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OPEN PEER REVIEW

Clinical and Functional Characteristics of Cardiovascular System in Children Who Have Undergone COVID-19

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 4 May 2025 – 13 May 2025

Referee 1 Reviewer

ACCEPT 4 May 2025

accepted

Associate Editor

MAJOR REVISION 12 May 2025

Dear Authors,

Thank you for submitting your manuscript, "Clinical and functional characteristics of cardiovascular system in children who have undergone COVID-19," to International Cardiovascular Research Journal. After careful consideration by the reviewers, I invite you to revise and resubmit your work to address significant concerns.

The reviewers identified several issues requiring attention. While the topic is of interest, these revisions are essential to ensure the manuscript meets the journal's standards.

Address all reviewer comments thoroughly in a point-by-point response, provide detailed explanations for any disagreements with reviewer suggestions, highlight changes in the revised manuscript, and resubmit your revised manuscript for further evaluation.

Please note that this decision does not guarantee acceptance, as the revised manuscript will undergo another round of review. We encourage you to carefully consider the reviewers' feedback to strengthen your work.

Final Decision: Major Revision

Kind Regards | Publisher Supervisor

Editor-in-Chief

MAJOR REVISION 13 May 2025

Please make the revisions based on the comments and resubmit the paper.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Clinical and functional characteristics of cardiovascular system in children who have undergone COVID-19

Dear Editor of the “International Cardiovascular Research Journal”,

We highly appreciate your support and recommendations. We have received all of your comments and happy to reply to all of them bellow.

Reviewer 1:

1. Question:

Sample Size and Selection: While the retrospective study included 400 records, the in-depth analysis in Stage 3 was limited to 40 children. Further details on the selection criteria for these 40 children would be beneficial to understand the representativeness of this subgroup. Was this a consecutive series of children with detected changes, or were other factors involved?

Reply:

We thank the reviewer for this important question regarding the selection process for the Stage 3 subgroup (n=40). Below, we provide a detailed explanation.

The 40 children included in Stage 3 were not a random or consecutive sample. They were purposefully selected from the main group based on objective cardiovascular abnormalities identified during Stage 2 follow-up (24–36 months post-COVID-19): persistent cardiovascular symptoms, ECG abnormalities (e.g., PQ interval shortening ≥9.3%, QT prolongation, ventricular extrasystoles), blood pressure irregularities.

The sample size reflects the prevalence of actionable findings within the Stage 2 cohort (n=228): 9.3% of adolescents exhibited PQ interval shortening. Approximately 35% of symptomatic children demonstrated rhythm disturbances or BP irregularities.

The Stage 3 cohort was enriched for pathology in order to meet the study’s objective of characterizing long-term cardiovascular sequelae in high-risk cases.

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2. Question:

Deep Learning Stage: The description of Stage 3 as “a deep learning of the cardiovascular system” is vague. Please clarify what “deep learning” specifically entails in this context. Does this refer to a specific analytical approach or a more in-depth clinical assessment?

Reply:

We thank the reviewer for the comment. We agree that clarifying the selection criteria for the subgroup of 40 children who underwent an in-depth examination at

the third stage is important for understanding the representativeness of the sample.

We clarify that “deep learning” refers to a more in-depth clinical assessment.

In particular, only those children from the main group of the Stage 2 with complaints indicating possible cardiovascular pathology (e.g., heart pain, dyspnea, dizziness, fainting, arrhythmias) and/or ECG changes or abnormalities in blood pressure levels were included in the in-depth examination at the third stage. More detailed exploration of possible cardiac abnormalities in the most vulnerable part of the cohort included immunological and biochemical examination, coagulogram, cardiac ultrasound, 12-lead Holter monitoring and 24-hour BP monitoring.

We hope that this clarification will increase the understanding of the logic of forming this subgroup and the representativeness of the data obtained in the context of the study objectives.

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3. Question:

Methodology Detail: More detailed information on the methods used for ECG interpretation, blood pressure measurement, and assessment of heart rhythm disorders would be valuable. For instance, what specific criteria were used to define “P wave and QT interval change” or “insufficient blood pressure reduction at night”?

Reply:

We thank the reviewer for the comment. We agree that clarification of the methodology of ECG interpretation, blood pressure measurement and assessment of heart rhythm disorders is important for understanding the results of the study.

ECG interpretation was performed by qualified pediatric cardiologists according to the standards accepted in pediatric cardiology. P wave changes were evaluated with regard to its amplitude and duration in different leads, according to age-appropriate norms. The QT interval was measured manually in standard leads, with subsequent conversion to QTc using the Bazett formula. Values exceeding age references were taken as prolonged QTc interval:

- >450 ms in boys
- >460 ms in school-aged and adolescent girls.

Blood pressure was measured in a quiet environment, in a sitting position, using automatic tonometers calibrated before the study. Daily blood pressure monitoring (DBPM) using the BPLab devices (model MnSDP-2) were used to clarify the daily BP profile. Insufficient BP reduction at night was considered to be the level of daily index (DI) <10%, which corresponds to the criteria of non-dipper profile.

Daily ECG monitoring was performed by 12-lead recorders manufactured by Inkart LLC (Russia). Data analysis included assessment of heart rate, presence of supraventricular and ventricular extrasystoles, episodes of tachy- or bradycardia,

and conduction disorders. The criteria for rhythm disturbances were based on the recommendations of the European Society of Cardiology (ESC) and national clinical protocols.

We hope that this explanation will help to interpret the applied methods more accurately and increase the transparency of the results obtained.

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4. Question:

Discussion: The conclusion highlights important findings, but a more detailed discussion section would strengthen the manuscript. This section could:

***Compare the findings with existing literature on pediatric COVID-19 cardiovascular complications.**

***Discuss potential mechanisms underlying the observed cardiovascular changes (e.g., direct viral effects, inflammatory responses, autonomic dysfunction).**

***Address any limitations of the study (e.g., sample size in Stage 3, potential for selection bias, reliance on retrospective data in Stage 1).**

Reply:

We thank the reviewer for the comment. We agree that a more detailed discussion section strengthens the manuscript.

We have added more comparison with relevant literature reviews devoted to pediatric COVID-19 cardiovascular complications in the discussion section. The added paragraphs are highlighted using yellow color.

New literature references are highlighted with yellow color as well.

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5. Question:

Language and Clarity:*Ensure consistent terminology throughout the manuscript.*Some sentences could be rephrased for better clarity. For example, “The clinical course mostly used to be mild to moderate” could be improved.*Proofread carefully for grammatical errors and typos.

Reply:

We thank the reviewer for the comment. A part of sentences was rephrased, some words were changed in order to achieve a higher academical level. The article was reread several times for grammatical purpose. All the corrections are highlighted with yellow color.

Thank you for your time and consideration. We truly appreciate your willingness to support the article and share your expertise.

Kind regards,

Zhamiliya Issanguzhina,

Candidate of Medical Sciences,

The associate professor of the Department of Children Diseases #2,

West Kazakhstan Marat Ospanov Medical University,

Aktobe, Kazakhstan.

2 Revision 1

3 comments · 31 May 2025 – 1 Jun 2025

Referee 2 Reviewer

MINOR REVISION 31 May 2025

What does STATISTICS 10.0 mean in the working method? (in the abstract)
What does Statistika 10.0 mean in the working method? (in the main body)
You have provided a significance level, so you must have used statistical tests. Please include the tests used in the methods section of the abstract and the main body of the paper. It is best to seek the help of an experienced biostatistician in this field and perform the analyses with standard software.

Associate Editor

MINOR REVISION 1 Jun 2025

minor revision

Editor-in-Chief

MINOR REVISION 1 Jun 2025

Please make the revisions based on the comments.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Clinical and functional characteristics of cardiovascular system in children who have undergone COVID-19

We sincerely thank the reviewers and the editorial board of the International Cardiovascular Research Journal for time, expertise, and thoughtful evaluation of our manuscript. Your opinion is a valuable contribution to the refinement of the work. The detailed analysis and constructive feedback make our article more scientifically valuable and informative.

We have thoroughly revised the article in accordance with the comments provided. A point-by-point response to each of the reviewers' and editor's suggestions is presented below.

Reviewer 1:

1. Question:

What does STATISTICS 10.0 mean in the working method? (in abstract)

What does Statistika 10.0 mean in the working method? (in main body)

You have provided a significance level, so you must have used statistical tests. Please include the tests used in the methods section of the abstract and the main body of the paper. It is best to seek the help of an experienced biostatistician in this field and perform the analyses with standard software

Reply:

Thank you for pointing out this discrepancy. It was caused by a technical error that did not alter the study's results or conclusions.

Statistical analyses were performed using IBM SPSS Statistics, version 25. Descriptive statistics, including medians, interquartile ranges (IQR), frequencies and percentages, were used to characterize clinical variables. Normality of distribution of quantitative variables was tested using the Shapiro-Wilk test. As most variables deviated from a normal distribution ($p < 0.05$), nonparametric methods were applied for further analyses. The Mann-Whitney U test was used to evaluate group differences. Tests were two-tailed and results were considered statistically significant at $p < 0.05$ and $p < 0.001$.

Questions of the checklist:

1. Question:

Title and abstract - Did the abstract provide an informative and balanced summary of what was done and what was found?

Peer Review: The abstract provides a clear summary of the study's background, objective, methods, results, and conclusion. It effectively communicates the focus on the cardiovascular system in children post-COVID-19 and the key findings related to cardiac changes and the need for long-term follow-up.

Reply:

We appreciate the reviewer’s positive evaluation of the abstract. We are pleased to hear that it clearly communicated the study's background, objectives, methodology, and key findings. Our aim was to ensure that the abstract provides a comprehensive and balanced summary, and we are glad that this was recognized. Thank you for your constructive feedback.

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2. Question:

Background/rationale - Did the authors explain the scientific background and rationale for the investigation being reported?

Peer Review: The background section explains the scientific context, highlighting the uncertainties about the effects of COVID-19 on children's organs and systems, particularly the cardiovascular system. This provides a rationale for the study.

Reply:

Thank you for your thoughtful feedback. We are pleased that the background section was found to clearly convey the scientific context and effectively justify the rationale for our investigation. Our goal was to highlight the existing knowledge gaps regarding the impact of COVID-19 on the pediatric cardiovascular system, and we appreciate your recognition of this effort.

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3. Question:

Objectives - Did the authors state specific objectives, including any prespecified hypotheses?

Peer Review: The objective is clearly stated: to study the clinical and functional state of the cardiovascular system in children with a history of COVID-19. However, no specific hypotheses are mentioned.

Reply:

A specific scientific hypothesis is not explicitly mentioned in the title's formulation (or structure), it is implied and can be outlined as following: children who have experienced various clinical forms of laboratory-confirmed COVID-19 are at significant risk of developing cardiovascular disorders. This is fully consistent with findings from various researchers and forms the basis of our scientific hypothesis.

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4. Question:

Study design - Did the authors present key elements of study design early in the paper?

Peer Review: The study design is described in the "Materials and methods" section, detailing the three stages of the research. This includes a retrospective study and prospective follow-up, which are key elements of the cohort study design.

Reply:

Thank you for your constructive feedback. We appreciate your acknowledgment of the clarity with which the study design was presented. Our aim was to outline the key elements of the cohort study design—including the retrospective and prospective components—clearly in the "Materials and Methods" section. We are pleased that this structure was found to be appropriate and informative.

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5. Question:

Setting - Did the authors describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection?

Peer Review: The setting is described as the Regional Infectious Diseases Hospital of Aktobe, Kazakhstan. However, specific dates for recruitment, exposure, and follow-up are not provided in the abstract.

Reply:

The specific enrollment dates are indicated in the abstract and Methods section of the research article now — patients were hospitalized in the Regional Infectious Diseases Hospital from October to December 2020, with subsequent study phases conducted in 2023- 2024. All corrections are highlighted with yellow color.

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6. Question:

Participants - Did the authors give the eligibility criteria, and the sources and methods of selection of participants?

Peer Review: The abstract mentions the age range of participants (1 to 18 years) and that they were hospitalized with a confirmed diagnosis of coronavirus infection. However, detailed eligibility criteria and selection methods are not provided.

Reply:

Inclusion criteria: children from 1 to 18 years old with a history of PCR-confirmed COVID-19. Exclusion criteria: children with no laboratory-confirmation of COVID-19. The initial cohort included 400 children with PCR-confirmed COVID-19. During the second stage, children with congenital anomalies, genetic syndromes, or chronic somatic conditions that could potentially influence cardiovascular function were excluded. As a result, the final study group comprised 228 participants. The 40 children included in Stage 3 were selected from the main group based on objective cardiovascular abnormalities identified during Stage 2

follow-up: persistent cardiovascular symptoms, ECG abnormalities (e.g., PQ interval shortening ≥9.3%, QT prolongation, ventricular extrasystoles), blood pressure irregularities.

In addition, we wrote “children from 1 to 18 years old with a history of PCR-confirmed COVID-19” in the Methods section (highlighted with yellow color).

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7. Question:

Variables - Did the authors clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers?

Peer Review: The abstract mentions outcomes related to cardiovascular changes, such as ECG changes and blood pressure issues. However, exposures, predictors, potential confounders, and effect modifiers are not explicitly defined.

Reply:

Limitations and shortcomings are attached in the Appendix file now. The study population is limited to children and adolescents from the city of Aktobe, which restricts the generalizability of the findings to other regions and populations. Some age subgroups include an insufficient number of participants, potentially reducing the statistical significance and reliability of the results.

The analysis did not account for potential factors that may influence the long-term consequences of COVID-19, such as pre-existing health conditions, socioeconomic status, and access to medical care. The cross-sectional study design does not allow for the establishment of causal relationships between the observed symptoms, cardiovascular changes, and prior COVID-19 infection.

Although elevated IgG levels were detected, data on the durability of immunity remain limited, warranting further investigation. All of these limitations will be addressed in our future research through broader regional coverage, increased sample size, and the inclusion of additional variables for more comprehensive analysis.

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8. Question:

Data sources/measurement - Did the authors give sources of data and details of methods of assessment (measurement)?

Peer Review: The abstract describes the use of clinical, laboratory, and instrumental examinations, including ECG and serum IgG antibody levels, as methods of assessment.

Reply:

Thank you for your positive assessment. We appreciate your recognition of the clarity in describing the data sources and assessment methods in the abstract. Our

intention was to ensure that the use of clinical evaluations, laboratory testing, ECG, and serological analysis was communicated concisely and accurately. We are glad it was effectively conveyed.

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9. Question:

Bias - Did the authors describe any efforts to address potential sources of bias?

Peer Review: The abstract does not mention any efforts to address potential sources of bias.

Reply:

According to the comment, the abstract was supplemented with the following: In order to increase reliability, strict selection criteria were followed, standardized methodologies and standardized surveys were used, and interpretation was done by independent specialists. Social factors were omitted.

The following was added to the Methods section of the article: In order to increase the reliability of the results and eliminate potential bias, the following measures were taken: inclusion and exclusion criteria were strictly observed, which ensured homogeneity of the sample in terms of clinical and demographic characteristics. Retrospective analysis of medical records was performed using standardized data collection form minimizing the influence of subjective factors. All clinical, laboratory, and instrumental examinations were performed according to unified standards and on certified equipment, and interpretation of the results (in particular, ECG) was performed by specialists unaware of the patients' clinical history, which excluded observational bias. The sample at the 3 stage was formed exceptionally on the basis of objective medical indications, with omitting socioeconomic factors.

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10. Question:

Study size - Did the authors explain how the study size was arrived at?

Peer Review: The abstract mentions the number of participants (400 pediatric medical records and 40 children for in-depth assessment) but does not explain how these numbers were determined.

Reply:

The Methods section of the article is supplemented with following: The total sample comprised 400 children with PCR-confirmed COVID-19, enabling broad age representation and providing sufficient statistical power to identify general patterns and assess the frequency of clinical-functional alterations… The 40 children included in Stage 3 were purposefully selected from the main group based on objective cardiovascular abnormalities identified during Stage 2 follow-up: persistent cardiovascular symptoms, ECG abnormalities (e.g., PQ interval shortening ≥9.3%, QT prolongation, ventricular extrasystoles), blood pressure

irregularities. The selection was clinically justified and aimed at a more detailed study of possible cardiac disorders in the most vulnerable part of the subjects.

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11. Question:

Quantitative variables - Did the authors explain how quantitative variables were handled in the analyses?

Peer Review: The abstract does not provide details on how quantitative variables were handled in the analyses.

Reply:

Quantitative data were described as medians and quartiles (Q1 and Q3). We added following to the Methods section: Descriptive statistics, including medians, interquartile ranges (IQR), frequencies and percentages, were used to characterize clinical variables.

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12. Question:

Statistical methods - Did the authors describe all statistical methods, including those used to control for confounding?

Peer Review: The abstract mentions the use of descriptive statistics and STATISTICS 10.0 but does not detail methods used to control for confounding.

Reply:

Statistical analyses were performed using IBM SPSS Statistics, version 2, as mentioned in the Methods section of the article and in the abstract as well.

Major Comments:
1. Question:
The abstract lacks specific details on eligibility criteria, selection methods, and potential confounders.
Reply:

Thank you for your insightful observation. We agree that a more detailed mention of eligibility criteria, participant selection methods, and control of confounding variables could strengthen the clarity of the abstract. Due to space constraints inherent in structured abstracts, we provided a concise summary. However, these aspects are fully addressed in the main text (Methods section).

Specifically:

Eligibility Criteria: As outlined in the "Methods" section, inclusion was limited to children aged 1–18 years with PCR-confirmed COVID-19. Exclusion criteria

included children with no laboratory confirmation and, in the second stage, those with congenital malformations, genetic syndromes, or chronic somatic diseases that could independently affect the cardiovascular system.

Selection Methods: The study utilized a staged cohort design. The retrospective component analyzed 400 medical records. From this, 228 eligible children were selected for long-term follow-up using clearly defined clinical criteria, and 40 children with persistent cardiovascular abnormalities (persistent cardiovascular symptoms, ECG and BP irregularities) were purposefully selected for in-depth analysis.

Control of Confounders: To minimize bias, standardized clinical and instrumental assessment protocols were used. Interpretation of key diagnostic tests, such as ECG, was blinded to patient history. Additionally, socioeconomic and other non-clinical variables were deliberately excluded during the final stage to ensure focus on biologically relevant outcomes.

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2. Question:
There is no mention of efforts to address potential sources of bias.
Reply:

Thank you for your comment. We would like to clarify that the study design incorporated several methodological steps specifically aimed at minimizing potential sources of bias, which are described in the "Methods" section of the manuscript (highlighted in yellow).

In particular:

Strict Inclusion and Exclusion Criteria: To ensure sample homogeneity and minimize selection bias, children included in the study had PCR-confirmed COVID-19 and no congenital, genetic, or chronic somatic conditions affecting the cardiovascular system.

Standardized Assessment Tools: All clinical, laboratory, and instrumental assessments (e.g., ECG, BP monitoring, echocardiography) were conducted using certified equipment and standardized protocols, which helped control measurement bias.

Blinded Interpretation: Diagnostic data, including ECG results, were interpreted by qualified specialists who were blinded to the patients’ clinical histories, reducing the risk of observational bias.

Controlled Sampling at Stage 3: Participants selected for in-depth examination at the third stage were chosen solely based on objective clinical findings, without influence from social or demographic factors, thereby avoiding confounding by socioeconomic status.
We believe these measures substantially reduced the risk of bias in our study and ensured greater internal validity. We are happy to further emphasize these efforts in the revised manuscript, should the reviewer deem it necessary.

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3. Question:
The abstract does not explain how the study size was determined or how quantitative variables were handled in the analyses.

Reply:

Thank you for this observation. Due to word limitations, the abstract provides only a concise overview, so we added a short mention of variables handling (highlighted with yellow). In particular: Descriptive statistics were used to characterize clinical variables. Normality was assessed with the Shapiro-Wilk test; group differences with the Mann-Whitney U test. Results were considered statistically significant at $p < 0.05$ and $p < 0.001$.

However, details regarding study size and statistical treatment of quantitative variables are included in the main text as well.

Study Size Determination: The study included a total of 400 children with PCR-confirmed COVID-19, selected retrospectively to ensure a broad age representation and sufficient statistical power. Following the application of exclusion criteria (e.g., presence of congenital or chronic somatic conditions), 228 children were included in the main cohort for prospective follow-up. A control group of 172 children with similar demographic characteristics but without laboratory-confirmed COVID-19 was used for comparative analysis.

Handling of Quantitative Variables: As described in the "Materials and Methods" section, normality of quantitative variables was assessed using the Shapiro-Wilk test. Given the non-normal distribution of most variables, non-parametric methods were applied. The Mann-Whitney U test was used for group comparisons, and descriptive statistics (medians, interquartile ranges) were used to summarize clinical data. Statistical significance was set at $p < 0.05$ and $p < 0.001$.

Minor Comments:
1. Question:
The abstract could benefit from specifying the dates of recruitment, exposure, and follow-up.
Including specific hypotheses would strengthen the objectives section.
Reply:

Thank you for this valuable suggestion. We acknowledge that specifying key temporal details and hypotheses in the abstract would improve its clarity and scientific rigor.

Recruitment, Exposure, and Follow-up Dates: As outlined in the abstract and the main text, the retrospective review of medical records (Stage 1) covered cases from October to December 2020. The prospective follow-up assessments (Stages 2 and 3) were conducted from 2023 to 2024. We briefly incorporated these timeframes into the abstract and the main text to enhance temporal context (highlighted with yellow).

Specific Hypotheses: The study was guided by the hypothesis that children who have experienced various clinical forms of laboratory-confirmed COVID-19 are at significant risk of developing cardiovascular disorders. This is fully consistent with findings from various researchers and forms the basis of our scientific hypothesis. Thank you again for your thoughtful input.

We look forward to hearing from you regarding the submission of our manuscript. We would be pleased to address any additional questions or comments you may have.

Sincerely,

3 Revision 2

2 comments · 16 Jul 2025 – 16 Jul 2025

Associate Editor

ACCEPT 16 Jul 2025

accept

Editor-in-Chief

ACCEPT 16 Jul 2025

accept