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Short Communication

Prophylactic effects of nirmatrelvir/ritonavir on reducing complications of cardiac surgery, reinfection, and post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with previous SARS-CoV-2 infection: a randomized clinical trial (PEP Trial)

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Patients undergoing cardiac surgery are significantly highly at risk of adverse outcomes due to comorbidities and aging [1]. A previous study indicated that perioperative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection substantially increased postoperative morbidity and mortality [2]. Despite the widespread vaccination efforts, cardiac surgery patients with a history of coronavirus disease 2019 (COVID-19) remain vulnerable to reinfection due to the persistence of the virus in the body, even after respiratory viral detection test results return negative [3]. The prolonged presence of the virus increased the risk of COVID-19 recurrence and post-acute sequelae of COVID-19 (PASC) [4]. Furthermore, COVID-19 antibodies tend to diminish in patients who underwent cardiac surgery [5]. As prevention strategies shift from population-based approaches to individualized care, targeted interventions for high-risk populations, such as cardiac surgery patients, who are commonly characterized by multiple chronic diseases or immune deficiencies, should be developed. Previous studies have reported that nirmatrelvir/ritonavir may prevent the progression of COVID-19 to severe disease; however, limited observational data have indicated its potential to reduce the incidence of post-acute sequelae of PASC [6,7]. Furthermore, no studies have demonstrated its efficacy in preventing SARS-CoV-2 infection or PASC. A recent randomized controlled trial investigated the role of nirmatrelvir/ritonavir in reducing PASC but reported negative results [8]. Given these gaps, further research is needed to assess the efficacy and safety of nirmatrelvir/ritonavir as a prophylactic strategy in high-risk inpatients, especially cardiac surgery patients.

This multicenter, randomized, open-label, parallel-controlled trial employed a 2×2 factorial design to evaluate the prophylactic use of nirmatrelvir/ritonavir and ursodeoxycholic acid (UDCA) to decrease the incidence of post-surgery complications, reinfection, and PASC among patients undergoing cardiac surgery. The study complied with the Declaration of Helsinki and was approved by the Ethics Committees of Fuwai Hospital (leading center ethical approval No. 2022-1913) and all participating centers, and registered on ClinicalTrial.gov (PEP Trial, NCT05690646). All participants provided written informed consent before randomization. The main inclusion criteria included patients aged ≥18 years, undergoing open-chest cardiac surgery, with a history of SARS-CoV-2 infection, the absence of respiratory infection-related symp-

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toms for > 2 weeks, and negative COVID-19 nucleic acid test results and without any signs of viral pneumonia on a chest computed tomography scan on the day of randomization. The main exclusion criteria included undergoing emergent/urgent surgery, renal insufficiency with an estimated glomerular filtration rate of ≤ 30 mL min^{-1} 1.73 m^{-2}, severe hepatic function impairment (Class C of Child-Pugh classification), nirmatrelvir/ritonavir contraindications, and drugs contraindicated with nirmatrelvir/ritonavir within 5 d preoperatively. The details of the inclusion and exclusion criteria are listed in Table S1 (online).

Eligible participants were assigned to nirmatrelvir/ritonavir or control in a 1:1 ratio stratified by SARS-CoV-2 infection duration (<7 weeks or ≥7 weeks), Society of Thoracic Surgeons (STS) risk score (<8 or ≥ 8), and sites. Randomization was initiated 2 d preoperatively through a centralized system using a sequence generated by the Medical Research and Biometrics Center, National Center for Cardiovascular Diseases. Due to the nature of the intervention, blinding was not feasible for participants, physicians, nurses, and site investigators; however, the Clinical Event Committee and statisticians remained blinded to group allocation. Participants in the nirmatrelvir/ritonavir group were administered 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 h for 5 d starting on the day of randomization. No intervention was given to the control group. Cardiac surgery was performed on the second day post-randomization, and participants were followed at 30 d and 1 year post-surgery for outcome assessment. Baseline characteristics were collected at enrollment, including demographics, clinical history, echocardiography, laboratory tests, and surgical details. Procedure details are shown in Text S1 (online).

The primary endpoint was a composite of all-cause death, myocardial infarction, stroke, moderate-to-severe acute kidney injury (AKI), and COVID-19 pneumonia within 30 d postoperatively. Secondary outcomes included individual components of the primary endpoint, as well as severe pneumonia, prolonged ventilation (≥24 h), pulmonary embolism, re-operation for bleeding within 30 d, all-cause death, cardiac death, myocardial infarction, stroke, renal insufficiency, and rehospitalization for cardiac or pulmonary disease within 1 year. Post-hoc analyses included myocardial injury, SARS-CoV-2 reinfection, all-cause pneumonia, major complications within 30 d, and PASC at 1 year, assessed using structured questionnaires based on the World Health Organization case definition. Comprehensive descriptions of outcome measures are shown in Text S2 (online) and Table S2 (online). All potential endpoints were independently adjudicated by at least two members of the Clinical Event Committee according to the pre-specified criteria.

Sample size calculation was based on expected 30-day adverse event rates (20% in controls vs. 8% in the nirmatrelvir/ritonavir group), with an assumed α of 0.0245 (O'Brien–Fleming-type adjustment for interim analysis), 90% power, and accounting for a 5% loss to follow-up, resulting in a target enrollment of 436 participants. Sample size calculation is detailed in Text S3 (online). The primary analysis was performed following the intention-to-treat (ITT) principles. The incidence rate of the 30-day primary outcome for each group was reported, and risk differences (RD) and their confidence intervals (CIs) were calculated based on approximation and null hypothesis testing. The adjusted risk ratios (RRs) were also reported using a generalized linear model, considering stratification factors such as infection time (<7 weeks or ≥7 weeks), STS risk score (<8 or ≥8), and site as covariates. Similar methods were used for secondary and post-hoc outcomes. Because of the 2 × 2 factorial design, a two-sided *P*-value of < 0.025 was considered statistically significant for the primary outcome. $P < 0.05$ was deemed statistically significant for other outcomes. To minimize the potential impact of surgery-related complications on PASC, patients with primary or secondary outcomes were excluded, and the analysis of the effects of nirmatrelvir/ritonavir on PASC was reperformed. The pre-specified subgroups for the primary outcome included age, sex, previous SARS-CoV-2 infection time, vaccination status, hypertension, diabetes, myocardial infarction, atrial fibrillation, left ventricular ejection fraction, body mass index, cardiopulmonary bypass, and whether participants received UDCA. Moreover, the incidences of adverse events and serious adverse events were reported and compared between the two groups using the χ^2 or Fisher's exact test. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA) and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

A total of 500 patients were recruited from four participating sites in China between January and March 2023 (a flow chart is shown in Fig. S1 online). The ITT analysis comprised 249 and 251 patients in the nirmatrelvir/ritonavir group and the control group, respectively. The mean age of participants was 57.1 ± 11.5 years, and 25.4% of them were females. There were 471 (94.2%) participants who underwent surgery within 7 weeks after SARS-CoV-2 infection and 454 (90.8%) who received at least one dose of COVID-19 vaccine (Table S3 online). The primary outcome occurred in 23 (9.2%) participants in the nirmatrelvir/ritonavir group versus 49 (19.5%) in the control group (RD, −10.3% (97.5% CI, −17.2%, −0.03%); RR, 0.49 (97.5% CI, 0.28, 0.87), Table 1). Regarding the secondary outcomes within 30 d post-surgery, the rates of moderate or severe AKI (5 (2.0%) vs. 17 (6.8%); RD, −4.8% (95% CI, −8.3%, −1.2%); RR, 0.31 (95% CI, 0.11, 0.84)) and COVID-19 pneumonia (14 (5.6%) vs. 31 (12.4%); RD, −6.7% (95% CI, −11.7%, −1.8%); RR, 0.47 (95% CI, 0.25, 0.89)) were significantly lower in the nirmatrelvir/ritonavir group than in the control group. For secondary outcomes within 1 year postoperatively, the rates of renal dysfunction (7 (2.8%) vs. 23 (9.2%); RD, −6.4% (95% CI, −10.5%, −2.2%); RR, 0.31 (95% CI, 0.13, 0.73)) was significantly lower in the nirmatrelvir/ritonavir group than in the control group. No significant difference was observed in the rates of other secondary outcomes between the two groups (Table 1). In addition, the benefits of nirmatrelvir/ritonavir were similar in most of the pre-specified subgroups (Fig. 1).

The PASC occurred in 150 (60.2%) participants in the nirmatrelvir/ritonavir group versus 193 (76.9%) participants in the control group (RD, −16.7% (95% CI, −24.7%, −8.6%; RR, 0.80 (95% CI, 0.71, 0.90), Table S4 online). Nirmatrelvir/ritonavir was associated with reduced risk of sequelae in the shortness of breath (43 (17.3%) vs. 79 (31.5%); RD, −14.2% (95% CI, −21.6%, −6.8%); RR, 0.55 (95% CI, 0.38, 0.80), muscle pain/spasms (36 (14.5%) vs. 58 (23.1%); RD, −8.6% (95% CI, −15.5%, −1.8%); RR, 0.62 (95% CI, 0.41, 0.94), fatigue and malaise (29 (11.6%) vs. 67 (26.7%); RD, −15.0% (95% CI, −21.9%, −8.3%); RR, 0.44 (95% CI, 0.28, 0.68), and dysautonomia (31 (12.4%) vs. 57 (22.7%); RD, −10.3% (95% CI, −16.9%, −3.7%); RR, 0.55 (95% CI, 0.36, 0.86)). After excluding patients with primary or secondary outcomes, the results remain consistent with the main analysis (Table S5 online). In the 30-day post-hoc analysis, the rates of myocardial injury (27 (10.8%) vs. 53 (21.1%); RD, −10.3% (95% CI, −16.6%, −3.9%); RR, 0.51 (95% CI, 0.32, 0.81)), SARS-CoV-2 infection (21 (8.4%) vs. 44 (17.5%); RD, −9.1% (95% CI, −14.9%, −3.3%); RR, 0.51 (95% CI, 0.30, 0.86)), and all-cause pneumonia (17 (6.8%) vs. 36 (14.3%); RD, −7.5% (95% CI, −12.9%, −2.2%); RR, 0.49 (95% CI 0.27, 0.87)) were lower in the nirmatrelvir/ritonavir group than in the control group. However, no significant difference was observed in the rate of composite major complications between the two groups (Table S6 online). Compared with the control group, the incidence of any adverse events in the nirmatrelvir/ritonavir group was lower. Specific adverse events are listed in Table S7 (online).

In this multicenter, open-label, randomized controlled trial, a prophylactic regimen of nirmatrelvir/ritonavir reduced half of the incidence of the primary composite outcome with a low risk of adverse events in vaccinated patients undergoing cardiac surgery.

Table 1
Primary and secondary outcomes.

Outcomes	Nirmatrelvir/ritonavir *n* = 249	Control *n* = 251	RD (%) (95% CI)	RR (95% CI)	*P*
Primary outcome, *n* (%)					
Composite endpoint	23 (9.2)	49 (19.5)	−10.3[a] (−17.2, −0.03)	0.49[a] (0.28, 0.87)	0.005
30-day secondary outcomes, *n* (%)					
All-cause mortality	0 (0)	3 (1.2)	−1.2 (−2.5, 0.1)	0.99 (0.77, 1.27)	0.926
Cardiac death	0 (0)	2 (0.8)	−0.8 (−1.9, 0.3)	0.99 (0.77, 1.27)	0.952
Myocardial infarction	4 (1.6)	7 (2.8)	−1.2 (−3.7, 1.4)	0.58 (0.17, 1.99)	0.388
Stroke	1 (0.4)	0 (0)	0.4 (−0.4, 1.2)	1.00 (0.78, 1.29)	0.975
Moderate or severe AKI	5 (2.0)	17 (6.8)	−4.8 (−8.3, −1.2)	0.31 (0.11, 0.84)	0.021
COVID-19 pneumonia	14 (5.6)	31 (12.4)	−6.7 (−11.7, −1.8)	0.47 (0.25, 0.89)	0.021
Severe pneumonia	11 (4.4)	16 (6.4)	−2.0 (−5.9, 2.0)	0.67 (0.31, 1.44)	0.305
Ventilation ≥ 24 h	6 (2.4)	5 (2.0)	0.4 (−2.2, 3.0)	1.12 (0.34, 3.67)	0.852
Pulmonary embolism	1 (0.4)	0 (0)	0.4 (−0.4, 1.2)	1.00 (0.78, 1.29)	0.975
Re-operation for bleeding	4 (1.6)	7 (2.8)	−1.2 (−3.7, 1.4)	0.61 (0.18, 2.10)	0.433
1-year secondary outcome, *n* (%)					
Cardiac death	1 (0.4)	4 (1.6)	−1.2 (−2.9, 0.5)	0.25 (0.03, 2.25)	0.216
All-cause mortality	1 (0.4)	6 (2.4)	−2.0 (−4.0, 0.1)	0.16 (0.02, 1.36)	0.094
Myocardial infarction	4 (1.6)	7 (2.8)	−1.2 (−3.7, 1.4)	0.58 (0.17, 1.99)	0.388
Stroke	8 (3.2)	7 (2.8)	0.4 (−2.6, 3.4)	1.15 (0.42, 3.19)	0.784
Renal dysfunction	7 (2.8)	23 (9.2)	−6.4 (−10.5, −2.2)	0.31 (0.13, 0.73)	0.007
Rehospitalization for cardiac disease	23 (9.2)	25 (10.0)	−0.7 (−5.9, 4.4)	0.96 (0.54, 1.71)	0.898
Rehospitalization for pulmonary disease	23 (9.2)	31 (12.4)	−3.1 (−8.5, 2.3)	0.75 (0.44, 1.29)	0.299

AKI: acute kidney injury; CI: confidence interval; COVID-19: coronavirus disease 2019; RD: risk difference; RR: relative risk.
[a] Since a two-sided *P*-value of < 0.025 was considered statistically significant for the primary outcome, we calculated the RD 97.5% CI and RR 97.5% CI separately.

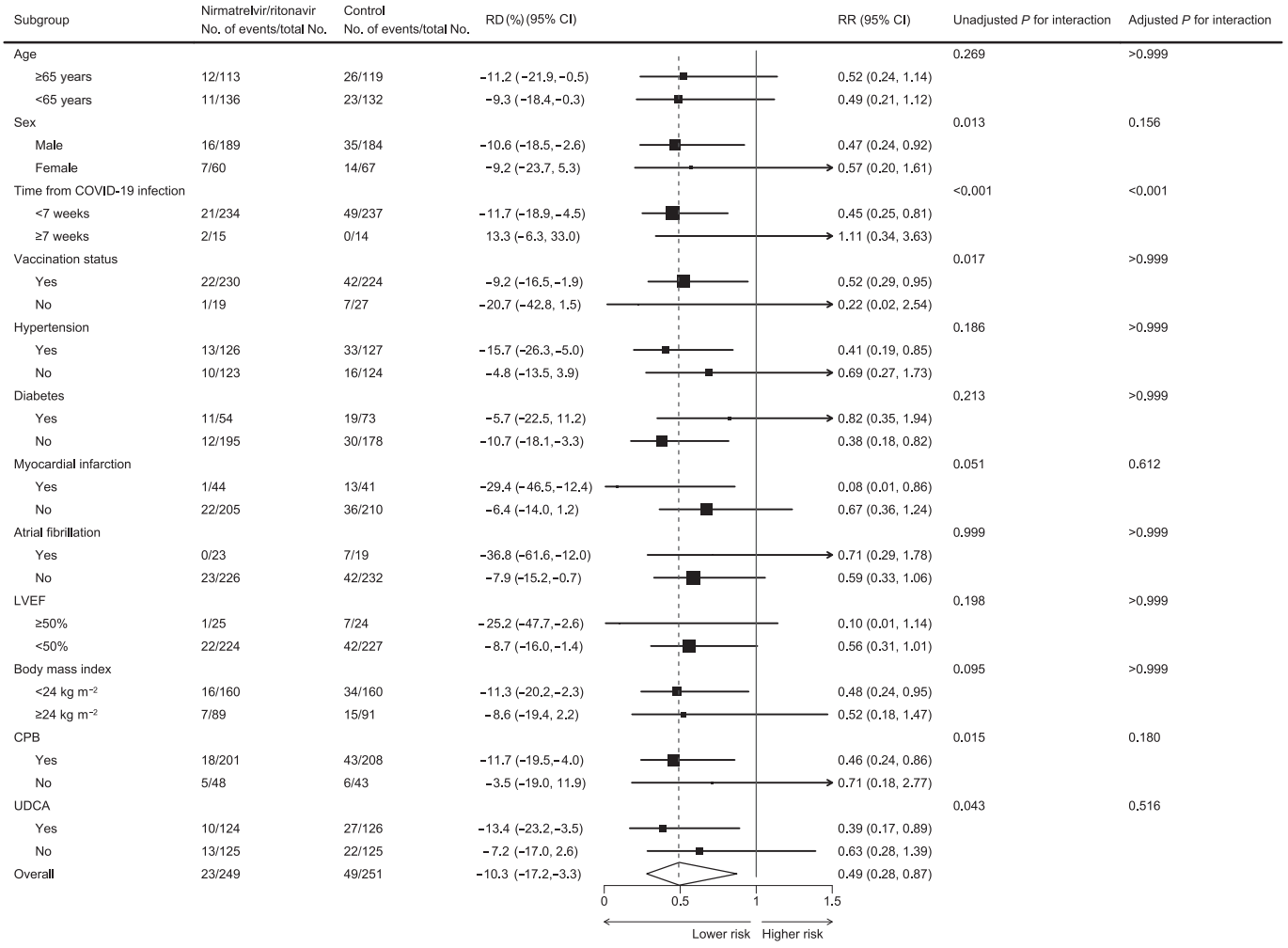

Fig. 1. Subgroup analysis for the primary outcome. CBP: cardiopulmonary bypass; LVEF: left ventricular ejection fraction; UDCA: ursodeoxycholic acid.

Regarding precise and differentiated COVID-19 prevention strategies, our trial offers a promising prevention strategy to reduce postoperative complications and improve prognosis by targeting populations vulnerable to persistent COVID-19.

As population immunity increases, the benefit of virus prevention depends on individual patient vulnerability [9]. Previous trials have reported that nirmatrelvir/ritonavir reduces the risk of severe illness in high-risk outpatients [6,10]; however, the evidence in high-risk inpatients with comorbidities remains limited [11,12]. A trial of 264 inpatients with severe comorbidities reported that nirmatrelvir/ritonavir favored 28-day mortality or SARS-CoV-2 clearance but did not reach significance. This might be explained by the low event rates.

In our study, approximately 90% of vaccinated patients undergoing cardiac surgery had a history of COVID-19. Recent studies demonstrated that patients undergoing cardiac surgery had a higher risk of reinfection because of decreased COVID-19 antibody levels [5]. Furthermore, hybrid immunity was less potent in older individuals [13]. The results extend the evidence on addressing potential viral recurrence and complications for hospitalized patients at high risk for progressing to severe COVID-19. In the current study, the benefits of prophylactic use of nirmatrelvir/ritonavir were primarily driven by a significant reduction in postoperative COVID-19 pneumonia. Despite the unclear underlying mechanism, nirmatrelvir/ritonavir is a peptidomimetic inhibitor of SARS-CoV-2 main protease (M^{pro}) and may help clear residual SARS-CoV-2 RNA [6], thereby reducing COVID-19-related complications including PASC.

Prophylactic treatment with nirmatrelvir/ritonavir was found to be associated with a reduced risk of PASC within 1 year postoperatively. However, a blinded, randomized, placebo-controlled trial involving 155 adults with moderate-to-severe PASC at least 3 months post-infection revealed no significant effects on PASC severity relief following a 15-day regimen of nirmatrelvir/ritonavir medication [8]. Differences in study populations, timing of medication administration, and definition of endpoint events may be the possible reasons for disparities between this trial and ours.

Our subgroup analysis showed that patients undergoing surgery within 7 weeks of SARS-CoV-2 infection had a lower risk of adverse events, possibly due to residual antiviral immunity that inhibits inflammation. Conversely, those with ≥7 weeks post-infection faced higher cardiovascular and inflammatory risks, likely from immune dysregulation and delayed recovery. Our findings indicate that surgical timing may influence clinical outcomes and provide potential evidence on optimal surgery scheduling for post-COVID-19 patients.

Our findings have important clinical and public health implications, particularly for the perioperative management of patients undergoing cardiac surgery with a COVID-19 history. The observed benefits of nirmatrelvir/ritonavir in reducing COVID-19 reinfection, AKI, and myocardial injury indicate a potential role for targeted antiviral prophylaxis in high-risk surgical populations, especially those with multiple comorbidities or immune dysfunction. From a public health perspective, these results highlight the persistent vulnerability of post-COVID-19 patients despite the widespread vaccination era, emphasizing the need for personalized prevention strategies beyond population-level approaches. Furthermore, the interaction between infection timing and surgical outcomes indicates that the optimal timing of elective surgery post-COVID-19 should be carefully considered to minimize complications.

The current study has some limitations. First, the trial adopted an open-label design, which likely did not affect the blinded ascertainment of major outcomes but could have influenced the self-reporting of adverse events. However, the distinct taste of nirmatrelvir/ritonavir raised participants' suspicions of taking the medication, potentially compromising the effectiveness of the blinding procedure. Future studies with blind assessment may further refine our findings. Second, the limited representation of higher-risk subgroups may reduce the generalizability of our findings to patients with delayed surgery or higher surgical risk, potentially affecting the robustness of stratified analyses. Although the primary analysis incorporated a generalized linear model to adjust stratification factors to mitigate potential bias and enhance the robustness of our findings, future studies with a more balanced distribution across risk categories are warranted to validate these findings in diverse patient populations. Third, the trial was conducted during the period in China when Omicron was the dominant strain. This epidemic feature may limit the generalizability of our results but should not influence the results because more recent real-world studies have reported the efficacy of nirmatrelvir/ritonavir across SARS-CoV-2 variants. Fourth, the vaccination status was self-reported. However, the vaccination rate in this study was similar to that reported in the same period in China [14]. Fifth, our post-hoc analysis approach does not rule out the impact of non-PASC factors on symptoms. To address this concern, a sensitive analysis was conducted by excluding patients with primary and secondary outcomes and still observed the association between nirmatrelvir/ritonavir and PASC.

In conclusion, the prophylactic use of nirmatrelvir/ritonavir reduced surgery-related complications, reinfection, and PASC in cardiac surgery patients with previous COVID-19 infection, providing robust evidence to current guidelines as a preventative measure for vulnerable individuals.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Shengshou Hu had full access to all the data in the study and took responsibility for the data integrity and data analysis accuracy. Xin Yuan, Lihua Zhang, Jingkuo Li, and Lubi Lei contributed equally as co-first authors. Xin Yuan, Lihua Zhang, Jingkuo Li, Lubi Lei, Kai Chen, Qing Chu, and Shengshou Hu designed the study. Xin Yuan, Lihua Zhang, Jingkuo Li, and Lubi Lei drafted the manuscript and interpreted the data. Xin Yuan, Jingkuo Li, Lubi Lei, and Yang Wang performed the statistical analysis. Qing Chu, Kai Chen, Wei Feng, Zhaoyun Chen, Xiaoqi Wang, Yan Yang, Shengshou Hu, Yunhu Song, Sheng Liu, Xianqiang Wang, Shuiyun Wang, Liqing Wang, Xin Wang, and Fei Xu made critical revisions of the manuscript for important intellectual content.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2025.04.027.

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