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Association of immune-related adverse events with COVID-19 pneumonia in lung cancer patients receiving immune checkpoint inhibitors: a cross-sectional study in China

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Abstract

Background Immune checkpoint inhibitors (ICIs) are commonly used to treat lung cancer patients, but their use can lead to immune-related adverse events (irAEs), which pose a challenge for treatment strategies. The impact of irAEs on the incidence of COVID-19 pneumonia in lung cancer patients during the ongoing COVID-19 pandemic is unclear. This study aims to investigate the association between irAEs and COVID-19 pneumonia in lung cancer patients receiving ICIs.

Methods We conducted a cross-sectional study of lung cancer patients who received ICIs and were infected with COVID-19 due to the Omicron variant between December 2022 and February 2023 in China. We collected data on irAEs and COVID-19 outcomes. Logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between irAEs and the incidence of COVID-19 pneumonia.

Results A total of 193 patients were enrolled, with 72 patients (37.30%) in the irAEs group and 121 patients (62.70%) in the non-irAEs group. Twenty-six patients (13.47%) developed COVID-19 pneumonia and 6 patients (3.11%) progressed to severe cases after COVID-19 infection. Multivariate logistic regression showed that the lung cancer patients who experienced irAEs was significantly associated with a higher incidence rate of COVID-19 pneumonia (OR = 9.56, 95%CI: 2.21–41.33; P = 0.0025).

Conclusion Our study suggests that lung cancer patients receiving ICIs and experiencing irAEs may have a higher risk of developing COVID-19 pneumonia due to the Omicron variant. Therefore, close monitoring of these patients during the COVID-19 pandemic is necessary to mitigate this risk.

Keywords COVID-19 Pneumonia, Immune checkpoint inhibitors, irAEs, Lung Cancer, Omicron variants

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Background

Immune checkpoint inhibitors (ICIs) are commonly used to treat lung cancer, either alone or in combination with chemotherapy and radiotherapy [1, 2]. While ICIs enhance immune function against tumor cells [3, 4], they also carry the risk of immune-related adverse events (irAEs) affecting multiple organs through immunological mechanisms [5]. The incidence of these events varies based on ICI type, dosage, and treatment duration. Immunotherapy-related pneumonitis is a common irAE affecting up to 3%~19% of lung cancer patients treated with ICIs [6–8].

The COVID-19 pandemic has created significant disruptions in healthcare and social and economic systems worldwide [9]. Cancer patients face heightened risks of hospitalization and mortality from the disease due to age-related declines in immune function and immunosuppression from chemotherapy and radiation therapy [10–13]. IrAEs may contribute to these risks by inducing cytokine dysregulation, which can parallel the cytokine storm observed in some cases of COVID-19-induced acute respiratory distress syndrome [14–17]. Previous studies suggest that COVID-19 vaccines are safe for cancer patients receiving anti-PD-1 treatment and that ICIs do not worsen outcomes in cancer patients with COVID-19 [18–22]. Some studies have evaluated the safety and efficacy of ICIs in lung cancer patients with COVID-19 infection [23, 24]. The Omicron variant has presented a new challenge to Chinese healthcare systems and care of cancer patients due to its persistent spread in the end of 2022. However, the impact of irAEs in lung cancer on the incidence of Omicron variant COVID-19 pneumonia remains obscure.

Therefore, this cross-sectional study seeks to investigate the association between irAEs and COVID-19 pneumonia in lung cancer patients infected with the Omicron variant in China. By understanding the impact of irAEs on COVID-19 pneumonia incidence, we can improve the management and monitoring of these patients during the ongoing pandemic.

Methods

Design and patients

This cross-sectional study was conducted at the Second Affiliated Hospital of Nanchang University in China between December 8, 2022 and February 1, 2023, during the Omicron variant epidemic. We reviewed lung cancer patients diagnosed with COVID-19, who received at least one cycle of immune checkpoint inhibitors (ICIs), including programmed cell death protein 1 (PD-1)/pro-programmed death-ligand 1 (PD-L1) inhibitors, either as monotherapy or combination therapy at our institution. All enrolled patients had confirmed lung cancer by pathology and COVID-19 diagnosis through reverse transcriptase-polymerase chain reaction (RT-PCR) using nasopharyngeal swabs. Patients diagnosed solely on the basis of rapid antigen testing were excluded. This study adhered to the Declaration of Helsinki principles and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [25]. The institutional ethics committees of the Second Affiliated Hospital of Nanchang University approved the study protocol.

Data collection

We collected data on patient characteristics, including age, sex, tumor stage, Eastern Cooperative Oncology Group (ECOG) performance status score at the time of COVID-19 infection, previous treatment history, ICI-related data, irAE-related data, and routine blood tests. The Common Terminology Criteria of Adverse Events (version 5.0) was utilized to grade irAE at its peak severity [5]. Solid tumor TNM staging was based on the AJCC staging system's eighth edition. COVID-19 pneumonia diagnosis was confirmed via chest computed tomography (CT) scans, and patients were categorized based on the NCCN Guidelines for cancer-related infections as having mild, moderate, severe, or critical COVID-19 severity [26].

Statistical analysis

We used R software (version 3.6.3) to analyze all data. Categorical variables were reported as frequency and percentage, while continuous variables were expressed as mean ± standard deviation. Groups were compared using independent sample t-tests or analysis of variance (ANOVA). Univariate and multivariate logistic regression analyses were conducted to evaluate the connection between immune-related adverse events (irAEs) and COVID-19 pneumonia incidence; Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

We excluded 46 patients with non-lung cancer, leaving 326 patients diagnosed with both lung cancer and COVID-19 infection for further investigation. Out of these, 133 patients who did not receive immune checkpoint inhibitor (ICI) treatment were excluded, resulting in a total of 193 patients enrolled in the study. Of these, 72 patients (37.30%) experienced immune-related adverse events (irAEs), while 121 patients (62.70%) did not belong to the irAEs group (Fig. 1). Table 1 presents patients' baseline demographics, clinical, and biochemical characteristics. The median age for the non-irAEs group was 64.55 years, with 85.95% being male. The irAEs group had a median age of 62.83 years, with 86.11% male.

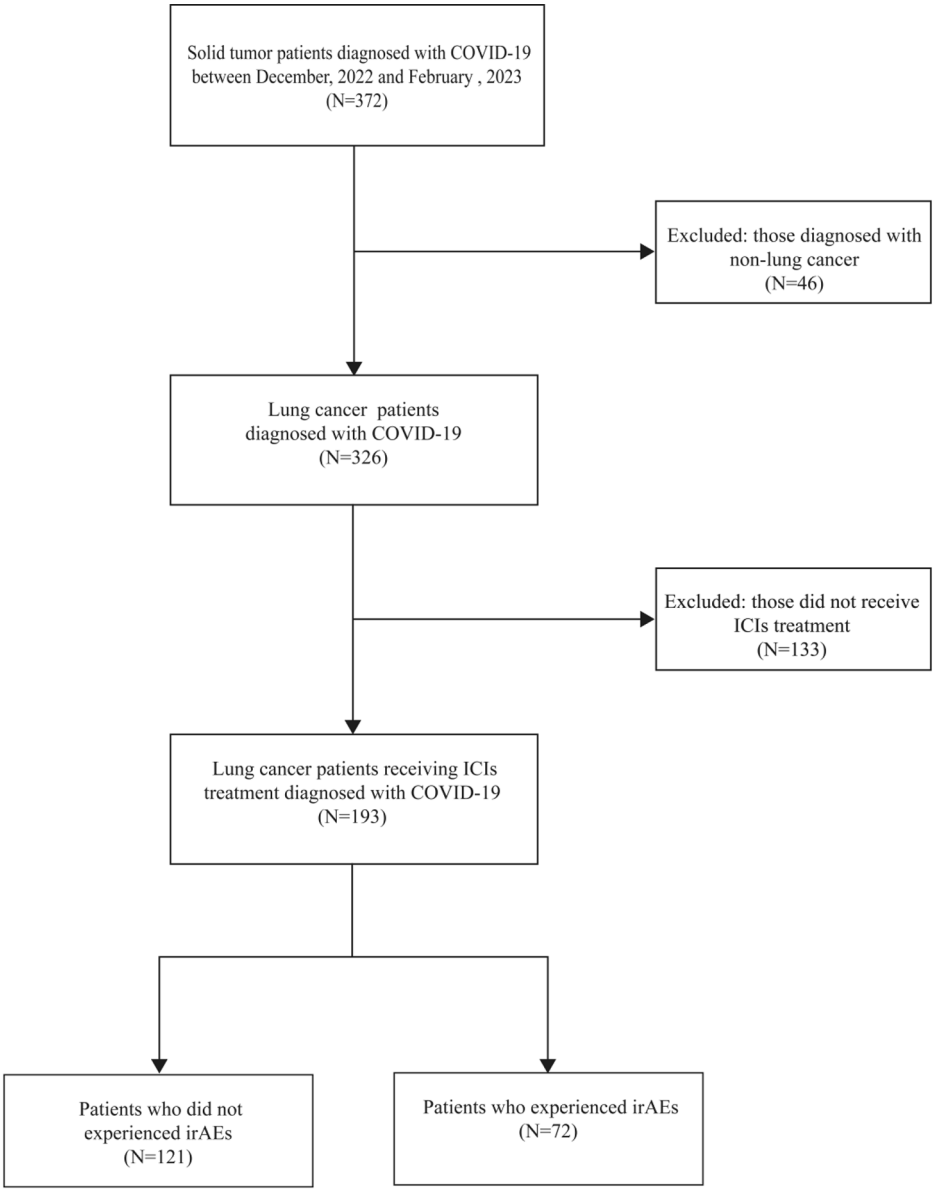

Fig. 1 Flowchart of patient selection. **Abbreviations:** COVID-19, coronavirus disease 2019; ICIs, Immune checkpoint inhibitors; irAEs, Immune-Related Adverse Events

Among the entire cohort, 26 patients (13.47%) developed COVID-19 pneumonia, while six (3.11%) progressed to severe cases after COVID-19 infection. We observed a higher incidence rate of COVID-19 pneumonia in the irAEs group compared to the non-irAEs group (27.78% vs. 4.96%, $P<0.01$). Furthermore, the irAEs group had a higher incidence rate of different COVID-19 pneumonia grades ($P<0.01$).

Profiles of irAEs

Table 2 showed the types of irAEs in the 72 lung cancer patients. A total of 104 irAE trips were documented after immune checkpoint inhibitor (ICI) treatment. Most common types of irAEs were dermatitis/rash (33.65%), thyroiditis (23.08%), pneumonitis (22.12%), hepatitis (8.65%), colitis (7.69%), and other types (3.85%) in the 72 lung cancer patients. For patients who had multisystem irAEs, the highest grade was considered a priority. Most irAEs were mild, with grade 1 accounting for 50.00% and grade 2 accounting for 29.81%. Eleven patients experienced grade 3 or grade 4 irAEs. No severe (grade 5) irAEs were reported after ICI therapy, with only one patient experiencing grade 1 myocarditis.

Table 1 Baseline characteristics of all enrolled patients

Characteristics	Total Mean (SD)/ Median (Q1-Q3) / N(%)	Without irAEs Mean (SD)/ Median (Q1-Q3) / N(%)	With irAEs Mean (SD)/ Median (Q1-Q3) / N(%)	P
Age (range)year	65.00 (33.00–84.00)	66.00 (60.00–70.00)	64.00 (57.00–69.00)	0.20
Age year				0.33
< 70	148 (76.68%)	90 (74.38%)	58 (80.56%)	
≥70	45 (23.32%)	31 (25.62%)	14 (19.44%)	
Sex				0.98
Female	27 (13.99%)	17 (14.05%)	10 (13.89%)	
Male	166 (86.01%)	104 (85.95%)	62 (86.11%)	
Comorbidities				0.51
No	159 (82.38%)	98 (80.99%)	61 (84.72%)	
Yes	34 (17.62%)	23 (19.01%)	11 (15.28%)	
ECOG PS				0.62
≤ 2	183 (94.82%)	114 (94.21%)	69 (95.83%)	
≥ 3	10 (5.18%)	7 (5.79%)	3 (4.17%)	
TNM stage				0.28
I-III	43 (22.28%)	30 (24.79%)	13 (18.06%)	
IV	150 (77.72%)	91 (75.21%)	59 (81.94%)	
Chemotherapy				0.17
No	24 (12.44%)	12 (9.92%)	12 (16.67%)	
Yes	169 (87.56%)	109 (90.08%)	60 (83.33%)	
Radiotherapy				0.18
No	111 (57.51%)	74 (61.16%)	37 (51.39%)	
Yes	82 (42.49%)	47 (38.84%)	35 (48.61%)	
Targeted therapy				0.37
No	123 (63.73%)	80 (66.12%)	43 (59.72%)	
Yes	70 (36.27%)	41 (33.88%)	29 (40.28%)	
Anti-angiogenic therapy				0.04
No	120 (62.18%)	82 (67.77%)	38 (52.78%)	
Yes	73 (37.82%)	39 (32.23%)	34 (47.22%)	
COVID-19 pneumonia				< 0.01
No	167 (86.53%)	115 (95.04%)	52 (72.22%)	
Yes	26 (13.47%)	6 (4.96%)	20 (27.78%)	
COVID-19 pneumonia grade				< 0.01
No	167 (86.53%)	115 (95.04%)	52 (72.22%)	
1–2	20 (10.36%)	3 (2.48%)	17 (23.61%)	
3–4	6 (3.11%)	3 (2.48%)	3 (4.17%)	
WBC (10^9/L)	5.66 (4.58–7.13)	5.66 (4.51–7.17)	5.69 (4.71–7.02)	0.95
Neutrophil(10^9/L)	3.67 (2.87–5.03)	3.65 (2.75–4.97)	3.74 (3.13–5.05)	0.68
Lymphocyte (10^9/L)	1.09 (0.81–1.53)	1.13 (0.81–1.50)	1.08 (0.83–1.57)	0.66

Note: Comorbidities included chronic obstructive pulmonary disease, hypertension and cardiovascular disease. **Abbreviation**: WBC white blood cell; COVID-19, coronavirus disease 2019; ECOG PS Eastern Cooperative Oncology Group performance status score; irAEs Immune-Related Adverse Events

Association between irAEs and COVID-19 pneumonia

As shown in Table 3, in the univariate analysis, irAEs (OR=7.37, 95%CI: 2.80, 19.43; P<0.01) and lymphocyte count (OR=0.37, 95%CI: 0.15, 0.89; P=0.03) were associated with a higher incidence of developing COVID-19 pneumonia after infection. However, we did not find a significant association between all-grade irAEs and COVID-19 pneumonia (OR=1.00, 95%CI: 0.30, 3.29; P=1.00). In the multivariate analysis, the incidence of COVID-19 pneumonia remained significantly associated with irAEs (OR=9.56, 95%CI: 2.21,41.33; P=0.0025) and lymphocyte count (OR=0.35, 95%CI: 0.14, 0.9; P=0.0033). Comorbidities (OR=2.38, 95%CI: 0.76, 7.49; P=0.14), chemotherapy (OR=0.64, 95%CI: 0.18, 2.28; P=0.49), targeted therapy (OR=2.24, 95%CI: 0.46,10.84; P=0.32), and anti-angiogenic therapy (OR=0.73, 95%CI: 0.15, 3.54; P=0.70) were not significantly associated with COVID-19 pneumonia.

Table 2 The types of irAEs in lung cancer patients

Types of irAEs	Grade 1	Grade2	Grade 3	Grade 4	Total
Pneumonitis	7	6	4	6	23 (22.12%)
Hepatitis	4	3	1	1	9(8.65%)
Thyroiditis	13	8	3	—	24(23.08%)
Dermatitis/rash	19	11	2	3	35(33.65%)
Colitis	5	2	1	—	8 (7.69%)
Myocarditis	1	—	—	—	1(0. 96%)
others	3	1	—	—	4(3.85%)
Total	52(50.00%)	31 (29.80%)	11 (10.58%)	10 (9.62%)	104(100%)

Abbreviations: ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events

Discussion

COVID-19 infection can cause immune dysregulation, leading to excessive inflammation and high levels of pro-inflammatory cytokines [27, 28]. This study examines the impact of Omicron variant COVID-19 on lung cancer patients in China receiving ICIs. Specifically, we conducted a cross-sectional analysis of patients diagnosed between December 2022 and February 2023. Our results confirm that lung cancer patients who develop irAEs while receiving ICIs suffer a higher risk of Omicron variant COVID-19 pneumonia.

There has been growing concern about the potential for unopposed T-cell activation and downstream cytokine excess resulting from the convergence of ICIs treatment toxicity and COVID-19 in cancer patients [28, 29]. In line with this view, our study found that lung cancer patients who developed irAEs while receiving ICIs had a significantly higher incidence of COVID-19 pneumonia compared to those without irAEs (27.78% vs. 4.96%, $P<0.01$). It has been suggested that patients who experience irAEs are those who can mount a more robust reconstitution of anticancer immunity [30]. As a result, lung cancer patients receiving ICIs who become infected with COVID-19 may face a higher risk of immune hyperactivation and cytokine storm. Our multivariate analysis revealed that the development of irAEs was significantly associated with a higher incidence rate of COVID-19 pneumonia. Interestingly, previous studies have yielded conflicting results. For example, Mengni Guo et al. reported that COVID-19 infection may pose a risk of severe irAEs in cancer patients receiving ICIs [24]. On the other hand, a registry for thoracic cancers did not find a significant impact of ICIs on COVID-19 outcomes [31, 32]. A New York study reported that prior ICIs therapy was associated with an increased risk of severe respiratory illness and hospitalization among COVID-19 patients [33]. In contrast, a US study of 25 patients found no association between ICIs therapy and COVID-19-related outcomes [20]. Likewise, a prospective study of 44 patients showed that ICIs therapy within 4 weeks of COVID-19 diagnosis trended toward reducing the risk of COVID-19 mortality [34]. Furthermore, a study involving 41 lung cancer patients found no significant association between ICIs therapy and an increased risk of COVID-19 mortality [35]. Differences in cancer types, COVID-19 variants and patient characteristics may account for these discrepancies. However, in our study, we observed a significant difference in the incidence of COVID-19 pneumonia between different grades of irAEs in the univariate analysis. In the multivariate analysis, no difference was observed. This may be attributed to the relatively low number of irAE events, especially in the Grade 3–4 category.

Our study also found that the absolute lymphocyte count was significantly associated with a higher incidence rate of COVID-19 pneumonia (OR=0.36, 95%CI: 0.14, 0.94; P=0.04). Prior research has established that reduced CD4+/CD8+T cells and lymphocyte count are associated with severe COVID-19 [29] and mortality [36]. Meanwhile, the mechanisms leading to irAEs include the expansion of intertumoral and peripheral T-cell receptor repertoire, as well as the mobilization of large numbers of T cells [37]. These findings suggest that there may be an immunological link between irAEs and COVID-19 pneumonia in lung cancer patients, but further mechanistic studies are needed to fully elucidate this relationship.

While our study has limitations - including its retrospective design and small sample size - it provides valuable real-world data from a Chinese institution during a specific timeframe. What's more, our study specifically focused on lung cancer patients used ICIs. This focus was chosen because distinguishing immunotherapy-related pneumonitis from COVID-19 pneumonia when both occur simultaneously can be challenging, and CT scanning is often necessary for tumor evaluation and monitoring adverse reactions. Our analysis was limited to the Omicron variants (BA.2 and BA.5), and given the emergence of new strains, more investigation is needed to explore the association between irAEs and COVID-19 infection outcomes in cancer patients. Nonetheless, our findings underscore the importance of close monitoring and timely intervention for lung cancer patients receiving ICIs who contract COVID-19.

Conclusion

In conclusion, our study firstly evaluated the impact of irAEs on COVID-19 pneumonia incidence in lung cancer patients receiving ICI therapy. We found that patients who developed irAEs were at higher risk of contracting Omicron variant COVID-19 pneumonia. This highlights the importance of increased vigilance for COVID-19 infections in this patient population, along with closer

Table 3 Univariate and multivariate analyses for risk factors associated with COVID- 19 pneumonia

Variate	COVID- 19 Pneumonia				
	Patients n (%)	Univariate		Multivariate	
		OR (95%CI)	P	OR (95%CI)	P
Age(years)			0.98		
< 70	148 (76.68%)	1			
≥ 70	45 (23.32%)	0.98 (0.37, 2.62)			
Sex			0.33		
Female	27 (13.99%)	1			
Male	166 (86.01%)	2.11 (0.47,9.50)			
Comorbidities			0.06		
No	159 (82.38%)	1		1	
Yes	34 (17.62%)	2.41 (0.95, 6.12)		2.38 (0.76, 7.49)	0.14
ECOG PS			0.74		
≤ 2	183 (94.82%)	1			
≥ 3	10 (5.18%)	0.70 (0.09,5.78)			
TNM stage			0.69		
I-III	43 (22.28%)	1			
IV	150 (77.72%)	1.24 (0.44, 3.50)			
irAEs			< 0.01		
No	121 (62.69%)	1		1	
Yes	72(37.31%)	7.37(2.80,19.43)		9.56 (2.21,41.33)	0.0025
IrAEs Grade					
G 0	121 (62.69%)	1		1	
G 1–2	54 (27.98%)	7.37 (2.67, 0.32)	0.0001	0.79 (0.20, 3.11)	0.74
G 3–4	8 (9.33%)	7.37 (1.9,27.54)	0.003	1.0	
Chemotherapy			0.09		
No	24(12.44%)	1		1	
Yes	169(87.56%)	0.40 (0.14, 1.13)		0.64 (0.18, 2.28)	0.49
Radiotherapy			0.38		
No	111(57.51%)	1			
Yes	82 (42.49%)	0.68 (0.29, 1.62)			
Targeted therapy			0.05		
No	123 (63.73%)	1		1	
Yes	70 (36.27%)	2.31 (1.00, 5.33)		2.24 (0.46,10.84)	0.32
Anti-angiogenic therapy			0.08		
No	120 (62.18%)	1		1	
Yes	73 (37.82%)	2.14 (0.93, 4.92)		0.73 (0.15, 3.54)	0.70
WBC (10^9/L)	5.66 (4.58,7.13)	1.08 (0.97, 1.19)	0.16		
Neutrophil (10^9/L)	3.67 (2.87,5.03)	1.03 (0.97, 1.09)	0.37		
Lymphocyte (10^9/L)	1.09 (0.81,1.53)	0.37 (0.15, 0.89)	0.03	0.35 (0.14, 0.92)	0.033

Note: Comorbidities included chronic obstructive pulmonary disease, hypertension and cardiovascular disease. **Abbreviation**: WBC white blood cell; COVID-19, coronavirus disease 2019; ECOG PS Eastern Cooperative Oncology Group performance status score; irAEs Immune-Related Adverse Events; OR Odds ratio; CI, confidence interval; G grade

monitoring, including timely chest CT scans, and potentially more aggressive treatment if necessary.

List of abbreviations

ICIs	immune checkpoint inhibitors
irAEs	Immune-Related Adverse Events
COVID-19	coronavirus disease 2019
PD-1	programmed cell death protein 1 inhibitors
PD-L1	pro-programmed death-ligand 1inhibitors
ECOG	PS Eastern cooperative oncology group performance status score
CT	computer tomography
AJCC	American Joint Committee on Cancer
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
CI	confidence interval
WBC	white blood cell

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Authors' contributions
ZM Z and AW L: Conceptualization, project administration and statistical analysis. KJ C and C H: Data acquisition, methodology, and writing original draft. AW L and YQ H: Data collection and revising the manuscript. DY P: Writing assistance. All authors drafted the work and revised it critically for important intellectual content, approved the final version of the manuscript for publication.

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Data Availability
Data are available on request from the corresponding author Zhimin Zeng upon reasonable request (2zm@163.com).

Declarations

Ethics Statement
This study was conformed to the Declaration of Helsinki. reviewed and the institutional ethics committees of the Nanchang University approved the study protocol. As it was a retrospective study, the informed consent for this study was waived by the institutional ethics committee of Second Affiliated Hospital of Nanchang University.

Consent for publication
Not applicable.

Competing interests
All authors report no potential conflicts.

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