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Global expert perspectives on the future of hematopoietic cell transplantation and cell therapies

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ABSTRACT

Setting: Hematopoietic cell transplantation (HCT) remains a cornerstone therapy for hematologic malignancies and several non-malignant disorders. At the same time, emerging therapies, particularly chimeric antigen receptor T cell (CAR-T) cells and other immunotherapies, are transforming the treatment landscape. Understanding how specialists anticipate these changes is critical for strategic planning in healthcare systems. **Methodology:** We conducted a global expert survey using a foresight-informed framework to explore expected developments in HCT and related technologies over the next decade. Following a literature review of 4,312 publications indexed in Web of Science (2018–2022), a questionnaire was distributed to specialists in hematologic cancers and bone marrow transplantation identified through publication databases. Personalized email invitations were sent in April and May 2023. Descriptive analyses and non-parametric tests were used to examine differences according to self-reported knowledge levels. **Results:** A total of 1,711 valid responses were analyzed. Haploidentical transplantation was identified as the most promising transplantation modality for the next decade, particularly among respondents with higher knowledge levels. Severe combined immunodeficiency and sickle cell disease were the most frequently cited non-malignant indications. Knowledge gaps, regulatory barriers, and treatment costs were perceived as major obstacles to innovation, while limited health system infrastructure was identified as the main barrier to expanding access in middle-income countries. CAR-T cell therapy was considered the most promising emerging technology overall, although highly knowledgeable respondents more often identified bispecific antibodies as the most promising innovation. **Conclusion:** Experts anticipate continued growth in haploidentical transplantation alongside the expansion of advanced immunotherapies such as CAR-T cells. However, regulatory, financial, and infrastructure constraints may delay their widespread implementation, particularly in middle-income settings. Although several emerging therapies discussed in this study – such as CAR-T cell therapy and certain autologous cellular approaches – do not directly depend on unrelated donor registries, the anticipated persistence of allogeneic transplantation as a core therapeutic modality suggests that maintaining robust national donor registries will remain strategically important. In particular, donor registries are expected to retain substantial relevance for malignant and non-malignant indications in which allogeneic HCT remains clinically indicated despite the parallel expansion of non-registry-dependent advanced therapies.

Keywords: Hematopoietic stem cell transplantation; Transplantation, haploidentical; Immunotherapy, chimeric antigen; Health services accessibility; Registries.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a potentially curative therapeutic strategy used in selected hematologic malignancies and in some non-malignant disorders, particularly when durable restoration of hematopoiesis or immune function is required.[1,2] Broadly, the procedure involves the infusion of hematopoietic stem cells after disease-directed or conditioning therapy to reconstitute bone marrow function.[2]

HCT may be classified according to the source of stem cells, distinguishing autologous procedures from allogeneic ones. In allogeneic transplantation, donor selection is influenced by histocompatibility, as suboptimal HLA matching is associated with higher risks of graft failure and graft-versus-host disease.[1,3]

Although HCT remains a high-complexity intervention, advances in donor selection, conditioning strategies, and supportive care have substantially improved survival and post-transplant outcomes.[4] In Europe alone, 46,143 hematopoietic cell transplant procedures were reported in 2022, including 19,011 allogeneic and 27,132 autologous transplants.[5]

Two developments have particularly altered the contemporary HCT landscape: the rapid expansion of haploidentical transplantation and the emergence of cellular immunotherapies, especially chimeric antigen receptor T cell (CAR-T) therapy.[6-8] Haploidentical transplantation has become increasingly feasible because of advances in donor selection and post-transplant management,[7] while CAR-T therapies have shown high activity in relapsed or refractory hematologic malignancies.[8,9]

These developments have raised questions regarding the future role of unrelated donor registries, including the Registro Brasileiro de Doadores Voluntários de Medula Óssea (REDOME), within the evolving transplantation landscape.[10,11] In this study, foresight is used as an anticipatory framework to examine plausible future developments and to inform decision-making in uncertain settings.[12] In health systems research, foresight-based methods have been used to identify innovation priorities, anticipate emerging technologies, and support strategic planning.[13-16]

Despite the rapid evolution of transplantation and cellular immunotherapy, empirical evidence on how specialists anticipate the future interaction between these modalities remains scarce.

To address this gap, we conducted a large international survey of specialists in hematologic malignancies and transplantation, using a foresight-informed framework to assess expected clinical trends, technological change, and system-level barriers to HCT access.

MATERIALS AND METHODS

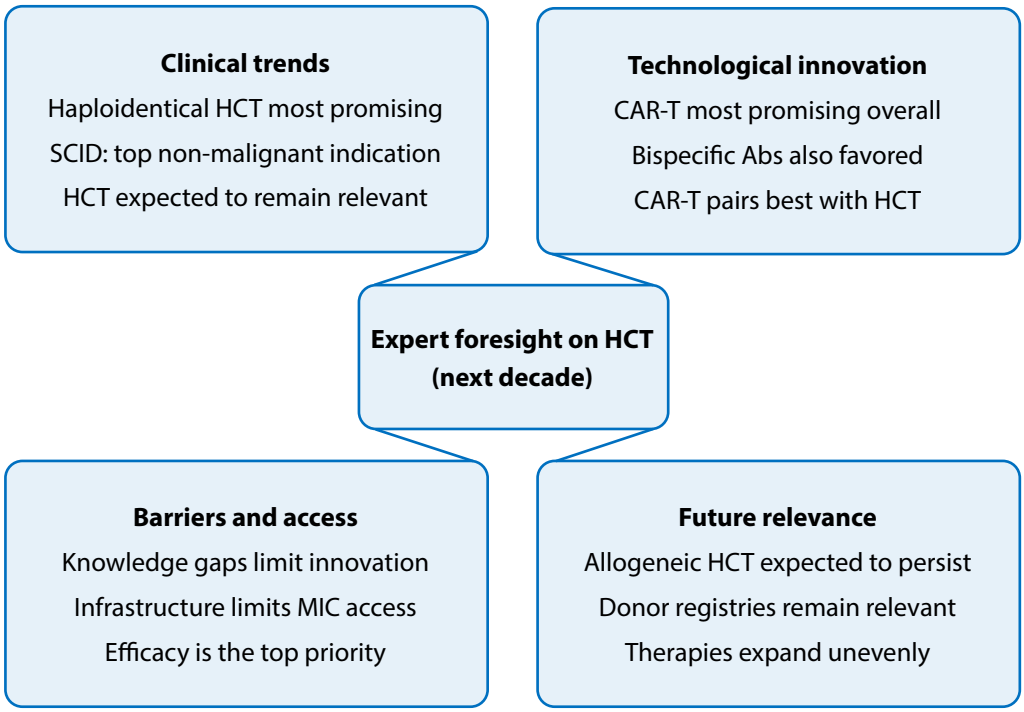
Literature review and questionnaire development

We conducted a literature review to identify emerging technologies and future-oriented perspectives in bone marrow transplantation (BMT). We searched publications indexed in the Web of Science (WoS), specifically the Science Citation Index Expanded (SCI-EXPANDED), covering the period from 2018 to 2022. The search combined Medical Subject Headings (MeSH)-based terms with additional free-text expressions related to future developments and was applied to article titles. The full search strategy is presented as follows. Title: (hematologic* and cancer*) OR (blood* and cancer*) OR (hematologic* and neoplasms*) OR (hematological* and malignancy*) OR leukemia* OR lymphoma* OR (multiple* and myeloma*) AND (future* OR foresight* OR forthcoming* OR prospective* OR imminent*).

Of the 4,312 publications retrieved, 618 were selected for detailed review. Insights from this review guided the questionnaire design (S1 Dataset – Publications reviewed).

The questionnaire included items on respondent characteristics, such as self-reported knowledge of BMT, academic background, professional role, institutional affiliation, years of experience, and geographic region

(S2 Questionnaire – Full version of the questionnaire licensed under CC BY 4.0). It also included prospective questions on innovation trajectories, health system barriers, emerging technologies, and the expected clinical relevance of HCT in malignant and non-malignant conditions over the next decade (Fig. 1).



Source: Elaborated by the authors.

Figure 1. Conceptual map of the domains explored in research on HCT.

Selection of respondent groups

Respondents were divided into two expert groups: hematologic cancer specialists (Group 1) and BMT specialists (Group 2). To identify potential participants, we conducted a structured search in WoS for researchers with relevant publications from October 2018 to March 2023. Only English-language articles and reviews indexed in SCI-EXPANDED were considered.

For Group 1, the search criteria were: Title: (((hematologic* and cancer*) OR (blood* and cancer*) OR (Hematologic* and Neoplasms*) OR (Hematological* and Malignancy*) OR (leukemia*) OR (lymphoma*) OR (multiple* and myeloma*)) AND LA=(English)) AND DT=(Article OR Review).

For Group 2, the search criteria were: TS=((bone* and marrow* and graft*) OR (hematopoietic* and stem* and cell* and transplant*) OR (bone* and marrow* and transplantation*) OR (bone* and marrow* and cell* transplantation*) OR (transplantation* and bone* and marrow* and cell*)) AND LA=(English) AND DT=(Review OR Editorial Material OR Article).

Retrieved records were exported to CSV files containing author names, emails, and publication titles. Duplicate contacts were removed using a Python script developed by the foresight study group at Fundação Oswaldo Cruz. After processing, Group 1 comprised 41,528 unique contacts and Group 2 comprised 21,734 contacts.

Data collection

Pilot surveys were conducted for both groups. In April 2023, the pilot for Group 1 involved 1,757 non-personalized emails and yielded 16 responses (1.74%). In May 2023, the pilot for Group 2 involved 500

non-personalized emails and yielded five responses (1%). As no problems requiring adjustment were identified, pilot responses were retained in the final dataset.

The main data collection occurred from April to May 2023, using personalized emails sent via SurveyMonkey. Due to platform limitations, distribution was managed in batches. In total, 39,771 emails were sent to Group 1 and 16,597 to Group 2.

Ethical aspects

Contact information, limited to names and email addresses, was obtained exclusively from publicly available publication metadata. Because participation was voluntary, responses were anonymous, no sensitive personal data were collected, and informed consent was obtained electronically, formal ethics committee approval was not required. The study was conducted in accordance with Brazilian Resolution No. 510/2016, which exempts anonymous public opinion research from mandatory ethics review.

Statistical methods

Respondent characteristics were first described using summary statistics. Distributional assumptions were assessed with the Shapiro-Wilk test and the Kolmogorov-Smirnov test with Lilliefors correction. Because the variables did not follow normal distributions, subsequent analyses relied on non-parametric methods.

Inferential analyses were used to assess whether response patterns varied according to self-reported knowledge of HCT. Participants who reported having "no knowledge" were excluded from this stage. The Wilcoxon signed-rank test was used to assess whether the distribution of ordinal responses systematically deviated from the predefined central response categories in the questionnaire. Its use was considered appropriate given the ordinal nature of the survey responses and the presence of predefined reference categories within the questionnaire structure.

All statistical analyses used IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Statistical significance was defined at $p < 0.05$.

RESULTS

Descriptive analysis

A total of 1,711 valid responses were received, comprising 918 from Group 1 (hematologic cancer specialists) and 793 from Group 2 (BMT specialists), corresponding to response rates of 2.21% and 3.64%, respectively. The main characteristics of respondents are summarized in Table 1.

Most participants reported having either "good" or "some" knowledge of HCT. The distribution of self-assessed knowledge differed significantly between groups ($p < 0.001$), with Group 2 showing a higher proportion of respondents with "high knowledge" and a lower proportion with "no knowledge." Respondents who reported "no knowledge" (8.17% in Group 1 and 1.64% in Group 2) were excluded from the inferential analyses.

Geographic distribution differed significantly between groups ($p = 0.0084$), with Group 1 including a higher proportion of respondents from Europe and Group 2 a higher proportion from North and Central America. By contrast, the groups did not differ significantly in professional experience ($p = 0.8098$), institutional affiliation ($p = 0.1573$), occupation ($p = 0.0821$), or highest educational attainment ($p = 0.0863$).

The majority of respondents in both groups held a doctoral degree (76.60% in Group 1; 80.06% in Group 2) and were primarily employed as researchers, professors, or clinical physicians. Most were affiliated with universities or research institutions (over 62%), followed by hospitals. Approximately 45% had more than 20 years of professional experience.

Complete disaggregated response data by group are provided in the S3 Dataset – Survey responses.

Table 1. Characteristics of participants by specialty group: hematologic cancers and BMT.

Characteristics	GROUP 1 Specialists in hematologic cancers (n = 918) n (%)	GROUP 2 Specialists in BMT (n = 793) n (%)	Total	p-value*
Knowledge level on hematological cancer care				
High	236 (25.71)	273 (28.12)	509	< 0.001
Good	329 (35.84)	284 (35.81)	613	
Some	278 (30.28)	223 (34.43)	501	
No	75 (8.17)	13 (1.64)	88	
Region				
Africa	20 (3.04)	13 (2.01)	33	< 0.001
Asia	158 (24.01)	151 (23.34)	309	
Australasia	12 (1.82)	9 (1.39)	21	
Europe	277 (42.10)	249 (38.49)	526	
North and Central America	106 (16.11)	146 (22.57)	252	
South America	85 (12.92)	79 (12.21)	164	
Experience, years				
> 5 y	51 (7.76)	40 (6.19)	91	0.809
5–9	115 (17.50)	109 (16.87)	224	
10–20	193 (29.38)	205 (31.73)	398	
> 20	298 (45.36)	292 (45.20)	590	
Institution				
Government	11 (1.67)	17 (2.63)	28	0.157
Hospital	227 (34.55)	200 (30.91)	427	
Industry	6 (0.91)	18 (2.78)	24	
University/research	413 (62.86)	412 (63.68)	825	
Occupation				
Manager/executive	6 (0.91)	11 (1.70)	17	0.0821
Student (MSc/PhD)	36 (5.47)	18 (2.78)	54	
Physician/clinician	278 (42.25)	230 (35.49)	508	
Policymaker	1 (0.15)	1 (0.15)	2	
Professor/researcher	303 (46.05)	333 (51.39)	636	
Public health professor	22 (3.34)	33 (5.09)	55	
Other	12 (1.82)	22 (3.40)	34	
Educational level				
Associate degree	33 (5.02)	37 (5.72)	70	0.086
Bachelor's degree	27 (4.10)	19 (2.94)	46	
Doctoral degree	504 (76.60)	518 (80.06)	1,022	
Master's degree	94 (14.29)	73 (11.28)	167	

*Comparison between groups. Source: Elaborated by the authors.

Clinical trends

Haploidentical transplantation was identified as the most promising BMT modality for the next decade. Responses varied significantly by knowledge level: participants with high self-reported knowledge were more likely to select haploidentical transplantation, whereas those with lower knowledge more frequently favored autologous options.

Among non-malignant diseases, severe combined immunodeficiency (SCID) was consistently identified as the most relevant future indication for BMT. No significant differences were observed across knowledge groups.

Most respondents considered the continued relevance of BMT in the treatment of hematologic cancers to be highly likely. Participants with higher knowledge expressed greater confidence in BMT's future role, whereas those with lower knowledge reported more moderate expectations.

Barriers and access to BMT

Knowledge-related barriers were most frequently identified as the main obstacle to innovation in BMT over the next decade, followed by regulatory and financial barriers. Response patterns did not differ significantly across knowledge levels.

Health system infrastructure was consistently identified as the main limiting factor for access to BMT in middle-income countries, regardless of participants' level of expertise.

When asked about the most important factor for improving BMT in the treatment of hematologic cancers, most respondents emphasized increased treatment efficacy. However, knowledge-level differences emerged: participants with high or good knowledge prioritized efficacy, while those with some knowledge more often highlighted donor compatibility as a key area for improvement.

Emerging technologies

CAR-T cell therapy was identified as the most promising emerging technology for the treatment of hematologic cancers over the next decade. Responses differed across knowledge levels: participants with some or good knowledge more frequently selected CAR-T cell therapy, whereas those with high knowledge more often identified bispecific monoclonal antibodies as the most promising innovation.

A similar pattern was observed when participants were asked which technologies were most likely to succeed in combination with BMT. CAR-T cell therapy remained the most frequently cited option, although differences across knowledge levels were not statistically significant.

A summary of all statistical results, including sample sizes, median responses, and significance values by knowledge level, is provided in Table 2.

Table 2. Summary of statistical results by survey question and knowledge level.

Question	Sample size	Median response	Wilcoxon (Z)	Wilcoxon (p-value)	Kruskal-Wallis (χ^2)	Kruskal-Wallis (p-value)
The most promising type of BMT in the next 10 years	1,508	Haploidentical	-2.044	0.041	23.683	0.001
Regarding non-malignant diseases, for which disease BMT will be most relevant in the next 10 years	1,411	SCID	-0.221	0.825	3.781	0.151
The main barrier to an innovative revolution in BMT transplantation is happening in the next 10 years	1,389	Knowledge barrier	2.304	0.21	1.192	0.551
The main barrier to accessing BMT in middle-income countries in the next 10 years	1,379	Health system	1.908	0.056	5.148	0.076
Technology most likely to be applied for HCT in the next 10 years	1,350	CAR-T	-0.011	0.991	7.48	0.024
Technology has a greater chance of success in the HCT treatment when combined with BMT in the next 10 years	1,325	CAR-T	-1.894	0.058	2.399	0.301
The likelihood of BMT will remain relevant for HCT treatment in the next 10 years	1,327	Highly likely	-1.475	0.041	9.074	0.011
The most important factor in the improvement of BMT as a treatment for hematological cancer in the next 10 years	1,318	Increased efficacy	-0.65	0.516	30.134	0.001

Source: Elaborated by the authors.

Perceived knowledge level in HCT

Self-assessed knowledge levels were examined in the first survey question. Among the 1,623 valid responses, 25.71% of participants reported "high knowledge," 35.84% reported "good knowledge," and 30.28% reported "some knowledge." Respondents who selected "no knowledge" were excluded from subsequent analyses.

The percentile distribution indicated that the first quartile corresponded to "high knowledge," whereas both the median and the third quartile corresponded to "good knowledge." To assess whether the observed distribution differed significantly from a central tendency represented by the category "good knowledge," a Wilcoxon signed-rank test was performed. The result was not statistically significant ($Z = -0.067$, $p = 0.947$), suggesting that "good knowledge" was an appropriate summary of the typical self-reported expertise level in the sample.

DISCUSSION

This foresight-informed study provides a structured assessment of specialist expectations regarding the future trajectory of HCT (HCT) and related cellular therapies. Overall, the findings suggest that experts anticipate the continued relevance of HCT over the next decade, albeit within an increasingly complex therapeutic landscape shaped by the parallel expansion of advanced immunotherapies.

Haploidentical transplantation emerged as the modality most frequently identified as promising for the coming decade, particularly among respondents with higher self-reported knowledge of HCT. This finding is consistent with the growing clinical adoption of haploidentical transplantation and with accumulating evidence demonstrating improved feasibility, broader donor availability, and increasingly favorable outcomes in contemporary practice.[17] By contrast, respondents with lower knowledge levels more frequently favored autologous transplantation, possibly reflecting greater familiarity with historically established transplantation paradigms rather than with more recent shifts in donor-selection strategies.[18]

Among non-malignant diseases, SCID and sickle cell disease were the conditions most frequently identified as relevant future indications for HCT. This pattern is consistent with the established curative role of transplantation in these disorders and with the continued expansion of hematopoietic-based therapeutic strategies for non-malignant hematologic and immunologic diseases.[19,20] It is important, however, to distinguish conventional allogeneic HCT from emerging gene-therapy approaches in some inherited disorders, particularly SCID. Although both may involve hematopoietic stem cell manipulation and conditioning regimens, gene therapy represents a distinct therapeutic modality with different regulatory, logistical, and economic implications. Accordingly, the prominence of SCID in respondents' expectations may be interpreted more broadly as reflecting the anticipated persistence of hematopoietic-based curative therapies, rather than exclusively conventional allogeneic transplantation.

CAR-T cell therapy was identified as the most promising emerging technology overall, although respondents with higher knowledge levels more frequently selected bispecific monoclonal antibodies. This divergence may reflect greater familiarity among more specialized respondents with the rapid diversification of T-cell-redirecting immunotherapies and with the expanding clinical role of bispecific platforms in hematologic malignancies. Taken together, these findings suggest that while CAR-T therapy remains the most visible paradigm-shifting innovation in the field, more specialized experts may perceive a broader competitive therapeutic landscape than less specialized respondents.[21]

At the same time, respondents consistently identified knowledge-related barriers, regulatory constraints, and treatment costs as the principal obstacles to innovation in HCT and related cellular therapies. Health system infrastructure was likewise identified as the main barrier to expanding access in middle-income countries. These perceptions align with the documented operational and financial challenges associated with implementing advanced cellular therapies in resource-constrained settings,[22] suggesting that technological innovation alone is unlikely to ensure equitable dissemination absent parallel institutional and infrastructural development.[14,15,22]

These findings also carry important implications for public policy and strategic planning. In countries with universal health systems, such as Brazil, maintaining national unrelated donor registries such as REDOME may remain an important medium-term strategy while access to newer cellular therapies continues to expand unevenly. Although several emerging therapies discussed in this study – such as CAR-T cell therapy and certain autologous cellular approaches – do not directly depend on unrelated donor registries, the anticipated persistence of allogeneic transplantation as a core therapeutic modality suggests that donor registries will remain strategically relevant. This continued importance is reinforced by the expected persistence of malignant and non-malignant indications for allogeneic HCT, the uneven incorporation of advanced cellular therapies across healthcare systems, and persistent disparities in the probability of identifying suitably matched unrelated donors across populations.[23] Even in the context of expanding haploidentical transplantation, unrelated donor registries remain clinically relevant for patients lacking suitable family donors and in situations where a well-matched unrelated donor remains preferable or necessary.[17,23]

Consistent with prior applications of foresight methods in health research and policy, the present study illustrates the value of expert consultation not only for anticipating technological change but also for identifying system-level bottlenecks likely to shape future implementation. Strategic planning for HCT and related therapies should therefore combine technology monitoring with proactive investments in regulatory capacity, workforce development, and equitable service infrastructure.[13,14]

A key limitation of this study is the relatively low response rate, which, although consistent with large-scale unsolicited international expert surveys, raises the possibility of non-response bias. In addition, because participants were identified through publication databases, the sample may overrepresent academically active specialists relative to clinicians with more limited publication records, potentially introducing an additional source of selection bias. Individuals who chose to participate may systematically differ from non-respondents in their degree of engagement with emerging technologies, academic productivity, or interest in transplantation-related policy debates. Consequently, the findings should not be interpreted as statistically representative of the global population of HCT specialists, but rather as reflecting the expectations of a large and internationally diverse sample of engaged experts. Accordingly, the present study should be understood as a structured assessment of expert perceptions rather than a direct measure of global professional consensus.

A further limitation relates to the temporal gap between data collection and publication. Because the survey was conducted in 2023, respondents' expectations were formed prior to several recent developments in transplantation and cellular therapy, including advances in mismatched unrelated donor transplantation strategies and the continued expansion of real-world evidence regarding cellular immunotherapies. Given the rapid pace of innovation in this field, expert perceptions may evolve substantially over relatively short periods. The findings should therefore be interpreted as reflecting expert expectations at a specific stage of technological development rather than as a contemporaneous prediction of current clinical practice.

Future studies employing repeated survey waves or Delphi-based consensus approaches may help monitor how expert expectations evolve as transplantation technologies and cellular therapies continue to develop.

CONCLUSION

This study suggests that experts expect haploidentical transplantation and advanced cellular immunotherapies to remain central to the future of HCT over the next decade. At the same time, regulatory, financial, and infrastructural barriers are expected to continue limiting the widespread implementation of newer therapies, particularly in middle-income settings. These findings underscore the need for strategic planning that aligns technological innovation with health system capacity, regulatory preparedness, and equitable access. In this context, national donor registries such as REDOME may remain strategically relevant, particularly given the expected persistence of selected indications for allogeneic HCT despite the expansion of non-registry-dependent cellular therapies.

CONFLICTS OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Conceptualization: Cabral B, Monteiro R. **Investigation:** Conte Filho C, Lopes P, Amorim I, Silva D, Santana I. **Methodology:** Cabral B. **Formal Analysis:** Cabral B, Amorim I, Silva D, Santana I. **Data Curation:** Cabral B. **Project Administration:** Oliveira D. **Funding Acquisition:** Oliveira D. **Writing:** Bhering M. **Supervision:** Bhering M. **Final Approval:** Bhering M.

DATA AVAILABILITY STATEMENT

Data will be provided upon request.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors used artificial intelligence tools to improve language, clarity, and readability. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the final content of the manuscript.

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