India ink	NA	Negative	NA	Negative	Negative	Negative
Cryptococcal Antigen	>1:32	>1:32	NA	>1:32	>1:32	1:2
Culture	NA	*C. neoformans*	NA	*C. neoformans*	*C. neoformans*	NG
Serum cryptococcal antigen	NA	NA	>1:16	NA	Negative	>1:32
Hemoculture for fungus	NA	No growth	No growth	No growth	No growth	*C. neoformans*
Blood test at the onset						
Glucose (mg/dL)	NA	135	NA	103	108	145
WBCs (cells/mm^3)	5,390	6,540	16,350	13,170	3,490	9,310
PMN/L (%)	56.0/33.4	91.0/4.9	87.7/9.2	91.9/6.2	79.8/11.5	84.1/8.3
Lymphocyte (cells/mm^3)	1,800	320	1,504	816	401	772
Hb/DCT/ICT	9.9/NA/NA	9.5/1+/Neg	8.4/Neg/Neg	12.7/Neg/Neg	10.4/2+/1+	9.9/Neg/Neg
PLT	238,000	85,000	54,000	446,000	262,000	166,000
Cr (GFR)	0.78 (94.20)	3.45 (20.45)	1.38 (55.50)	0.67 (124.30)	0.23 (181.70)	0.76 (112.50)
Albumin (mg/dL)	3.1	1.8	2.6	1.8	2.6	3.0
AST/ALT (U/L)	23/24	66/27	51/19	25/13	127/141	22/48
Urine examination						
Albumin	Negative	4+	4+	4+	Negative	3+
24 hours protein (mg)	NA	7,149	4,190	1,782	288	5,270
Disease active (organs)	No	Lupus nephritis Hematological	Lupus nephritis Hematological Serositis	Lupus nephritis Hematological Serositis	Hematological	Lupus nephritis
Treatment						
Induction (2 weeks)	Amphotericin B	Amphotericin B + fluconazole 800 mg/day	Amphotericin B	Amphotericin B	Amphotericin B + fluconazole 800 mg/day	Amphotericin B + fluconazole 800 mg/day
Consolidation (10 weeks)	Fluconazole 400 mg/day	Fluconazole 400 mg/day	Fluconazole 400 mg/day	Fluconazole 800 mg/day	NA	Fluconazole 400 mg/day
Maintenance (lifelong)	Fluconazole 400 mg/week	Fluconazole 400 mg/week	NA	NA	NA	NA
CT brain	Normal	Normal	NA	Normal	Brain atrophy	NA
Complications	No	HT, CHF	HT, AKI	HT, AKI	HAP, ARDS	AKI, UGIB
Status	Alive	Alive	Alive	Alive	Against advice	Alive

PMN=polymorphonuclear; L=lymphocyte; WBCs=white blood cells; Hb=hemoglobin; DCT=direct Coomb's test; ICT=indirect Coomb's test; PLT=platelet; Cr=creatinine; GFR=glomerular filtration rate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HT=hypertension; CHF=congestive heart failure; AKI=acute kidney injury; HAP=hospital-acquired pneumonia; ARDS=adult respiratory distress syndrome; IVMP=intravenous methylprednisolone; CT=computed tomography; NA=not available

examination, four of the six patients displayed normal characteristics, including no papilledema or stiff neck. The average time from the initial symptoms to diagnosis was 4.5 days (1.9) (Table 2). Only one patient had hemolytic anemia. Lymphopenia of less than 1,500 cells/mm³ associated with disease activity was observed in four patients. Platelets were decreased in two patients. Leukocytes were decreased, normal, or even slightly increased in these patients. The mean opening pressure of the lumbar puncture was 25.0 (5.3) cmH_2O. CSF examination showed a median (IQR) WBC of 112.0 (6.0 to 294.5) cells/mm³, a median protein level of 116.3 (56.5 to 164.8) mg/dL, and a median glucose level of 35.5 (16.3 to 67.3) mg/dL. India-ink staining of CSF for cryptococcal organisms was negative in four patients and no data in two patients, whereas CSF cryptococcal antigen was positive in five patients and no data in one patient. The CSF culture was positive for *C. neoformans* in three of the six patients. While serum cryptococcal antigen was positive in two of the six patients, fungal hemoculture revealed *C. neoformans* in only one patient. Disease active including lupus nephritis, hematological system, and serositis was observed in 83.3% (Table 2). Antifungal therapy was initiated as soon as the diagnosis was confirmed. Three patients were initially treated with amphotericin B 0.7 to 1 mg/kg per day concomitant use of fluconazole 800 mg/day, while others were treated with amphotericin B 0.7 to 1 mg/kg per day for about two weeks during the induction phase. Oral fluconazole 400 to 800 mg/day was continued in the consolidation phase for about ten weeks in five patients and no data in one patient. Finally, oral fluconazole 400 mg/week was continued lifelong as a maintenance phase for two patients and no data in four patients. Five patients (83.3%) recovered completely, and one patient was against the advice (Table 2).

Discussion

CNS infection is a rare disease in 1.4% to 3% of all infections in SLE. Whereas, cryptococcal meningitis is the most common cause of CNS infection with a high mortality rate of 25% to 40% in patients with SLE[12,15,22]. From the present study, six patients developed cryptococcosis. Of these six patients, five patients had cryptococcal meningitis and one patient had cryptococcocemia. Of the six cases, 83.3% of patients were female with a mean age of 22.2 years (4.1) at SLE diagnosis, which was corresponding to the previous studies[9,10,13,16-21]. All these patients were receiving prednisone with a mean dose of 23.3 (3.3) mg/day, and prednisolone in combination with immunosuppressants in three patients, including AZA and MMF. Consistent with the previous studies, the major risk factors for CNS infection and cryptococcal meningitis in SLE patients are 1) active disease or higher SLEDAI, 2) lupus nephritis or proteinuria, 3) low complement level, 4) lymphopenia, or decline in CD_4+ T cells, 5) moderate to high dose steroids, and 6) previous immunosuppressive drugs such as cyclophosphamide and AZA[2,10,11,17,19,23,24]. In this context, all the patients had fever and headache, followed by altered mental status, nausea, vomiting, blurred vision, and seizure. Four of the six patients displayed normal neurological examination, including no papilledema or stiff neck. These data suggested that the diagnosis of cryptococcal meningitis in patients with SLE cannot be based merely on clinical manifestations and is difficult to discriminate from Neuropsychiatric systemic lupus erythematosus (NPSLE), which is the same as in the previous studies[9,10,13,16-21]. In addition, the mean opening pressure of lumbar puncture was 25.0 (5.3) cmH_2O, which was slightly high and consistent with the previous study which found that the opening pressure in the CSF may be elevated with a pressure of at least 18 cm H_2O occurring in more than 60% of patients[25]. CSF examination showed a slight increase in WBC, high protein level, and low sugar that similar to other CNS infections[26]. India-ink staining of CSF for cryptococcal organisms was negative in four patients, whereas CSF cryptococcal antigen was positive in five patients. The CSF culture was positive for *C. neoformans* in three of the six patients, serum cryptococcal antigen was positive in two of the six patients, and fungal hemoculture revealed *C. neoformans* in only one patient. Computed tomography (CT) brain scans were performed in four patients and results showed no intracranial space-occupying lesions or abnormal meningeal enhancement in three patients and brain atrophy in one patient. Therefore, these results suggest that CSF cryptococcal antigens are the effective screening tools to establish an early diagnosis, which is similar to the study of Sivalingam et al[20]. Five of the six patients had a favorable response to induction therapy of amphotericin B 0.7 to 1 mg/kg per day or amphotericin B 0.7 to 1 mg/kg per day combined with fluconazole 800 mg/day about two weeks as there was no flucytosine in Nongkhai Hospital, followed by long-term consolidation therapy with fluconazole 400 to 800 mg/day after about ten weeks. This was consistent with recommended treatments in the previous

Table 3. Case report of cryptococcosis in SLE patients[9,10,13,16-21]

Authors (year)	Age/ sex	Steroid	Immuno-suppression	Diagnosis	Treatment			Outcomes
					Induction	Consolidation	Maintenance	
Zimmermann, et al. (1992)[13]	21/F	Prednisolone 20 mg/day	No	Meningitis	Amphotericin B + flucytosine 6 weeks	No	No	Alive
	22/F	Prednisolone 10 mg/day	No	Meningitis	Amphotericin B + flucytosine 3 weeks	No	No	Alive
Hung, et al. (2005)[18]	25/M	Prednisolone	Endoxan	Meningitis	Amphotericin + fluconazole 6.2±1.8 weeks	Fluconazole 17.6±5.5 weeks	No	Death
	17/F	Prednisolone	No	Meningitis			No	Alive
	19/F	Prednisolone	No	Meningitis			No	Death
	42/F	Prednisolone	AZA	Meningitis			No	Death
	37/M	Prednisolone	No	Meningitis			No	Alive
	56/F	No	No	Meningitis			No	Death
	19/F	Prednisolone	AZA, Endoxan	Meningitis			No	Alive
	17/F	Prednisolone	No	Meningitis			No	Alive
	65/F	Prednisolone	No	Meningitis			No	Relapse
	19/F	Prednisolone	No	Meningitis			No	Death
Kwok, et al. (2008)[21]	32/M	Deflazacort 24 mg/day	MMF	Meningitis	Amphotericin B + flucytosine 3 weeks	Fluconazole 8 weeks	No	Alive
Vargas, et al. (2009)[17]	25/F	NA	NA	Meningitis	Amphotericin B	Fluconazole	NA	Alive
	37/F	NA	NA	Meningitis			NA	Death
	20/F	NA	NA	Meningitis			NA	Death
	18/F	NA	NA	Meningitis			NA	Death
	40/F	NA	NA	Meningitis			NA	Death
	16/F	NA	NA	Meningitis			NA	Sequelae
	22/F	NA	NA	Meningitis			NA	Alive
Matsumura, et al. (2011)[19]	47/M	Prednisolone 30 mg/day	No	Meningitis	Fluconazole 800 mg/day + flucytosine 8 weeks	Fluconazole 400 mg/day + flucytosine 12 weeks	Fluconazole 400 mg/day 12 months	Alive
Sivalingam, et al. (2012)[20]	21/M	Prednisolone 60 mg/day	CTX	Meningitis	Lipid amphotericin B + flucytosine 6 weeks	No	No	Alive
Zhong, et al. (2015)[9]	31/F	Prednisolone 5 mg/day	AZA	Meningitis	Fluconazole + flucytosine	NA	Fluconazole 200 mg/day lifelong	Satisfied
	32/F	Prednisolone 15 mg/day	AZA	Meningitis	Lipid amphotericin B, amphotericin B, flucytosine, fluconazole	NA		Satisfied
	42/F	IVMP 25 mg/day	NO	Meningitis	Fluconazole + flucytosine	NA		Unsatisfied
	24/F	IVMP 45 mg/day	CTX	Meningitis	Fluconazole + flucytosine, amphotericin B	NA		Satisfied
	20/F	Prednisolone 15 mg/day	MTX, AZA	Meningitis	Amphotericin B + flucytosine, fluconazole	NA		Satisfied
	14/F	IVMP 40 mg/day	MTX, AZA	Meningitis	Fluconazole + flucytosine, amphotericin B	NA		Satisfied
	24/F	IVMP 45 mg/day	CTX	Meningitis	Fluconazole + flucytosine, amphotericin B	NA		Satisfied
	20/F	Prednisolone 15 mg/day	MTX, AZA	Meningitis	Amphotericin B + flucytosine, fluconazole	NA		Satisfied
	14/F	IVMP 40 mg/day	MTX, AZA	Meningitis	Fluconazole + flucytosine, amphotericin B	NA		Satisfied

F=female; M=male; IVMP=intravenous methylprednisolone; CNS=central nervous system; NA=not available

Table 3. (continued)

Authors (year)	Age/ sex	Steroid	Immuno-suppression	Diagnosis	Treatment			Outcomes
					Induction	Consolidation	Maintenance	
Gonzalez-Duarte, et al. (2015)[10]	29/F	A mean dose of prednisolone 38.33±13 mg	A mean dose of AZA 95±37 mg	Meningitis	Amphotericin B + fluconazole 2 weeks	Fluconazole 800 mg/day 8 weeks	Fluconazole 400 mg/day 6 to 12 weeks	Sequalae
	20/M			Meningitis				Good
	28/M			Meningitis				Sequalae
	32/F			Meningitis				Good
	30/F			Meningitis				Good
	42/F			Meningitis				Sequalae
	33/F			Meningitis				Sequalae
	28/F			Meningitis				Death
See, et al. (2019)[16]	71/M	Prednisolone	No	Blood, CNS, lung, skin	Liposomal amphotericin B + flucytosine 3 weeks	NA	NA	Alive
Present study (2021)	20/F	Prednisolone 30 mg/day	No	Meningitis	Amphotericin B 2 weeks	Fluconazole 400 mg/day 10 weeks	Fluconazole 400 mg/week lifelong	Alive
	43/M	Prednisolone 30 mg/day	No	Meningitis	Amphotericin B + fluconazole 2 weeks	Fluconazole 400 mg/day 10 weeks	Fluconazole 400 mg/week lifelong	Alive
	18/F	Prednisolone 30 mg/day	AZA	Blood	Amphotericin B 2 weeks	Fluconazole 400 mg/day 10 weeks	NA	Alive
	23/F	Prednisolone 10 mg/day	MMF	Meningitis	Amphotericin B 2 weeks	Fluconazole 800 mg/day 10 weeks	NA	Alive
	19/F	Prednisolone 20 mg/day	No	Meningitis	Amphotericin B + fluconazole 2 weeks	NA	NA	Against advice
	21/F	Prednisolone 20 mg/day	MMF	Meningitis	Amphotericin B + fluconazole 2 weeks	Fluconazole 400 mg/day 10 weeks	NA	Alive

F=female; M=male; IVMP=intravenous methylprednisolone; CNS=central nervous system; NA=not available

studies[9,27-29]. In the present study, none of the patients had a relapse of cryptococcal meningitis after 1-year follow-up while receiving long-term maintenance of fluconazole therapy 400 mg/week combined with glucocorticoids and immunosuppressive agents compatible with the Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017[30]. Whereas the clinical practice guideline for the management of cryptococcal disease in non-HIV patients by the Infectious Diseases Society of America 2010[31] recommended treatments with Amphotericin B at 0.7 to 1.0 mg/kg per day IV, plus flucytosine at 100 mg/kg per day orally in four divided doses, for at least four weeks for induction therapy, followed by consolidation with fluconazole with 800 mg or 12 mg/kg, per day orally, for eight weeks. After induction and consolidation therapy, used maintenance therapy with fluconazole with 200 mg as 3 mg/kg, per day orally, for six to twelve months. To date, the information about these newer strategies for cryptococcal meningitis in non-HIV-infected and non-transplant patients remain limited, retrospective, and extrapolative. This is because there is a very heterogeneous population ranging from hosts who are normal to those with hematological malignancies and severe liver disease. Therefore, it is impossible to tailor a single regimen that fits all patients as shown in Table 3[9,10,13,16-21]. The present study has some limitations due to the small number of patients and its retrospective design, as well as, there were some missing or incomplete data. Therefore, these facts may limit the generalization of the results to other population.

Conclusion

The present study suggested that SLE patients presenting with fever and headache along with a history of moderate to high dose steroids and immunosuppressants administration should be always suspected of cryptococcal infection and cryptococcal meningitis. Meanwhile, CSF cryptococcal antigens are the effective screening tools to establish an early diagnosis. Accordingly, cryptococcal meningitis is

the most common cause of CNS infection with a high mortality rate in patients with SLE. Early appropriate treatment is crucial to a favorable outcome.

What is already known on this topic?

The clinical features of cryptococcal meningitis may be non-specific, which may lead to missing or delaying diagnosis and treatment.

What does this study add?

SLE patients presenting with fever and headache along with a history of moderate to high dose steroids and immunosuppressants administration should be always suspected of cryptococcal infection and cryptococcal meningitis. CSF cryptococcal antigens are the effective screening tools to establish an early diagnosis. Early appropriate treatment is crucial to a favorable outcome.

Ethical approval

Ethics approval was attained from The Research Ethics Committee (REC) of Nongkhai Hospital (No.22/2564).

Conflicts of interest

The authors declare no conflict of interest.

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