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ORCHESTRA Delphi consensus: diagnostic and therapeutic management of SARS-CoV-2 infection in patients with rheumatological diseases

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ABSTRACT

Objectives: The clinical management of COVID-19 in immunocompromised patients remains a challenge. This work aimed to develop a consensus to establish recommendations for the clinical, diagnostic, and therapeutic management of patients with rheumatic diseases and COVID-19.
Methods: A panel of 14 international experts was selected, and Delphi methodology was used for the consensus, after a systematic literature review. Twenty-four questions were formulated and presented to the panel. The experts voted using a 6-point Likert scale (1) 'Strongly disagree' (SD); (2) 'Disagree' (D); (3) 'Somewhat disagree' (SWD); (4) 'Somewhat agree' (SWA); (5) 'Agree' (A); (6) 'Strongly agree' (SA). To establish consensus, simple or cumulative agreement ≥80% was required over a maximum of three rounds. Cumulative agreement was defined as the sum of response percentages on items 1–2 (SD + D); 2–3 (D + SWD); 4–5 (SWA + A); or 5–6 (A + SA), distinguishing a strong degree of agreement (A + SA) or disagreement (SD + D) from a moderate degree of agreement (SWA + A) or disagreement (D + SWD).
Results: After the three rounds, consensus was reached on 23 of the 24 questions and 10 recommendations were made.
Discussion: The Delphi methodology allowed consensus on recommendations in areas with insufficient scientific evidence, which can be considered for decision-making in the management of patients with rheumatological diseases while awaiting better evidence. **Maria Giulia Caponcello, Clin Microbiol Infect 2025;31:S37**

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Introduction

The prognosis of COVID-19 is influenced by patients' characteristics, including age, underlying conditions, and exposure to immunosuppressive drugs [1], which are frequent among patients with rheumatological diseases. Evidence on the specific impact of COVID-19 in this population is limited and sometimes contradictory. In some studies, the risk of poorer outcomes appears similar to the general population and linked to age and comorbidities [2–4], whereas other studies have found worse outcomes associated with disease activity and the use of certain immunosuppressive drugs [5].

Providing evidence-based recommendations for the management of patients with rheumatological diseases and COVID-19 is challenging because of the lack of adequate studies and the heterogeneity of these patients, which could jeopardize the design and development of future epidemiological studies. Prior recommendations mostly targeted vaccination and rheumatic disease management but not COVID-19 itself and have not been updated after the emergence of the omicron variant [2]. We developed consensus recommendations for the management of COVID-19 in symptomatic patients with rheumatological diseases using a Delphi process. This work was conducted within the Working Package 4 (fragile population cohorts) of the H2020 funded ORCHESTRA study (https://orchestra-cohort.eu/).

Methods

Study design

We used a Delphi consensus method to provide recommendations for the management of COVID-19 in patients with rheumatological diseases. The definitions for rheumatological disease and for risk factors for severe COVID-19 are specified in Supplementary material.

Identification and selection of a panel of experts

Invitations for participation in the questionnaire were sent by e-mail (twice if needed) to ORCHESTRA investigators and to selected members and international collaborators of the Spanish Society of Rheumatology. Experts were contacted via e-mail individually to guarantee anonymity. Of the 26 experts invited based on their expertise, 14 accepted; 6 were from Spain, 6 from Italy, 1 from Sweden and 1 from Portugal; 8 were specialists in rheumatology, 4 in infectious diseases and 2 in clinical immunology. This number of experts was considered adequate for a Delphi consensus [6].

Questionnaire elaboration

The Steering Committee selected topics based on available literature including systematic reviews if exists, and clinical guidelines for the treatment of COVID-19 and vaccination in patients with rheumatological diseases [2,5,7,8]. This report was developed following Accurate Consensus Reporting Document (ACCORD) guidelines (Table S1). The questionnaire comprised 24 questions across six sections: risk of progression to severe COVID-19; COVID-19 prevention; COVID-19 diagnostic; management of COVID-19 in patients under rheumatological treatment; COVID-19 treatment; and COVID-19 vaccination (Table S2).

Questions rounds and agreement

The survey was carried out on the REDCap platform. The three rounds were performed in February 2024, May 2024, and June 2024, respectively. Experts voted using a 6-point Likert scale to indicate the level of agreement for each question: (1) strongly disagree; (2) disagree; (3) somewhat disagree; (4) somewhat agree; (5) agree; (6) strongly agree [8]. During all rounds, experts could provide comments and suggestions in a free text section, and they also could suggest changes in the questionnaire during the first round. After each round, the results were summarized and provided in the next round, alongside questions not reaching the pre-specified agreement. A total cumulative agreement (TCA) was defined as the sum of response percentages in items 1–2 (strongly disagree and disagree); 2–3 (disagree and somewhat disagree); 4–5 (somewhat agree–agree); or 5–6 (agree–strongly agree). Strength of agreement was defined as the sum of response percentages on items 1–2; 2–3; 4–5; or 5–6, distinguishing a strong degree of agreement (5 + 6) or disagreement (1 + 2) from a moderate degree of agreement (4 + 5) or disagreement (2 + 3). A TCA of 80% or more of the questions was required to establish consensus, with a maximum of three rounds to reach consensus [9].

Data analysis and consensus statements

Statements were formulated based on the consensus reached, along with the percentage of agreement/disagreement, the round of consensus, and a strength of agreement/disagreement (moderate or strong) (Table 1).

Results

All 14 experts completed the three rounds. In the first round, consensus was reached for 11/24 questions (45.8%); 8 of them were finalized with no modification. In the second round, consensus was reached for 10/13 remaining questions (76.9% of all questions), without amendments. In the third round, consensus was reached for two of the three questions remaining (95.8% all questions). Therefore, consensus was not achieved for only one question (see Table S2, question #19). The results of each question and round are provided in Table S2. The statements, including agreement and strength of suggestion, are available in Table 1.

Statements

COVID-19 prevention and vaccine

Statement 1. Patients with rheumatological diseases should be included in COVID-19 prevention campaigns.

Initial vaccination recommendation for the rheumatological population was extracted from prior experience with other infectious diseases like influenza [10]. Considering that this population was excluded from clinical development and phase III efficacy trials for SARS-CoV-2 vaccines [11], suboptimal vaccine responses [12], risk of waning immunity and vaccine's efficacy with the emergence of new variants of concern [13], we asked the experts for their opinion on prevention campaigns for COVID-19, referring to all to all general prevention campaigns implemented, including hospital protocols for prevention and national preventions campaigns. The panel generally agreed on including the rheumatological population in COVID-19 prevention campaigns. Although a strong agreement was reached for systemic autoimmune rheumatological diseases, it was only after three rounds that a moderate agreement for patients with musculoskeletal diseases was reached (see question #3, 80% TCA; see question #4, 86.6% TCA, Table S2).

Statement 2. The rheumatological population should be prioritized in vaccination campaigns and vaccinated annually for COVID-19. When in treatment with rituximab, vaccination should be administered at least 6 months after the last cycle and/or a minimum of 4 weeks before the next cycle.

Table 1
Statements, percentage of agreement, and strength of suggestion

		# Questions	% agreement	Round	Strength
COVID-19 prevention and vaccine					
Statement 1	Patients with rheumatological disease should be included in COVID-19 prevention campaigns.	3–4	80–86.6	3–1	Moderate/strong
Statement 2	The rheumatological population should be prioritized in vaccination campaigns and vaccinated annually for COVID-19. In patients receiving rituximab treatment, vaccination should be administered at least 6 months after the last cycle and/or a minimum of 4 weeks before the next cycle.	22–23–24	86.6–93.3	1–2	Strong
Statement 3	Early antiviral treatment should be initiated in patients with rheumatological disease receiving immunomodulatory treatment on diagnosis of symptomatic COVID-19, regardless of symptoms severity and general risk factors	5–6	80	2	Moderate/strong
Diagnosis of COVID-19					
Statement 4	In patients with clinical and radiological signs of a lower respiratory tract viral infection but a negative nasopharyngeal antigen test, a SARS-CoV-2 PCR test should be performed to confirm or rule out COVID-19.	7	86.6	1	Strong
Risk of progression to severe COVID-19					
Statement 5	The risk of severe COVID-19 is heterogeneous among patients with rheumatological disease with no other specific risk factors for developing severe COVID-19. This applies to patients with autoimmune, autoinflammatory, and musculoskeletal rheumatological diseases.	1–2	86.6–80	1	Strong
Management of COVID-19 in patients under rheumatological treatment					
Statement 6	Treatment with immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, or tacrolimus); synthetic DMARDs (JAK inhibitors and apremilast) and/or biological DMARDs (TNF inhibitors, IL-6 inhibitors, IL-1 inhibitors, IL-17A/17F/17AF, IL-12/23 inhibitors, Cytotoxic T lymphocyte-associated antigen-4-Ig (CTLA4-Ig), and anti-BAFF) should be withdrawn in patients with rheumatological disease with a confirmed COVID-19 diagnosis who present mild or severe symptoms.	8–9–11 13–14–16	80–86.6–93.3 80–80–100	2 1	Moderate Strong
Statement 7	Treatment with rituximab should be postponed or changed, when possible, in patients with rheumatological disease with a confirmed COVID-19 diagnosis who present mild or severe symptoms.	10–15	86.6–100	1	Strong
Statement 8	Treatment with glucocorticoids should not be withdrawn in patients with rheumatological disease with a confirmed COVID-19 diagnosis who present mild or severe symptoms.	12–17	80–86.6	1–2	Moderate
Statement 9	In case of a documented COVID-19 infection in patients with rheumatological disease, an individual risk assessment is advised and if deemed beneficial patients should be treated with either nirmatrelvir/ritonavir or remdesivir. Combination of the two treatments or administration of either with a monoclonal antibody is not advised.	18–19–20	80	2–3	Moderate
Statement 10	Routine anti-S serology testing is not recommended for guiding COVID-19 treatment decisions in patients with rheumatological disease.	21	80	2	Moderate

BAFF, B-cell activating factor; DMARD, disease-modifying anti-rheumatic drugs; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor, CTLA4-Ig, Cytotoxic T lymphocyte-associated antigen-4-Ig.

As stated above, patients with rheumatological diseases can have a lower and slower response to vaccination. However, COVID-19 vaccination was not associated with increased rate of flares in patients with rheumatoid arthritis and psoriatic arthritis [14]. The emergency of SARS-CoV-2 variants with increased infectivity has impacted the effectiveness of vaccine protection [14]. Rituximab treatment impairs the humoral immune response to COVID-19 vaccines, making the timing between rituximab administration and vaccination crucial for effectiveness [14,15]. When questioned on these topics, the panel strongly agreed, after the first round, on prioritizing the rheumatological population in vaccine campaigns (see question #22, 86.7% TCA, Table S2). After the second round, the panel strongly agreed with an annual vaccination for COVID-19 in patients with rheumatological diseases. The panel also agreed that for patients in treatment with rituximab vaccination should be timed either 6 months after the last cycle or at least 4 weeks before the next cycle (see questions #23 and 24, 86.6% and 93.3% TCA, respectively, Table S2). Although the experts strongly supported these recommendations, they noted that individual factors such as type of rheumatic disease, type of rheumatological treatment, and individual risk factors should be considered. This aligns with recent findings suggesting a minimum of 9 months between rituximab infusion and vaccination [16].

Statement 3. Early antiviral treatment should be initiated in patients with rheumatological diseases receiving immunomodulatory treatment upon diagnosis of symptomatic COVID-19, regardless of symptoms severity and general risk factors.

The panel generally agreed with the administration of early antiviral treatment in patients with rheumatological diseases receiving immunomodulatory drugs, regardless of general risk factors. For patients with such factors, a strong agreement was reached after two rounds (see question #6, 80% TCA, Table S2), and for patients without general risk factors, a moderate agreement was reached after two rounds (see question #5, 80% TCA, Table S2). The panel expressed the need for more data on antiviral treatment in this population to evaluate its benefits against the risk of severe disease progression. The panel also underlined the importance of instructing patients to have a test performed in case of possible infection and to contact their treating physician as soon as possible if a diagnosis is confirmed. Early antiviral treatment should be started preferably within the first 5 days after symptom onset, according to the WHO and Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) guidelines.

Diagnosis of COVID-19

Statement 3. In patients with clinical and radiological signs of lower respiratory tract viral infection but a negative nasopharyngeal antigen test, SARS-CoV-2 RT-PCR test should be performed to confirm or rule out COVID-19.

The panel, after the first round, strongly agreed with performing a SARS-CoV-2 RT-PCR in patients with evidence of lower respiratory tract viral infection despite a nasopharyngeal antigen test (see question #7, 86.7% TCA, Table S2). It was noted by the panel that this decision was based on the experience of potential lower sensitivity of antigen test specially for new circulating strains and different clades. RT-PCR for SARS-CoV-2 is considered the reference standard for diagnosis.

Risk of progression to severe COVID-19

Statement 1. The risk of severe COVID-19 is heterogeneous among patients with rheumatological diseases with no other specific risk factors for developing severe COVID-19. This applies to patients with autoimmune, autoinflammatory, and musculoskeletal rheumatological diseases.

Patients with rheumatological diseases were intuitively considered among high-risk populations for developing severe COVID-19 at the start of the pandemic [17]. Evidence from large population-based studies showed that the increased risk became non-significant when adjusted for age or sex and applies primarily to specific rheumatological conditions such as rheumatoid arthritis, lupus, or psoriatic arthritis [18,19]. The panel agreed that not all patients with rheumatological diseases, with autoimmune/autoinflammatory or musculoskeletal disease, have the same risk for progression to severe disease in case of COVID-19 (see questions #1–2, TCA 86.6% and 80%, respectively; Table S2). The panel noted that rheumatological diseases encompass a wide range of conditions with varying disease burdens. The risk of progression, excluding general risk factors, largely depends on the disease type (i.e. inflammatory versus non-inflammatory conditions), as well as the severity and treatment of the disease. Thus, it is crucial to identify individuals at higher risk of progressing to severe disease.

Management of COVID-19 in patients under rheumatological treatment

Statement 4. Treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs) (methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate or tacrolimus); targeted synthetic DMARDs (Janus kinase inhibitors and apremilast) and/or biological DMARDs (tumour necrosis factor inhibitors [TNF], interleukin-6 [IL-6] inhibitors, IL-1 inhibitors, IL-17A/17F/17AF inhibitors, IL-12/23 inhibitors, abatacept (Cytotoxic T lymphocyte-associated antigen-4-Ig, CTLA4-Ig), anti-TNF family ligand B-cell activating factor) should be withdrawn in patients with rheumatological diseases with a confirmed COVID-19 diagnosis that present mild or severe symptoms.

Patients receiving immunosuppressive drugs may fail to control viral replication, possibly leading to complications and severe disease. Because of the heterogeneity of diseases and immunosuppressive drugs, there may be some uncertainty regarding the risk/benefit balance of interrupting treatment. However, immunosuppressants do not seem to be deleterious in this scenario, and the control of inflammatory activity seems to be key [20]. The panel reached a moderate agreement after the second round on withdrawing these drugs in patients with mild symptoms (see questions #8, 9 and 11; 80%, 86.6% and 86.6% TCA, respectively, Table S2) whereas a strong agreement was reached after the first round in the case of patients with severe symptoms (see questions #13, 14, and 16, all with 80% TCA, Table S2). Although we did not ask about specific immunomodulatory/immunosuppressive drugs, and even considering that the CDC includes all immunosuppressive drugs in the 'increased risk' group [21], the panel believed drug-related risks may vary. Synthetic DMARDs, specifically Janus kinase inhibitors, are under review for their potential increased risk of viral infections [22], suggesting temporary withdrawal unless the rheumatological disease is severe. Apremilast has a different safety profile and may be continued in patients with mild symptoms [23]. In contrast, TNF inhibitors have even been associated with lower risk of severe COVID-19 [24]. The final consensus was to proceed with a precautionary suspension in patients with severe COVID-19, although a dose reduction could also be considered when possible. We suggest that additional research be carried out to provide more specific and targeted recommendations regarding the different categories of DMARDs and their withdrawal.

Statement 5. Treatment with rituximab should be postponed or changed, when possible, in patients with rheumatological diseases with a confirmed COVID-19 diagnosis that present mild or severe symptoms.

Rituximab is consistently associated with worse outcomes in general [5], and data in patients with rheumatoid arthritis and receiving this drug are consistent with this statement [25]. The panel strongly agreed, after round 1, on postponing next dose at least until symptoms disappearance or therapy modification when feasible, for patients with mild and severe symptoms in treatment with rituximab (see question 10, 86.6% TCA and question #15, 100% TCA, Table S2). It is currently common practice to withhold or postpone the next dose of rituximab in case of any infection [8,17,26]. The panel also acknowledged that exception may be made for life-threatening rheumatological disease such as central nervous system-associated vasculitis.

Statement 6. Treatment with glucocorticoids should not be withdrawn in patients with rheumatological diseases with a confirmed COVID-19 diagnosis that present mild or severe symptoms.

Treatment with glucocorticoids has been implemented in COVID-19 treatment since the start of the pandemic, and although glucocorticoids have been demonstrated to be an effective treatment for COVID-19 in the acute setting [27], registry data suggest that chronic glucocorticoids increase the odds of hospitalization for COVID-19 in patients with rheumatic disease [7]. The panel moderately disagreed after the first round with the withdrawal of treatment with glucocorticoids in patients with mild symptoms (see question #12, 80% TCA), and moderately disagreed after the second round in the case of patients with severe symptoms (see question #17, 86.6% TCA). It was underlined by the panel that it mostly depends on the dose, duration, and the underlying condition. Glucocorticoids are known to have benefits when initiated for moderate-to-severe COVID-19, but are also associated with worse outcomes among those on baseline glucocorticoids at the time of infection, although this may be explained by residual disease activity [8]. At the same time, corticosteroids are not recommended for mild cases; therefore, probably more data are needed in patients treated with corticosteroids developing mild COVID-19. This further highlights the importance of appropriate patient management and controlling rheumatic disease activity in the context of a pandemic. The dose chosen must consider both the desired therapeutic response, the risk of undertreatment and development of glucocorticoid-related adverse event [28]. An abrupt suspension of glucocorticoids could lead to glucocorticoid-induced adrenal suppression in some patients, for which glucocorticoid supplementation in the context of COVID-19 should be implemented [29]. The panel suggest a general review of steroid therapy, aimed at tapering glucocorticoids down to the lowest possible dose.

COVID-19 treatment in patients with rheumatological diseases

Statement 7. In case of a documented COVID-19 infection in patients with rheumatological diseases, individual risk assessment is advised and if deemed beneficial, patients should be treated with either nirmatrelvir/ritonavir or remdesivir. Combination of the two treatments, or administration of a monoclonal antibody is not advised.

As stated before, patients with compromised immune systems may experience a prolonged viral replication phase, altering the typical progression of COVID-19. Consequently, treatment recommendations for the general population often need to be tailored for high-risk patients with rheumatic diseases [17]. The panel moderately agreed after the second round about treatment with either nirmatrelvir/ritonavir or remdesivir in patients with rheumatological diseases diagnosed with COVID-19, preferably after an individual risk assessment (see question #18, 80% TCA Table S2). The panel remarked that the selection of this treatment depends on general COVID-19 risk factors, the specific rheumatic disease and its treatment, and the patient's vaccination status. When asked about administering either of the above-mentioned treatments in combination with a monoclonal antibody, the panel moderately disagreed after the third round (see question #20, 80% TCA, Table S2). The panel generally disagreed with combination therapy for the general rheumatological population. Treatment decisions should be individualized based on general risk factors, the state of the rheumatological disease and its treatment, and vaccination status, aligning with most recommendations for these drugs [30]. For the use of nirmatrelvir/ritonavir, considering the potential interactions of ritonavir is mandatory, even if it is intended to be used for a few days.

Statement 8. Routine anti-S serology testing is not recommended for guiding COVID-19 treatment decisions in patients with rheumatological diseases.

Although vaccine efficacy in general population has been achieved 90–95% [31], most people with immune or inflammatory rheumatic disease generate antibody responses but with lower antibody titres [10]. Antibody-S can be considered as a parameter for immunogenicity of the vaccination. The panel moderately disagreed after the second round, where a clarificatory note was added to specify the type of serology in question, when asked if an anti-S should be performed on all patients with rheumatological diseases when evaluating treatments (see question #21, 80% TCA). The panel commented that it may be performed in specific patients, depending on the rheumatic disease and treatment plus other risk factors. Although anti-S can be used to assess the response of the patient to the vaccine, it is not a universal parameter to consider for treatment evaluation, especially for patients who have proven to be *naïve* to the vaccine, where pre- or post-exposure prophylaxis is a valid alternative to vaccination.

Limitations

The main limitation of this consensus document lies in the intrinsic limitations of the Delphi methodology. Because of the anonymity of the survey, live discussions among the experts were not possible. However, a comprehensive feedback section was provided after each round. This section informed the experts about the general voting results from the previous rounds, as well as comments made by other experts. Two geographical biases are to be considered as limitations to this paper: one concerning the research team, as it is formed by researchers from the same country that formulated the questionnaire, a bias that can affect topic selection and the other concerning the experts, with the vast majority being from Southern Europe (12/14) which may limit recommendation generalizability.

Finally, it is important to remark that statements derived from Delphi consensus are at a lower level within the pyramid of evidence and cannot substitute a critical assessment of data obtained by a systematic review of the literature or similar. However, in many scenarios, consensus of expert may be the only way to provide statements or recommendations in the lack of appropriate evidence.

Conclusions

In conclusion, this Delphi consensus study offers much-needed, evidence-informed guidance to rheumatologists and other clinicians involved in the care of patients with rheumatological diseases during the ongoing COVID-19 pandemic. By addressing critical knowledge gaps and achieving consensus among experts, this study empowers healthcare providers to make informed decisions regarding the management of SARS-CoV-2 infection in this vulnerable population.

Briefly, the panel agreed on the existence of a different risk of progression to severe COVID-19 infection, in absence of risk factors, in the different rheumatological populations and the need for this population to be included and prioritized in prevention campaigns and annual vaccination against SARS-Cov-2; it also agreed on the early administration of antiviral treatment in patients under immunomodulatory treatment, while also recommending an individual evaluation before administration of nirmatrelvir/ritonavir or remdesivir and avoiding combination or joint use with a monoclonal antibody; however, the panel does not consider anti-S antibody level as a parameter to take into account for establishing treatment; it recommends interruption of immunosuppressive treatments in patients with mild and severe symptoms, excluding corticosteroids; and strongly suggests postponement of rituximab administration in patients with a confirmed COVID-19 diagnosis; and regarding diagnostics they also agreed on the performance of a PCR test in the case of negative antigen but compatible symptoms with COVID-19 disease.

The recommendations presented herein, encompassing vaccination strategies, diagnostic approaches, and therapeutic interventions, are particularly valuable given the scarcity of randomized controlled trials in this specific patient group. Although acknowledging the evolving nature of COVID-19 and the potential for future therapeutic advancements, this consensus statement serves as a timely and practical resource to optimize patient care and outcomes.

Furthermore, this Delphi process underscores the importance of fostering collaboration and knowledge exchange among experts to address pressing clinical questions in the absence of definitive evidence. It also highlights key areas where future research, including randomized clinical trials and adaptive platform trials, is urgently needed to refine and expand our understanding of COVID-19 in the context of rheumatic diseases. By building upon this foundation of expert consensus, we can continue to advance the care of patients with rheumatological diseases and enhance their resilience in the face of ongoing and future infectious disease threats.

Author contributions

J.R.-B. and Z.R.P.-B. contributed to conceptualization, methodology, and supervision. M.G.C., P.O.N., and Z.R.P.-B. contributed to investigation. M.G.C. and P.O.N. contributed to writing—original draft. M.G.C., P.O.N., J.R.-B., and Z.R.P.-B. contributed to writing—review and editing and formal analysis. All authors reviewed the results and approved the final version of the manuscript. M.G.C. and P.O.N. contributed equally to this work. J.R.-B. and Z.R.P.-B. contributed equally to this work.

Transparency declaration

Potential conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.02.030.

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