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Early Versus Delayed Usage of Paxlovid in Severe Omicron-Infected Patients With Hypoxemia: A Prospective Multiple-Center Cohort Study

Yu-Ji Wang[1,2] | Xi-Yan Ma[1,2] | Xiao-Ying Wei[1,2] | Meng-Lan Zhang[1,2] | Nan Su[3] | Jun-Hong Jiang[1,2] | Guo-Peng Xu[4,5] | Ran Wang[6] | Da-Xiong Zeng[1,2]

[1]Department of Pulmonary and Critical Care Medicine, The Fourth Affiliated Hospital of Soochow University, Suzhou, People's Republic of China | [2]Medical Center of Soochow University, Suzhou, People's Republic of China | [3]Department of Pulmonary and Critical Care Medicine, First Affiliated Hospital of Soochow University, Suzhou, People's Republic of China | [4]Department of Pulmonary and Critical Care, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, People's Republic of China | [5]Gusu School, Nanjing Medical University, Suzhou, People's Republic of China | [6]Department of Pulmonary and Critical Care, The Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China

Correspondence: Da-Xiong Zeng (zengdaxiong@suda.edu.cn) | Ran Wang (wangran@ahmu.edu.cn)

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ABSTRACT

Background and Aims: Early stage administration of Paxlovid has been shown to improve the prognosis of mild to moderate COVID-19 patients with high risk. However, few evidence was validated in severe COVID-19 patients with hypoxemia. It is also unclear whether delayed usage of Paxlovid affected prognosis in COVID-19 patients or not.

Methods: In this multiple-centers prospective study, we collected the clinical data in hospitalized severe adult Omicron infection patients with hypoxemia. All patients were divided into two groups according to the time of Paxlovid usage after the symptom onset: early group (Paxlovid administration in 5 days after symptom onset) and delayed group (Paxlovid administration beyond 5 days after symptom onset). The 28-day composite outcomes were evaluated.

Results: Totally 198 hospitalized severe omicron-infected subjects with hypoxemia were enrolled. There was no difference between the two groups about the baseline characteristics and laboratory parameters, except for leukocytes (5.29×10^9 vs. 7.90×10^9/L, $p = 0.01$) and albumin levels (35 vs. 31 g/L, $p = 0.04$). The 28-day composite outcomes in early group were slightly lower than that in delayed group but with no difference (12.8% vs. 16.67%, $p = 0.602$). The viral clearance ratio at Day 7 after Paxlovid treatment in early group was higher than that in delayed group (79.48% vs. 58.33%, $p = 0.029$). The medium hospitalized duration in early group was shorter than that in delayed group (11.31 vs. 15.32 days, $p = 0.005$). Logistic analysis showed the independent risk factors of prognosis including underlying diseases ≥ 3 kinds (ORR = 1.72), D-dimer $\geq 2.0\,\mu g/mL$ (ORR = 1.35), and MODS (ORR = 14.01).

Conclusions: In Omicron-infected subjects with hypoxemia, early usage of Paxlovid received benefits in hospitalized time and viral clearance, but delayed usage did not result in a worse composite prognosis. This result might provide direct evidence of antiviral strategy in severe Omicron infection subjects with hypoxemia.

Yu-Ji Wang, Xi-Yan Ma and Xiao-Ying Wei contributed equally to this article.

1 | Introduction

Although the global prevention and control policies of COVID-19 has been changed, SARS-CoV-2 virus remains a critical threat to subjects with underlying diseases and olders. Although Omicron variant resulted in mild organ destruction and clinical symptoms, it showed a higher immune escape ability and stronger infectiousness [1]. Although Omicron was more infectious than other variants, it is far less virulent. However, there are remain many Omicron-infected patients died for viral infection or complications. There are some differences about the health impact of Omicron in China compared to Europe or North America. Although vaccination is a convenient and effective approach for COVID-19 prevention, most of the vaccines used in China were inactivated vaccines, not mRNA vaccines. It might be less effective for prevention. Furthermore, the vaccination ratios are not very high in China. This also limited the protection role of vaccines.

Based on these, antiviral drugs were also important for patients with high risks for severe disease. Nirmatrelvir/ritonavir (Paxlovid) selectively suppressed SARS-CoV-2 virus from making any functional proteins to replicate [2]. Previous EPIC-HR study has proved that Paxlovid reduced hospitalization and 28-day mortality rates by 89.1% and 88.9%, respectively, in unvaccinated COVID-19 patients [3]. Paxlovid also reduced risk of disease progression by 46% in COVID-19 patients with at least one comorbidity or condition associated with high risk for severe disease [4–6]. In these studies, Paxlovid was administrated in mild to moderate COVID-19 patients at early stage after disease onset.

However, there was few evidence about delayed usage of Paxlovid (beyond 5 days after onset) in COVID-19 patients. In the pandemic of COVID-19, antiviral drugs were obtained difficultly in many areas, especially in places with developing countries. In several previous reports, about 68%–87% patients received antiviral treatment beyond 5 days after diseases onset [7, 8]. Although these studies analyzed the efficacy of different antiviral agents, they did not compared the difference between early usage and delayed usage. Previous evidence has shown that viral load is related to disease severity, and that early suppression of viral replication could significantly improve outcomes for COVID-19 patients [9]. Theoretically, delayed usage of antiviral treatment might weaken the efficacy of drugs in COVID-19 patients. However, there was no direct evidence about the difference between early usage and delayed usage of Paxlovid in COVID-19 patients.

Glucocorticoids have been proven to play critical role in COVID-19 patients with hypoxemia or severe ill subjects [10]. RECOVERY study and other previous reports have demonstrated that low-dose corticosteroids reduced the risk of death in hospitalized COVID-19 patients requiring oxygen or ventilatory support [11–13]. These results indicated the importance of anti-inflammation treatment in COVID-19 patients with hypoxemia. However, multiple reports indicated that usage of corticosteroids could delay the viral clearance, which might result in virus rebound and secondary cytokines storm [14–16]. It is unclear whether additional extended antiviral treatment was benefit for the patients with hypoxemia or not.

In this prospective cohort study, we aimed to evaluate the clinical efficacy of Paxlovid in early or delayed stage after onset in hospitalized COVID-19 patients with hypoxemia in four hospitals.

2 | Methods

2.1 | Study Design

From December 15, 2022, to May 30, 2023, we performed a prospective multiple-center cohort study of hospitalized COVID-19 patients with hypoxemia in four centers (the Fourth Affiliated Hospital of Soochow University, the First Affiliated Hospital of Soochow University, the Affiliated Suzhou Hospital of Nanjing Medical University, the First Affiliated Hospital of Anhui Medical University). All subjects were diagnosed and confirmed for SARS-CoV-2 infection by positive RT-PCR. All patients were treated by their attending physician according to the disease severity and drug accessibility. All the hypoxemia patients with Paxlovid treatment were enrolled in this study. The patients were divided into two groups: early group (Paxlovid used within 5 days after COVID-19 symptom onset) and delayed group (Paxlovid used beyond 5 days after COVID-19 symptom onset).

The excluded criterion included: (1) younger than 18 years; (2) died in 48 h after hospitalization; (3) received Paxlovid administration for less than 5 days; (4) received other antiviral agents except for Paxlovid; (5) received mechanical ventilation on admission; and (6) the clinical data and prognosis information were missed.

This study was approved by the institutional review board of the Fourth Affiliated Hospital of Soochow University (2023404). The written informed consent was waived as we only collected the clinical data from anonymized data without additional drugs or treatment, according to the policy for public health outbreak investigation of emerging infectious diseases issued by the National Health Commission of the People's Republic of China.

2.2 | Data Collection

The baseline demographic characteristics (age, sex, underlying diseases) and clinical data (diagnosis, treatment, changes of plasma parameters, blood gas oxygenation index) were collected in four hospitals. The severity of COVID-19 on admission was evaluated by two independently physicians according to the ninh version Guideline of COVID-19 in China.

Severe subjects were defined as having one or more of the followings: (1) respiratory rate ≥ 30 times per minutes, (2) lung infiltrates $> 50\%$, (3) oxygen saturation $\leq 93\%$, (4) $PaO_2/FiO_2 < 300$ mmHg. Critical subjects were defined when he/she had one or more of the following: (1) shock required vasopressor support, (2) required intensive care unit management because of a combination of other organ failures, and (3) respiratory failure requiring ventilator treatment.

TABLE 1 | Baseline characteristics of Omicron-infected patients in early Paxlovid group and delayed Paxlovid group.

	Early Paxlovid ($n = 78$)	Delayed Paxlovid ($N = 120$)	p Value
Age (years)	75.28 ± 12.39	73.85 ± 13.62	0.60
Gender (n, %)			0.55
Male	50 (64.1)	78 (65.0)	
Female	28 (35.9)	42 (35.0)	
Body mass index	22.40 ± 4.03	23.95 ± 3.33	0.06
Vaccine injection (n, %)	59 (75.6)	87 (72.5)	0.62
Severity (n, %)			0.48
Severe	46 (59.0)	74 (61.7)	
Critical	32 (41.0)	46 (38.3)	
Underlying diseases			
Diabetes	20 (25.6)	22 (21.2)	0.27
Hypertension	34 (43.6)	74 (61.7)	0.08
Coronary heart disease	8 (10.3)	10 (8.3)	0.50
Cerebrovascular disease	6 (8.1)	6 (6.1)	0.52
Chronic pulmonary disease	14 (17.9)	14 (11.7)	0.28
Chronic kidney disease	2 (2.6)	10 (8.3)	0.24
Tumor	12 (16.2)	24 (22.6)	0.32
Lab findings			
Leukocytes (10^9/L)	5.29 (3.54, 6.71)	7.90 (4.91, 10.04)	0.01
Lymphocytes (10^9/L)	0.55 (0.35, 1.04)	0.85 (0.55, 1.27)	0.09
Platelets (10^{12}/L)	167 (114, 230)	177 (137, 267)	0.40
Hemoglobin (g/L)	131 (120, 141)	129 (112, 145)	0.50
C reactive protein (mg/L)	49.89 (16.51, 82.50)	32.47 (13.83, 94.50)	0.66
IL-6 (pg/mL)	22.68 (9.29, 57.18)	13.41 (4.41, 29.90)	0.26
Albumin (g/L)	35.45 (32.20, 38.75)	33.70 (27.40, 36.60)	0.04
Creatinine (μmol/L)	66.25 (57.08, 95.93)	68.80 (56.70, 84.30)	0.84
NT-proBNP (pg/mL)	314.60 (142.58, 674.90)	448.00 (236.35, 932.55)	0.70
D-dimer (mg/L)	0.74 (0.38, 1.47)	0.98 (0.60, 1.74)	0.17
Lactic dehydrogenase (IU/L)	203.30 (180.43, 233.55)	240.55 (185.83, 279.15)	0.20
Procalcitonin (ng/mL)	0.09 (0.03, 0.31)	0.07 (0.04, 0.20)	0.44
Troponin (pg/mL)	13.20 (8.00, 20.40)	19.17 (11.18, 35.90)	0.09
Respiratory support, n (%)			
Nasal catheter	44 (56.4)	80 (66.7)	0.21
Venturi mask	20 (25.6)	24 (20.0)	0.37
High-flow nasal oxygen	14 (17.9)	16 (13.3)	0.80
Treatment			
Antibiotics, n (%)	66 (84.6)	112 (93.3)	0.14
Duration of Paxlovid, days	6.56 ± 3.94	5.52 ± 2.56	0.17
Duration of GCs	7 (3, 15)	9 (7, 12)	0.58
GCs dose (convert to DXM, mg/day)	5 (3.75, 7.50)	5.63 (3.88, 7.48)	0.47

Note: Categorical variables were presented as n (%). The normal distribution data of continuous variables were presented as average and standard deviation. The skew distribution data of continuous variables were presented as median and quartile. χ^2 test or Mann–Whitney U test was used to compare differences between early group and delayed group.

Abbreviations: DXM, dexamethasone; GC, glucocorticoid; IL-6, interleukin 6.

TABLE 2 | Priamry and secondary outcomes of Omicron-infected patients after Paxlovid treatment with different stage.

	Early Paxlovid ($n = 78$)	Delayed Paxlovid ($N = 120$)	p Value
Comprise outcomes (n, %)	10 (12.82)	20 (16.67)	0.602
Hospitalized time (days)	11 (9, 13)	15 (13, 17)	0.005
Viral RNA clearance			
Day 1	6 (7.69)	8 (6.67)	0.846
Day 7	62 (79.48)	70 (58.33)	0.029
Day 15	74 (94.87)	106 (91.67)	0.269

The primary endpoint was a composite outcome of disease progression, including all-cause death, intensive care unit admission, noninvasive or invasive mechanical ventilation, whichever came first. The secondary endpoint was viral clearance and hospitalized time.

2.3 | Statistical Analysis

Statistical analysis was performed using SPSS (version 15.0). Categorical variables were presented as n (%), respectively. The normal distribution data of continuous variables were presented as average and standard deviation. The skew distribution data of continuous variables were presented as median and quartile. χ^2 test or Mann–Whitney U test was used to compare differences between early group and delayed group. Univariate and multivariate logistic analysis were used for confirming the independent risk factors. Survival curves were plotted using the Kaplan–Meier method by the log-rank test. The level of significance was two-sided 0.05 for statistical tests.

3 | Results

3.1 | Baseline Characteristics of COVID-19 Patients in Two Groups

All the baseline characteristics were shown in Table 1. There were totally 198 patients with hypoxemia enrolled in our study. No difference was found in age, gender, BMI, and underlying diseases. The leukocytes counts were significantly higher in delayed group as compared with that in early group (7.90×10^9 vs. 5.29×10^9/L, $p = 0.01$). The Lymphocyte counts and other inflammatory markers (C reactive protein, procalcitonin, and IL6) were similar in two groups. The albumin levels in delayed group was significantly higher than that in early group (33.70 vs. 35.45 g/L, $p = 0.04$). The levels of creatinine, D-dimer, lactic dehydrogenase, NT-proBN and troponin were similar in two groups.

The treatments were also shown in Table 1. No difference was found in the percentage of respiratory support treatment (nasal catheter or high-flow nasal oxygen) at admission. The duration of Paxlovid treatment were also similar in two groups (6.56 ± 3.94 vs. 5.52 ± 2.56 days, $p = 0.17$). There were no difference in the ratios of antibiotics, the duration, and average doses of glucocorticoids between two groups.

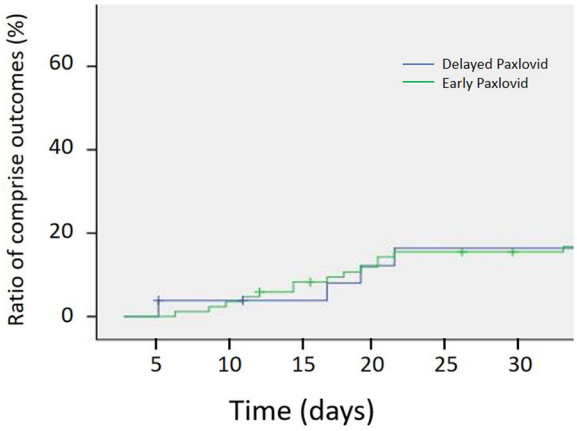

FIGURE 1 | Kaplan–Meier for the ratio of composite outcomes in two groups.

3.2 | Composite Outcomes of Omicron-Infected Patients After Different Treatment

We used composite outcomes for the primary point, as shown in Table 2 and Figure 1. The ratio of composite outcomes in early group was slightly lower than that in delayed group but without difference (12.82% vs. 16.67%, $p = 0.602$, Figure 1). The ratio of viral clearance at day 7 after Paxlovid treatment in early group was higher than that in delayed group (79.48% vs. 58.33%, $p = 0.029$), but they were similar at day 14 (94.87% vs. 91.67%, $p = 0.269$). The hospitalized time in early group was significantly shorter in early group than that in delayed group [11 (9, 13) vs. 15 (13, 17) days, $p = 0.005$].

3.3 | Univariate and Multivariate Analysis in Omicron Patients Treated With Paxlovid

Table 3 showed the logistic analysis results about the risk factors of composite outcomes. The univariate analysis results indicated that the risk factors of composite outcomes included underlying diseases ≥ 3 kinds (OR = 2.19, 95% CI: 1.05–7.43), lymphocyte $< 0.8 \times 109$/L (OR = 1.86, 95% CI: 1.05–4.39), CRP ≥ 70 mg/L (OR = 2.57, 95% CI: 1.06–5.99), D-dimer ≥ 2.0 μg/mL (OR = 3.88, 95% CI: 1.12, 8.67) and multiple organ dysfunction (MODS) (OR = 20.12, 95% CI: 3.96, 101.65). The multivariate analysis results showed that independent risk factors were underlying diseases ≥ 3 kinds (OR = 1.72, 95% CI: 1.05–4.35), D-dimer ≥ 2.0 μg/mL (OR = 1.35, 95% CI: 1.01–5.22) and MODS (OR = 14.01, 95% CI: 1.23–58.84).

TABLE 3 | Univariate and multivariate analysis of the composite prognosis in severe Omicron-infected patients with hypoxemia.

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Male	3.06 (0.63, 14.82)	0.166		
Underlying diseases (≥ 3 kinds)	2.19 (1.05, 7.43)	0.042	1.72 (1.05, 4.35)	0.031
Age (≥ 70 years)	2.67 (0.69–10.25)	0.215		
Leukocytes ($\geq 9.5 \times 10^9$/L)	1.41 (0.34, 5.81)	0.643		
Lymphocyte ($< 0.8 \times 10^9$/L)	1.86 (1.05, 4.39)	0.028	1.15 (0.81, 2.52)	0.362
CRP (≥ 70 mg/L)	2.57 (1.06, 5.99)	0.034	1.84 (0.88, 4.33)	0.269
IL6 (≥ 20 pg/mL)	1.95 (0.48, 7.35)	0.527		
Albumin (< 35 g/L)	1.33 (0.61, 3.72)	0.761		
D-dimer (≥ 2.0 μg/mL)	3.88 (1.12, 8.67)	0.039	1.35 (1.01, 5.22)	0.045
Troponin (≥ 30 pg/mL)	2.31 (0.49, 10.94)	0.292		
MODS	20.12 (3.96, 101.65)	0.000	14.01 (1.23, 58.84)	0.003

Note: Categorical variables were presented as *n* (%). The normal distribution data of continuous variables were presented as average and standard deviation. The skew distribution data of continuous variables were presented as median and quartile. χ^2 test or Mann–Whitney *U* test was used to compare differences between early group and delayed group.
Abbreviations: CRP, C reaction protein; MODS, multiple organ dysfunction.

4 | Discussion

In our study, we prospectively compared the efficacy between early usage (in 5 days after symptom onset) and delayed usage (beyond 5 days after symptom onset) of Paxlovid in severe Omicron patients with hypoxemia. Our result indicated that early usage of Paxlovid could significantly short hospitalized time and accelerate viral clearance, but did not improve the composite outcomes, when compared with delayed usage of Paxlovid. However, there is also evidence that systemic glucocorticoid administration was independently associated with delayed viral clearance time. Moreover, SARS-CoV-2 clearance was not affected by systemic use of glucocorticoids according to other studies. In our opinion, it is the first prospective study that directly compare the efficacy of antiviral drugs in different disease stages of severe Omicron infection. These results indicated the importance of antiviral treatment in Omicron patients with hypoxemia, even beyond early stage of SARS-CoV-2 infection.

In severe omicron-infected patients with hypoxemia, glucocorticoids have been proven to reduce the risk of death and decreased ventilator dependence. However, some reports and multivariate Cox regression analysis revealed that systemic glucocorticoid administration was the independent factor associating with delay of viral clearance time [17, 18]. Other studies identified that SARS-CoV-2 clearance did not affected by systematic glucocorticoids [19, 20]. Basing on these, antiviral drugs plus glucocorticoid treatment might benefit to prognosis. Some studies have focused on the combination of Remdesivir and dexamethasone in COVID-19, which showed contrary conclusions. Several reports demonstrated that remdesivir plus dexamethasone reduced the mortality, shorted hospitalization length, and hastened viral clearance [21, 22]. However, other reports found no association with shorter hospitalization or lower in-hospital mortality [23, 24]. In this study, all the enrolled patients received Paxlovid plus glucocorticoids treatment. Our results revealed that early usage of Paxlovid plus glucocorticoids strengthened viral clearance, and shorted hospitalized time, but did not improve composite outcomes, which supports the combination of antiviral drugs and glucocorticoids in severe ill Omicron infection patients or subjects with hypoxemia. It is consistent with the results of previous reports [21, 22]. But, we did not enroll the control subjects who administrated no antiviral drugs, as it is unethical for COVID-19 patients in real-world studies.

Antiviral drugs have been shown to play an important role in mild to moderate COVID-19 patients with risk factors [25–28]. Paxlovid reduced hospitalization and 28-day mortality rates by 89.1% and 88.9%, respectively, in unvaccinated COVID-19 patients [25, 26]. Early treatment with molnupiravir and azvudine also reduced the risk of hospitalization or death in high-risk, unvaccinated adults with COVID-19 [27, 28]. However, all these results confirmed the efficacy of antiviral drugs in early stage, mainly in 5 days after symptom onset. In the real-world, many subjects did not received timely antiviral treatment in 5 days after Omicron infection because of contraindications [7, 8]. Update, no direct evidence supported the benefit of antiviral treatment in these kinds of patients. It is undetermined whether delayed antiviral therapy could benefit to these subjects or not.

Our results demonstrated the clinical value of early usage of Paxlovid in patients with hypoxemia, which shortened the hospitalization time and accelerated viral clearance. These results support the early usage of antiviral drugs in Omicron patients with hypoxemia. Interestingly, delayed usage of Paxlovid did not worse the prognosis as compared with early usage group. It might be resulted from two reasons. First, glucocorticoids not only reduced cytokines storm but also inhibited SARS-CoV-2 replication in severe ill patients. Second, the most serious danger of severe ill patients is the cytokines storm, which resulting in worse prognosis. So, early usage of Paxlovid did not significantly improve composite outcomes, but markedly shorted hospitalized time and viral clearance time as compared with delayed usage group.

Although antiviral drugs have been shown to reduce hospitalization and mortality rates in patients with high risks in previous studies, the expensive cost significantly added the economic burden [29]. COVID-19 vaccination has been proven to reduce viral shedding time in high-risk COVID-19 patients [29]. High-risk patients should prioritize COVID-19 vaccination, which is a more cost-effective approach than antivirals [29, 30]. For low-risk patients with mild disease there are also harmless and inexpensive topical remedies as sweater for an early clearance of the nasal cavity from SARS-CoV-2, useful in care homes and other high-risk communities [31, 32].

There are some limitations in our study. First, it is only a prospectively observational report with the limited number of subjects, without additional interfering drugs or measurements. Randomized controlled trail reports would provide more convincing evidence. Second, we excluded the control subjects who received no antiviral treatment, because it is unethical for COVID-19 patients in real-world study. There are few evidence supporting antiviral treatment in severe ill COVID-19 patients, but physicians usually administrate antiviral drugs in these patients in the real-world.

In conclusion, this multiple-center prospective study demonstrated that early usage of Paxlovid in patients with hypoxemia shortened the hospitalization time and accelerated viral clearance, although composite outcomes were not improved compared with delayed usage. Regardless of timing of administration (early or delayed) administration antiviral drugs are therefore recommended to reduce length of stay and viral shedding time in hospitalized high-risk patients developing severe COVID-19. The results provide direct evidence of supporting usage of antiviral drugs in sever ill COVID-19 patients. Nevertheless, large-scale observational reports are still needed to confirm this conclusion.

Author Contributions

Yu-Ji Wang: data curation, formal analysis, investigation, methodology; writing–original draft. **Xi-Yan Ma:** data curation, formal analysis, investigation, methodology, writing–original draft. **Xiao-Ying Wei:** formal analysis, investigation, methodology, writing–original draft. **Meng-Lan Zhang:** investigation, methodology, software. **Nan Su:** data curation, formal analysis, investigation. **Jun-Hong Jiang:** methodology, writing–review and editing. **Guo-Peng Xu:** software; writing–review and editing. **Ran Wang:** methodology, software, writing–review and editing. **Da-Xiong Zeng:** conceptualization, funding acquisition, methodology, project administration, writing–review and editing. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All the data could be available through the requirement for the corresponding author. Corresponding authors had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency Statement

The lead author Ran Wang, Da-Xiong Zeng affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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