

Review Article



Late-Onset Granulomatous *Pneumocystis jirovecii* Pneumonia in A Renal Transplant Recipient: A Clinical Grand Round Conference Case in 2022

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ABSTRACT

Late-onset *Pneumocystis jirovecii* pneumonia (PCP) can be developed in solid organ transplant (SOT) patients. Granulomatous *P. jirovecii* pneumonia (GPCP) can occur in immunocompromised patients, but has rarely been reported in SOT recipients. The diagnosis of GPCP is difficult since the sensitivity of sputum and bronchoalveolar lavage is low and atypical patterns are shown. A 60-year-old man, who had undergone renal transplantation 24 years ago presented with nodular and patchy lung lesions. He was asymptomatic and stable. After empirical treatment with a fluoroquinolone, the condition partially resolved but relapsed 4 months later. The pulmonary nodule was resected, and GPCP was confirmed. The pathogenesis of GPCP remains unclear, but in SOT recipients presenting with an atypical lung pattern, GPCP should be considered. This case was discussed at the Grand Clinical Ground of the Korean Society of Infectious Disease conference on November 3, 2022.

Keywords: *Pneumocystis jirovecii* pneumonia; Granulomatous PCP; Solid organ transplantation

INTRODUCTION

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic fungal infection caused by *P. jirovecii* in immunocompromised individuals. The fatality rate of infection is significantly high, and without treatment,

the disease progresses rapidly in patients [1]. PCP is associated with intensified immunosuppression, including high-dose corticosteroids, which is often administered in the early period after organ transplantation [2]. Therefore, PCP prophylaxis is recommended 6 - 12 months after solid organ transplantation (SOT) [3]. The radiological

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finding of PCP infection is bilateral interstitial infiltration with ground-glass opacities (GGO). However, atypical patterns, including focal infiltrates, nodules, cystic air spaces, and pleural effusions, depending on the overall status of immunosuppression, have also been reported [4]. Herein, we report a case of late-onset asymptomatic granulomatous PCP in a patient who underwent kidney transplantation.

1. Case report

A 60-year-old kidney transplanted man who visited a nephrology clinic every 2 months was referred to an infectious disease clinic because of an asymptomatic chest X-ray abnormality. He underwent living-donor kidney transplantation 24 years previously and was on immunosuppressive therapy with tacrolimus, sirolimus, and deflazacort. He was also diagnosed with chronic kidney disease, osteoporosis, post-transplant diabetes mellitus, and dyslipidemia. Medications included calcium supplements, calcitriol, allopurinol, folic acid, ferrous sulfate, sodium bicarbonate, linagliptin, atorvastatin, and rebamipide. He had received denosumab two months prior.

He worked as a pipefitter, but quit the job a year ago and now lives in Seoul, a metropolitan city in Korea. He is an ex-smoker with no known sick contacts or contact with infectious animals. The patient did not initially complain of any symptoms on review of systems. However, upon questioning, he admitted to a slight sore throat. On physical examination, the patient was afebrile with blood pressure 90/50 mmHg, heart rate 77 beats/min,

and respiratory rate 18 breaths/min. Although oximetry was not performed, he did not present dyspnea or signs of hypoxemia on room air. He had a hemoglobin concentration of 9.7 g/dL, white blood cell count of $6,000 \times 10^3/\text{mm}^3$ (neutrophil percentage, 60.5%, and lymphocyte percentage, 26.7%), platelet count of $99 \times 10^3/\text{mm}^3$, C-reactive protein level of 0.04 mg/dL, serum creatinine level of 2.2 mg/dL, and calcium level of 7.9 mg/dL (**Table 1**).

Radiography revealed multifocal nodular or patchy opacities in the bilateral middle and lower lung lobes (**Fig. 1A**). Chest computed tomography (CT) showed multiple nodular consolidations and GGO in both lungs, suggestive of organizing pneumonia (**Fig. 1D**). Blood and sputum cultures did not reveal any organism. Multiplex real-time polymerase chain reaction (PCR) panel for bacterial pathogens causing pneumonia, acid-fast bacilli staining, Mycobacterium PCR, and cytomegalovirus (CMV) immunoglobulin M were all negative. Since he did not reveal respiratory symptoms, Pneumocystis PCR, beta-D glucan, Aspergillus galactomannan, and Legionella antigen tests were not done. Under the suspicion of atypical pneumonia, empirical antibiotic therapy with moxifloxacin was initiated for 4 weeks. After a month, the previously observed nodular consolidations and GGO partially resolved, but new nodules were observed in both lungs (**Fig. 1B** and **1E**). After four months of follow-up with chest CT and despite the absence of any other symptoms, newly appearing nodules or nodular consolidations were observed in both lungs, with a predominance in the lower lung (**Fig. 1C** for Chest X-ray; no Chest CT image provided).

The patient was admitted to the hospital and underwent F-fluorodeoxyglucose positron emission tomography/CT. The right lower lung mass showed high uptake, which was highly suggestive of malignancy (**Fig. 1F**), and multiple hypermetabolic lesions were observed (**Fig. 1G**). To identify the etiology of the lung nodule, the patient underwent wedge resection of the right lateral basal segment via video-assisted thoracic surgery.

Tissue pathology revealed intra-alveolar foamy casts and multiple granulomas with necrosis. Gomori methenamine silver staining revealed a cystic form of the organism, suggestive of PCP (**Fig. 2**). Other infectious etiologies related to granulomatous reactions were assessed, and sputum cultures for bacteria, fungi were negative. The galactomannan antigen test from serum and mycobacteria PCR test from resected tissue were also negative. Pneumocystis PCR from sputum specimen

Table 1. Laboratory data

Blood test	Initial visit	Before wedge resection	Normal range ^a
WBC, mm ³	6,000	3,800	3,700 - 9,000
Neutrophil, %	60.5	55.8	43 - 75
Lymphocyte, %	26.7	31.5	24 - 45
Monocyte, %	10.1	11.4	2 - 10
Hemoglobin, g/dL	9.7	8.6	11 - 16
Platelets, /uL	99	77	130 - 700 × 10 ³
BUN, mg/dL	37.4	29.3	7.3 - 20.5
Creatinine, mg/dL	2.2	2.23	0.49 - 0.91
AST, U/L	19	28	0 - 34
ALT, U/L	29	35	0 - 46
Calcium, mg/dL	7.9	7.4	8.6 - 10.2
Phosphate, mg/dL	2.4	1.8	2.5 - 4.5
ESR, mm/hr	22	11	1 - 20
CRP, mg/dL	0.04	0.04	0 - 0.5
Parathyroid hormone	34.21	18.9	15 - 65
25 (OH) Vitamin D	41.26	Ns	Ns

^aNormal range is based on the suggested value in the hospital. Ns, non specified.

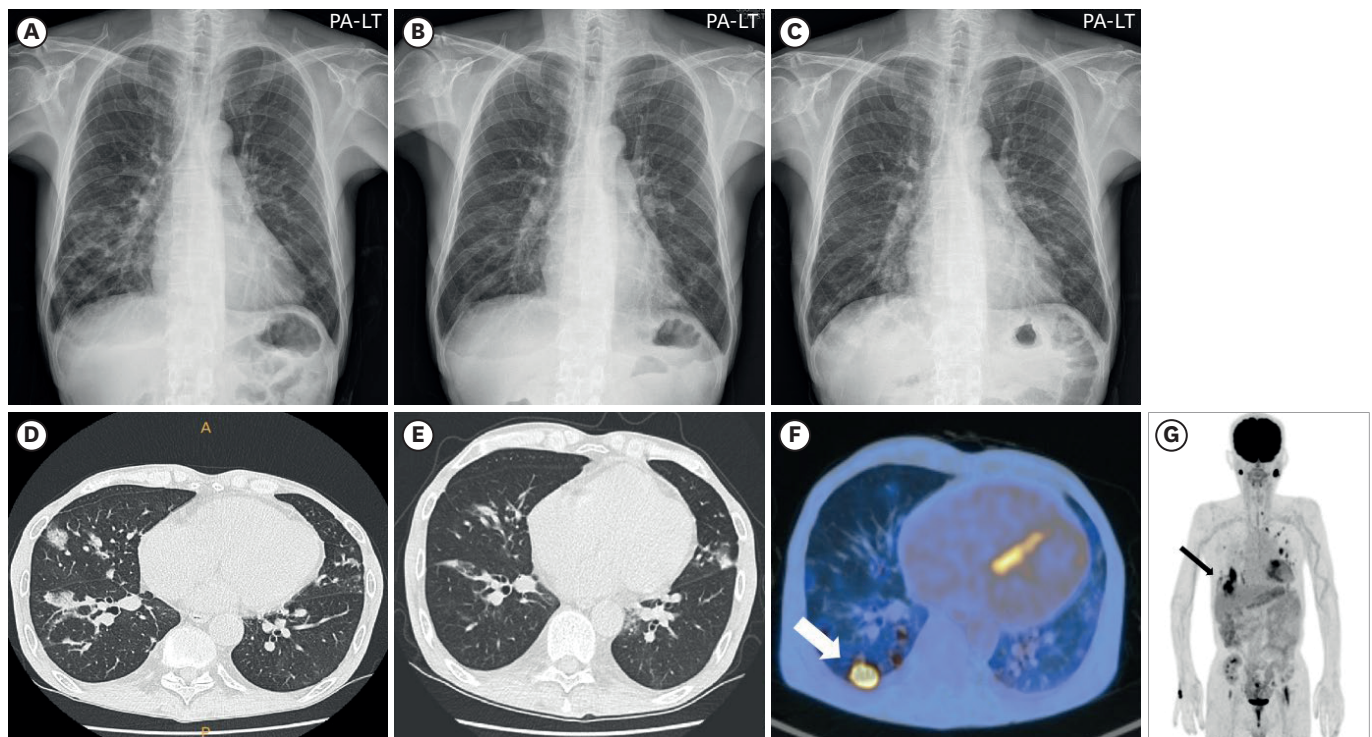


Figure 1. Radiologic findings with granulomatous *Pneumocystis jirovecii* pneumonia (PCP). (A) Chest X-ray (CXR) showing multifocal opacities in bilateral lungs, (B) Follow-up CXR after empirical antibiotic treatment, (C) CXR 4 months after the treatment, (D) Chest computed tomography (CT) demonstrating multiple nodular consolidations, (E) Follow-up CT showing resolution of initial nodules, but the appearance of new nodules, (F) Follow-up CT revealing newly appearing numerous nodules in both lungs with relatively predominance in the lower lungs, (G, H) Positron emission tomography-CT (PET-CT) highlighting hypermetabolic lesions in both lungs, with notably high uptake in a right lower lung mass.

A black arrow in Figure 1G and a white arrow in Figure 1H indicate the lung mass where the histopathologic analyses were performed.

was positive. After being diagnosed with granulomatous PCP (GPCP), the patient was started on trimethoprim-sulfamethoxazole (TMP/SMX) as anti-PCP treatment. Due to acute kidney injury, the treatment was switched to clindamycin and primaquine for 7 days. However, he ultimately completed his treatment with TMP/SMX for a total 21 days. The lung lesions improved, and the patient maintained a healthy status in the outpatient clinic.

2. Ethics statement

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent form is available for review upon request.

3. Minutes of the Clinical Grand Rounds on November 3, 2022

This case was discussed at the Grand Clinical Ground of the Korean Society of Infectious Disease (KSID) conference in 2022. The discussion began with the moderator's inquiry to the panel about the pathogen causing the disease. Subsequently, the audience engaged

in a free discussion on the implications of the case. The participants in the discussion are shown in Table 2, and the following are the minutes of the discussion:

(1) What is the impression of pathogen causing pneumonia in this case?

Dong-Gun Lee: The patient was receiving immunosuppressants and presented with localized pneumonia with nodular and diffuse patterns. Microorganisms, such as fungi or *Nocardia*, can be considered due to the dominant presence of nodules.

Table 2. Participants in the clinical grand round discussion

Moderator
Sang-Oh Lee (University of Ulsan College of Medicine)
Case presenter
Yae Jee Baek (Soonchunhyang University College of Medicine)
Panelist
Dong-Gun Lee (College of Medicine, The Catholic University of Korea)
Young Hwa Choi (Ajou University School of Medicine)
Shin-Woo Kim (Kyungpook National University College of Medicine)
Audience
Sung-Han Kim (University of Ulsan College of Medicine)
Jun Yong Choi (Yonsei University College of Medicine)

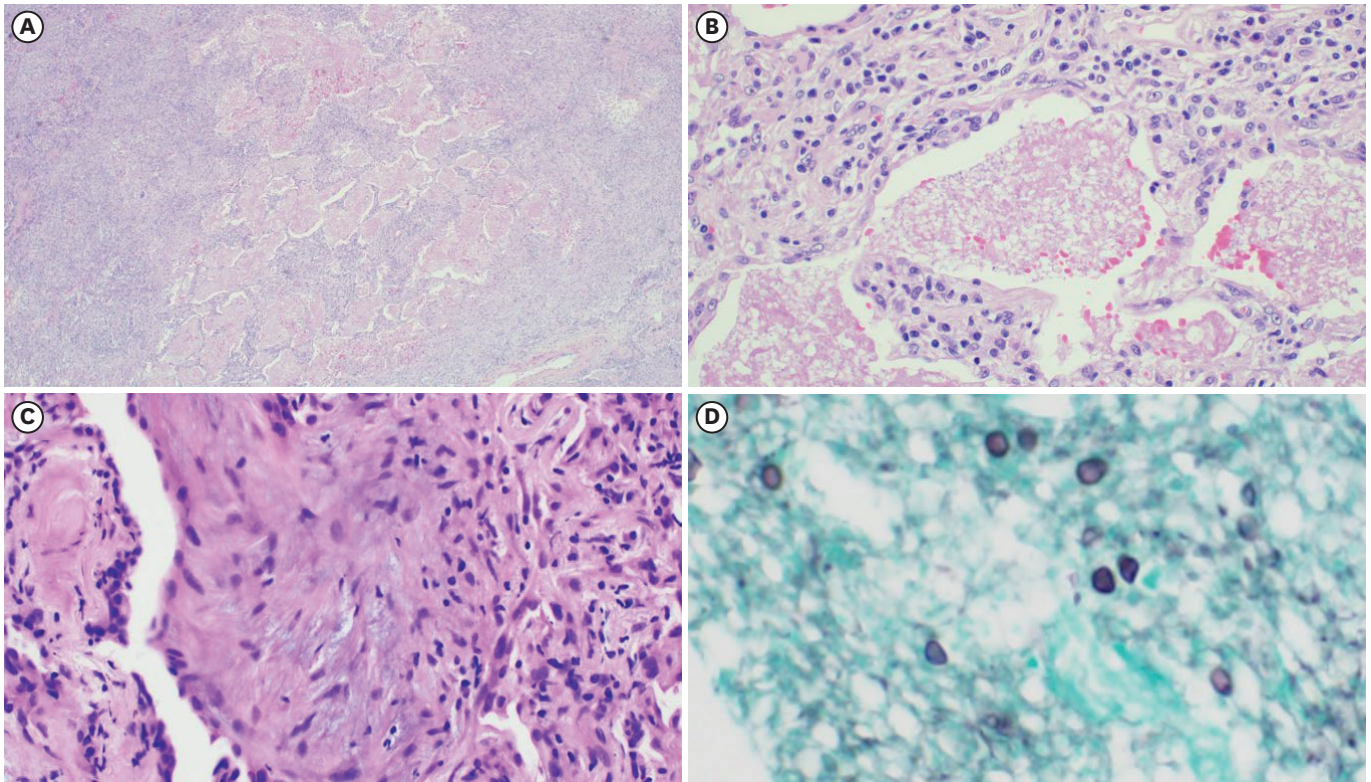


Figure 2. Histopathologic features of granulomatous PCP. (A, B) Intra-alveolar foamy alveolar casts (hematoxylin and eosin stain (H&E), $\times 40$, $\times 200$), (C) Multiple granulomas with necrosis (H&E, $\times 200$), (D) Cystic form of organism in the intra-alveolar space (Gomori methenamine silver stain, $\times 400$).

Viruses or *Pneumocystis pneumonia* could be responsible for the diffuse radiological patterns. Procedures such as bronchoscopy and percutaneous biopsy of lung lesions can be performed for diagnosis.

Young Hwa Choi: Because his occupation was a pipefitter, *Legionella* should also be included in the differential diagnosis, as the microorganism causes various patterns of occupational pneumonia.

Sin-Woo Kim: Considering host factors, atypical pathogens, such as *Nocardia*, *Cryptococcus*, and endemic fungi, can be traditionally considered.

Sung-Han Kim: Asymptomatic pneumonia is not commonly caused by *Aspergillus* species or PCP. *Legionella* or toxocariasis can be considered.

(2) What is the implication of this case?

Dong-Gun Lee: Compromised host with pneumonia requires prompt empirical intervention for diagnosis and treatment to improve survival.

Sung-Han Kim: I have seen only a few cases of PCP within 2

years of solid organ transplantation. I encountered nodular PCP in an acquired immunodeficiency syndrome (AIDS) patient, but nodular PCP during an unusual timeline after transplantation was quite unexpected and interesting.

Sang-Oh Lee: *Pneumocystis* prophylaxis prevents PCP. However, after the prophylaxis is discontinued, the disease can occur in immunocompromised hosts.

Jun Yong Choi: PCP in AIDS patients develops with various manifestations, such as nodules, cavities, or pneumothorax. In addition, worsening of existing PCP can be associated with immune reconstitution inflammatory syndrome (IRIS).

DISCUSSION

We report a case of late-onset GPCP in a patient who underwent kidney transplantation. Although its frequency has markedly decreased with widespread PCP prophylaxis, PCP can occur a year after SOT on immunosuppressants. The incidence of PCP is still 2.5 - 4.5% in SOT recipients [5, 6]. The risk of PCP after transplantation without PCP

prophylaxis can increase, particularly in SOT recipients with allogeneic rejection, CMV infection, and lymphopenia [2]. In a retrospective study, age (adjusted odds ratio [OR] 3.7, 95% confidence interval [CI]: 1.3 – 10.4), CMV infection (OR: 5.2, 95% CI: 1.8 – 14.7) and total lymphocyte count below 350 (OR: 3.9, 95% CI: 1.4 – 10.7) were found to be independently associated with late-onset PCP [7].

Although up to 65% of healthy adults may be colonized by the relatively ubiquitous *P. jirovecii* [8], the fungus can cause a severe form of pneumonia known as PCP in immunocompromised individuals. However, clinical manifestations can vary depending on the underlying disease. Patients with AIDS develop a more gradual onset of dyspnea and dry cough in PCP, while rapid progression and higher death rates have been noted in non-AIDS patients than in AIDS patients [9]. The patient in this case presented with mild, insidious symptoms. His nodular lung patterns, which did not respond to antibiotics, migrated in both lungs, complicating the diagnosis. Due to the atypical findings, PCP was not the initial suspicion, and therefore tests specific to it were not conducted. However, given the similarities in clinical symptoms and the nodular pattern, it is assumed that the condition was caused by the same microorganism. In this context, GPCP occurring after SOT was not fatal. According to a cohort study in France, SOT was an independent variable associated with low mortality in patients with PCP compared to other causes of immunodeficiency (OR 0.08; 95% CI: 0.02 – 0.31) [10]. However, according to a cohort study in Korea, SOT was frequently observed in the group that failed first-line

treatment [11]. Another study indicated that a low CD4+ lymphocyte count was associated with mortality in SOT patients with PCP, while patients presenting with the atypical pattern of PCP were less likely to experience mortality [12]. Therefore, the mechanisms and prognosis of PCP in patients with SOT should be further investigated.

A smaller subset of patients with PCP elicits a granulomatous response to *P. jirovecii* infection. GPCP is diagnosed when *Pneumocystis* organisms are present inside a granuloma, in the absence of other pathogens. Granuloma formation occurs in approximately 5% of PCP infections [13]. The granulomatous response is often represented as multiple distributed nodules on chest imaging, but different patterns including masses, diffuse infiltrates were also reported [14]. In addition, unlike classic PCP which is abundantly found within the alveoli, the diagnostic sensitivity of sputum and bronchoalveolar lavage for GPCP is low, possibly due to PCP encapsulation by the granuloma [15]. Therefore, invasive biopsy, including open surgery, is frequently performed.

There have been several reports of GPCP in patients with AIDS. Some patients with AIDS develop GPCP with an atypical presentation on PCP prophylaxis [16, 17], whereas others are diagnosed with IRIS and consequently treated with corticosteroids [18]. There has been a case report of an AIDS patient who was diagnosed with nodular GPCP on their first visit without having started any medications [19]. A few cases of GPCP have been reported in patients with hematological malignancies.

Table 3. Summary of reported cases of granulomatous *Pneumocystis Jirovecii* pneumonia (PCP) in solid organ transplanted patients

Year	Age/ Sex	SOT	Granulomatous PCP onset after transplantation	Immunosup- pressant	Symptoms	Radiological findings	PCP PCR	Confirmation	Hypercalcemia	Reference
1975	F/37	KT	7 months, rejection, no prophylaxis	Azathioprine, prednisone	Fever, yellow sputum	Patchy interstitial infiltration	Not done	Open lung biopsy, non-caseating epithelioid-cell granuloma, GMS+	Not described	[30]
2014	F/54	KT	2 years	Prednisolone, tacrolimus, MMF	Dry cough, fever	Ground glass opacities	Positive	Transbronchial biopsy granulomatous with exudates, GMS +	Yes	[22]
2019	M/53	KT	13 years, no rejection	Prednisolone, cyclosporine, MMF	Fatigue, dyspnea	Diffuse patchy ground glass and reticular opacities	Negative	Transbronchial biopsy, Granulomatous infiltration and giant cells, GMS +	Yes	[27]
Present case	M/60	KT	24 years, rejection	Tacrolimus, sirolimus, deflazacort	Sore throat	Multiple nodules	Positive	Open lung biopsy, Granuloma with necrosis, GMS +	No	

SOT, solid organ transplant; PCR, polymerase chain reaction; bronchoalveolar lavage; F, female; KT, kidney transplantation; GMS, Gomori methenamine silver stain; M, male; MMF, mycophenolic acid.

Some patients developed fever with progressive dyspnea [20-22], whereas others were asymptomatic [23-25]. Solitary or multiple nodules are observed in most cases. Granulomatous PCP in SOT recipients have rarely been reported. A summary of reported cases of granulomatous PCP in patients with transplants is presented in **Table 3**. To our knowledge, this is the fourth report of a granulomatous reaction to a PCP infection.

Some researchers have postulated that the granulomatous response results from a more robust immune status [26]. The increased number of CD4+ T cells following reduced immunosuppression may have facilitated a granulomatous response [22]. Asymptomatic nodular GPCP has been reported in an immunocompetent person [27]; therefore, a T-cell immune response may be necessary in the morphogenesis of GPCP. However, it is also hypothesized that the secretion of tumor necrosis factor- α by histiocytic cells could affect the granulomatous reaction of chronic *P. jirovecii* infection [25]. In the formation of granuloma, persistent antigens can induce macrophage activation, producing granulomas, while CD4+ T cells protect against infectious granulomas [28]. Because the enhancement of macrophage microbial capacity cannot compensate for CD4+ T cell deficiency, GPCP could develop in immunocompromised individuals. The pathogenesis of GPCP with respect to cellular immunity remains unclear.

Cases of Pneumocystis-induced hypercalcemia have been reported in renal transplant recipients [29]. According to a study of PCP cases among kidney transplant recipients, hypercalcemia was observed in 37% of PCP patients with high 1,25-(OH) $_2$ vitamin D and low parathyroid hormone (PTH), suggesting a granuloma-mediated mechanism [30]. This resolved after successful treatment of PCP pneumonia [31]. Hypercalcemia has also been reported in patients with PCP infection who have undergone liver transplant or have AIDS [32, 33]. PTH-independent hypercalcemia can occur after ectopic 1,25-(OH) $_2$ vitamin D production caused by activated macrophages in a granuloma or macrophage dysfunction [34]. Although not all PCP infections present with granulomas, the pathogenesis might be shared through macrophage activation against *P. jirovecii*. In our patient, the calcium level was normal, which might have been affected by osteoporosis medications, including calcitriol.

In conclusion, the diagnosis of GPCP can be challenging due to atypical manifestations on chest imaging and the insensitivity of microbiologic diagnostic modalities.

However, in SOT recipients with manifestations of chronic or relapsing atypical pneumonia with or without hypercalcemia, more vigilant efforts for histological diagnosis should be considered to avoid missing GPCP.

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Conflict of interest

No conflict of Interest.

Author Contributions

Conceptualization: KTH. Data curation: BYJ, NH, KTH. Formal analysis: BYJ, KK, NB. Methodology: BYJ, KK, JJ, LEJ, NH. Writing - original draft: BYJ. Writing - review & editing: LEJ, NH, KTH.

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