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Real-World Experience Using the Clinical Treatment Score at 5 Years (CTS5) and Breast Cancer Index (BCI) to Guide Extended Adjuvant Endocrine Therapy

Mohammed Qarmout[a], Yasir Alsaraf[c], Qasim Alameri[b], Grace D. Brannan[d], Susan E. Lyons*[a]

[a]*Department of Internal Medicine, Section of Hematology and Oncology, Henry Ford Hospital Southfield, Minnesota, USA*

[b]*Department of Internal Medicine, Henry Ford Hospital Southfield, Minnesota, USA*

[c]*Florida Cancer Specialists, W Dr Martin Luther King Jr Blvd, Tampa, Florida, USA*

[d]*GDB Research and Statistical Consulting, Lavelle Rd., Athens, Ohio, USA*

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ABSTRACT

Background: Accurately identifying patients with estrogen receptor (ER)$^{+}$HER2^{-} breast cancer benefiting from extended endocrine therapy (EET) remains challenging. While the Clinical Treatment Score at 5 Years (CTS5) and the Breast Cancer Index (BCI) are established tools for assessing late recurrence risk, their comparative utility in real-world practice is underexplored. The CTS5 only provides prognostic data, but the BCI provides both prognostic and predictive data.

Methods: We conducted a retrospective study evaluating concordance between the CTS5 and the BCI in patients with early-stage ER^{+}HER2^{-} disease who completed 5 years of adjuvant endocrine therapy (2023–2024). Intertest reliability was quantified using descriptive statistics and the Cohen κ coefficient.

Results: In 59 patients, overall concordance was 37.3%. Agreement was highest in low-risk, grade 1 tumors (54.5%). Discordance was significant in those with higher-risk features. Notably, 32.2% were CTS5 "intermediate," where the BCI offered binary guidance. Sankey diagrams revealed that 57.1% of patients with BCI-recommended EET were CTS5 low risk. The Cohen κ coefficient was 0.067 (95% CI, −0.156 to 0.290; $P = 0.56$).

Conclusion: Our study showed limited CTS5 and BCI concordance rates in clearly low-risk populations and non-statistically significant results overall. These limited findings warrant further exploration of integrating genomic assays to optimize therapy duration.

INTRODUCTION

Hormone receptor (HR)$^{+}$HER2^{-} breast cancer constitutes the predominant subtype of breast malignancy. Standard adjuvant endocrine therapy for 5 years reduces the 10-year recurrence rate by approximately 25% to 40%.[1] However, the risk of late distant recurrence (years 5 to 20) remains clinically significant.

In women with T1N0 disease, the cumulative risk of distant recurrence after 5 years is approximately 13%, correlating strongly with tumor size, nodal status, and histological grade.[1] Extended endocrine therapy (EET) with aromatase inhibitors for an additional 5 years improves disease-free survival and reduces contralateral breast cancer incidence.[2] However, this benefit must be weighed against

***Address for correspondence:**
Susan E. Lyons, MD, Ph.D.,
Department of Internal Medicine, Section of Hematology Oncology, Henry Ford Hospital, Southfield, 16001 West 9 Mile Rd., Southfield, MI, 48075
Email: lyonssu1@msu.edu

cumulative toxicities, including arthralgia and loss of bone density, which impact quality of life.[3] Consequently, precise risk stratification is essential to identify patients who derive a sufficient absolute benefit to justify prolonged treatment.[4]

Two primary tools aid this decision. The Clinical Treatment Score at 5 Years (CTS5) validates clinical-pathologic variables—age, tumor size, grade, and nodal status—to estimate late distant recurrence risk and is a prognostic tool.[5] While the CTS5 is a robust prognostic tool, it lacks a predictive component for therapeutic responsiveness. Conversely, the Breast Cancer Index (BCI) is a gene expression assay integrating the *HOXB13*:*IL17BR* (H/I) ratio and the Molecular Grade Index. The BCI is validated to provide both prognostic risk assessment and a predictive indication of benefit from EET.[6,7] Recent data from the TEAM trial confirmed the BCI's ability to stratify risk in node-negative and N1 populations where clinical tools might fail.[8] Similarly, safety-net hospital experiences have highlighted the BCI's utility in reclassifying clinically high-risk patients to low genomic risk.[9]

In this study, we evaluated the concordance of the CTS5 and BCI in a community-based cohort to determine their respective contributions to guiding EET recommendations. There are differences in the abilities of these tools to guide therapy given that the CTS5 is only a prognostic tool and the BCI is both a prognostic and predictive tool.

METHODS

We performed a retrospective analysis of premenopausal and postmenopausal women at diagnosis with early-stage, $ER^{+}HER2^{-}$ breast cancer treated at a large community-based oncology practice. Inclusion criteria required patients to have completed approximately 5 years of adjuvant endocrine therapy and to have undergone both CTS5 calculation and BCI testing. BCI samples were taken on consecutive patients tested between 2023 and 2024.

Risk stratification tools

CTS5: Patients were stratified into 3 risk categories for late distant recurrence: low (< 5%), intermediate (5% to 10%), and high (> 10%).[5]

BCI: Patients were classified based on the BCI score for prognostic risk (low or high) and the H/I ratio for predictive benefit from EET (yes or no).[6]

Statistical analysis

We assessed concordance between CTS5 risk categories and BCI predictive results across the total cohort and stratified by tumor grade using percentage rates and visually using a Sankey diagram. Concordance was defined as an agreement between BCI recommendation (yes or no) and CTS5 risk assignment (high, intermediate, and low). To quantify agreement using inferential statistics, we calculated the Cohen κ coefficient on the evaluable overall cohort. While we acknowledge the conceptual distinction between the CTS5 (prognostic tool) and the BCI (prognostic and predictive tool), the prognostic overlap between the CTS5 and BCI is the reason we deemed the Cohen κ as an appropriate analysis to inferentially explore whether any such agreement exists. We used IBM SPSS, version 30 (IBM Corp) for analysis. Statistical significance was set at $P < 0.05$.

RESULTS

The study cohort consisted of 59 women. The mean age at diagnosis was 60 years. There were 51 White individuals, 3 African American individuals, 4 Asian individuals, and 1 individual of unknown race. There were 14 premenopausal, 1 perimenopausal, and 44 postmenopausal patients at diagnosis in our sample. Patient characteristics are shown in Table 1. The mean tumor size was 1.7 cm. Briefly, the T status ranged from T1a to T3 (1 T1a, 18 T1b, 26 T1c, 13 T2, and 1 T3). Of the patients, 44 had N0 disease and 15 had N1 disease. The study showed that 57.1% of the patients identified as low risk by CTS5 were nonetheless identified by BCI as likely to benefit from extended therapy. Conversely, the CTS5 high-risk category included a small subset of patients who, based on BCI predictions, would derive no benefit. Thus, in some patients, there was discordance in risk stratification and the potential benefit or lack of benefit from EET.

Comparison of risk stratification

While the CTS5 tool provides only a prognostic risk stratification, the BCI also provides a recommendation regarding the benefit of extended hormonal therapy. As shown in Figure 1, the BCI provided a binary “yes” or “no” recommendation for all patients, whereas the CTS5 stratified patients into low, intermediate, and high risk. Basing recommendations for extended hormonal therapy solely on the CTS5 stratification may not capture potential predictive benefit.

A stacked bar chart illustrates the distribution of CTS5 risk categories within groups defined by BCI predictive recommendation (Figure 1).

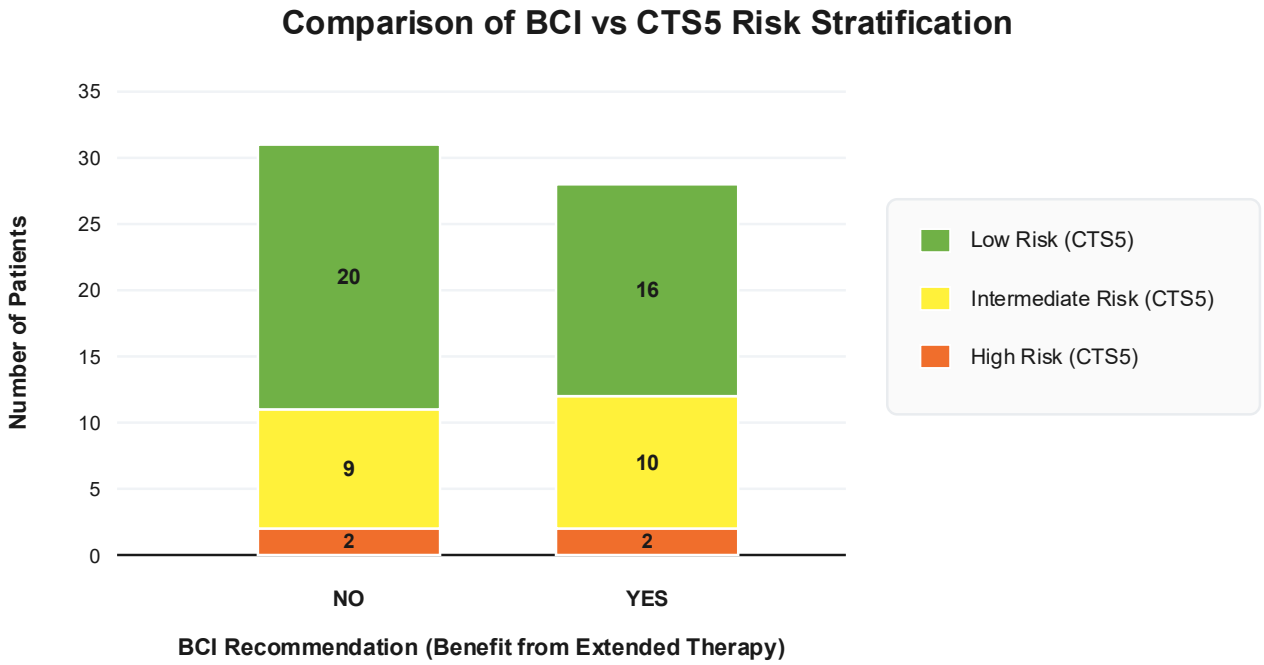

Figure 1. Comparison of Genomic (BCI) vs Clinical (CTS5) Risk Assessment

The "BCI Benefit (Yes)" group contains a high proportion of patients classified as low risk by CTS5 (green segment), highlighting that a significant proportion of the low-risk group defined by CTS5 might benefit from EET. A small group of patients defined as high risk by CTS5 might not, unfortunately, benefit from the continuation of EET.

Table 1 shows outcomes data, which are limited by the small sample size. From 59 patients, 2 were lost to follow-up after BCI testing, 3 patients had distant recurrence, and 1 had local recurrence. Fifty-three patients were without recurrence at the time of writing this manuscript. One patient who died of distant recurrence was shown to have no benefit from EET by BCI, with a prognostic risk of recurrence of 16.4% between years 5 to 10 by BCI and 26.7% by CTS5 (high risk). One patient who was alive with distant recurrence was shown to have no benefit from EET by BCI with a prognostic risk of recurrence of 4.2% between years 5 to 10 by BCI and 7.1% by CTS5 (intermediate risk). The other patient with distant recurrence was shown to benefit from EET by BCI with a 4.5% risk without EET that fell to 1.5% to 1.9% with EET and a 1.5% risk calculated by CTS5. Finally, the patient who had local recurrence was shown to benefit from EET, though the overall prognostic risk of recurrence was only 1.2%, brought down to 0.4% to 0.5% with EET. The risk of recurrence from years 5 to 10 was predicted as 5.3% by CTS5 (intermediate risk). Interestingly, this patient had refused radiation, which may have contributed to the local recurrence.

Concordance by tumor grade

Stratification by tumor grade revealed distinct patterns driving these discordance rates (Figure 2).

Grade 1 tumors exhibited the highest concordance (54.5%), generally categorizing patients as low risk for late recurrence by both methods. In contrast, grade 2 tumors were predominantly characterized by inconclusive results from CTS5 (57.1%), reflecting the limitation of clinical tools in stratifying mid-grade disease. Grade 3 tumors displayed the highest rate of discordance (55.6%), indicating a frequent mismatch between aggressive clinical features and genomic biology.

Reclassification flow and statistical agreement

To visualize the movement of patients between risk categories, a Sankey diagram was generated (Figure 3). This visualization highlighted a critical subset of patients identified as low risk by CTS5 (57.1%, n = 16) among the cohort where BCI recommended extended therapy ("Yes", n = 28). Conversely, in the BCI non-benefited group ("No", n = 31), 35.5% of patients were classified as intermediate or high risk by CTS5. While clinicians might decide to extend endocrine therapy in intermediate- or high-risk patients based on CTS5, the predictive score by BCI in our small cohort suggests these patients might not benefit from extended endocrine therapy.

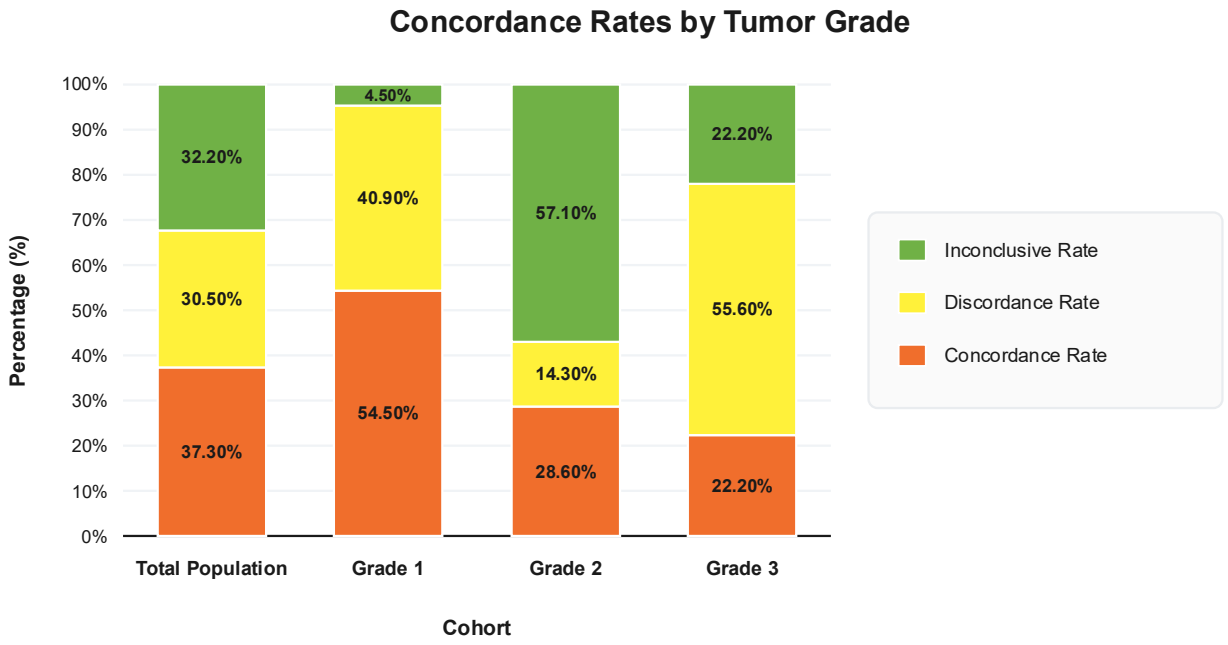

Figure 2. Concordance, Discordance, and Inconclusive Rates Stratified by Tumor Grade. The bar chart displays the performance of CTS5 against BCI across tumor grades. Grade 1 shows high concordance (Agreement). Grade 2 is dominated by Inconclusive (CTS5 Intermediate) results. Grade 3 shows the highest Discordance (Mismatch)

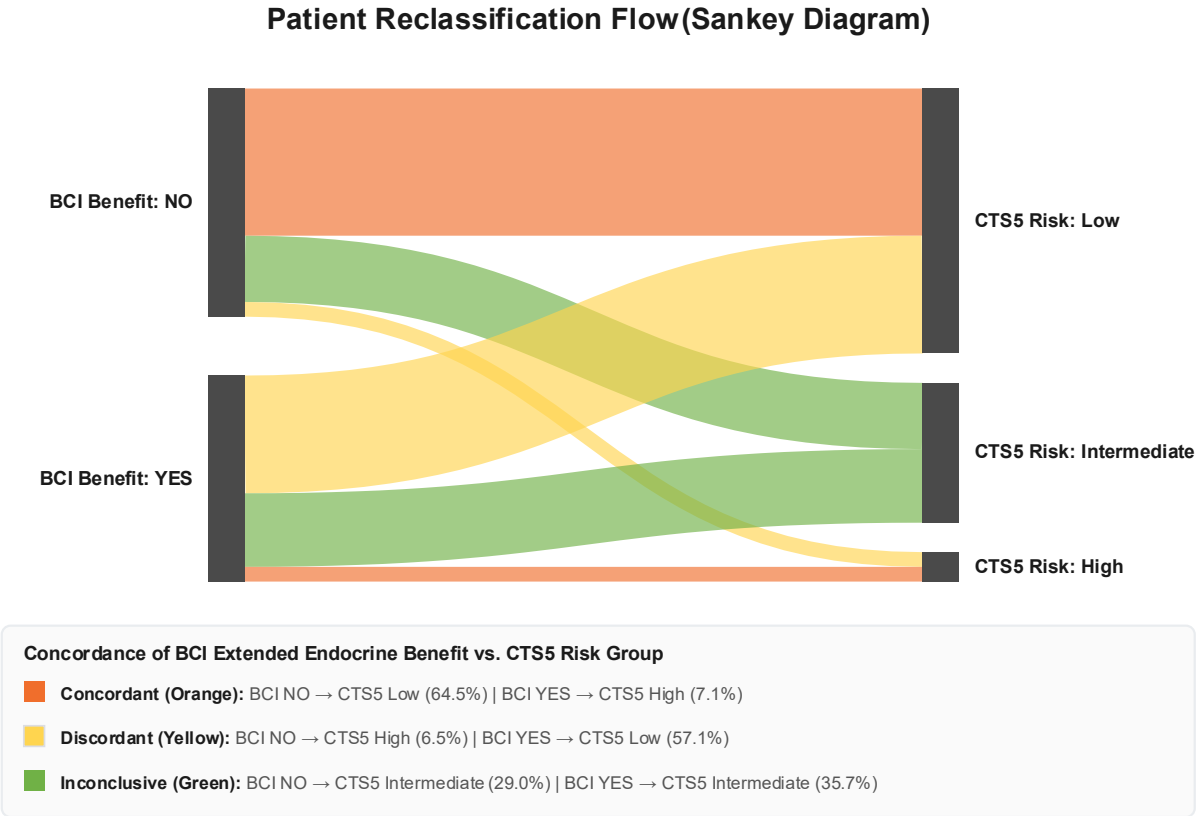

Figure 3. Patient Reclassification Flow (Sankey Diagram). A Sankey diagram visualizing the flow of patients from BCI recommendation (Left) to CTS5 Risk Category (Right). The yellow path indicates clinically significant discordance where either BCI predicts benefit but CTS5 predicts low-risk or where CTS5 predicts high risk, but BCI predicts no benefit from the continuation of endocrine therapy beyond 5 years. The green path indicates where BCI predictions can be made while CTS5 is "inconclusive" (intermediate). The orange path shows concordance between the tests.

To further quantify this relationship, we performed a statistical analysis of agreement on the total population only due to the small sample size. The calculated Cohen κ coefficient was 0.067 (95% CI, −0.156 to 0.290; $P = 0.56$). This value indicates "slight" to "no" agreement, confirming that for the total cohort population, the overlap between clinical risk (CTS5) and genomic benefit (BCI) was statistically negligible and likely due to chance.

DISCUSSION

The decision to extend endocrine therapy beyond 5 years remains a nuanced clinical equipoise. Our findings underscore the distinct biological contributions of genomic profiling versus clinical-pathological scoring. The statistical discordance observed in our study ($\kappa = 0.067$) reinforces that these tools are not interchangeable.

The conceptual distinction between a purely prognostic tool (CTS5) and a combined prognostic and predictive tool (BCI) introduces inherent methodological limitations when analyzed via concordance statistics. Specifically, the application of the Cohen κ is challenged by the fact that CTS5 categorical risks and BCI predictive outputs are fundamentally different constructs and not directly equivalent. However, since there is a prognostic overlap between CTS5 and BCI, we deemed the Cohen κ as an appropriate inferential analysis to explore the extent of this agreement, while the Sankey diagram served as a purely descriptive measure. The calculated Cohen κ determined if there is a definitive, statistically significant agreement between the 2 tools. Despite being severely limited by the very small sample size, our overall findings indicate no statistical agreement; however, the divergent results observed with CTS5 risk stratification merit additional exploration. The minimal agreement observed ($\kappa = 0.067$) in our study highlights the lack of interchangeability between CTS5 and BCI in clinical decision-making.

Our results align with recent findings by Shah *et al.*,[9] who reported that BCI reclassified 47% of clinically high-risk patients to a group not requiring extended therapy. However, our study builds upon this work by explicitly characterizing which subgroups benefit most from genomic stratification. While Shah *et al.* proposed that CTS5 could serve as a cost-saving tool to screen out low-risk patients, our data suggest a more targeted approach. We observed high concordance in grade 1, node-negative disease, supporting the use of clinical features for this specific subset to reduce costs. However, for patients falling into the "gray zone" of grade 2 or CTS5-intermediate risk—which comprised 32.2% of our total cohort—clinical tools were insufficient. In these cases, BCI provided a definitive recommendation, effectively resolving uncertainty.

This supports the "stepwise" utilization of genomic testing: foregoing BCI in clearly low-risk clinical scenarios but mandating it for intermediate cases where CTS5 fails to provide a binary treatment decision. Additionally, our results are consistent with the recent validation from the TEAM trial, which confirmed BCI's prognostic performance in N0 or N1 populations.[8] This validation mirrors our study's demonstration of BCI's ability to identify patients with aggressive biology (high H/I ratio) even when standard clinical markers like tumor size might suggest lower risk. Specifically, the identification of the "genomically high, clinically low" group (57.1% of BCI-benefit patients) may represent a critical opportunity to hone recommendations for EET for our patients, a finding also supported by long-term data from the ATLAS trial.[10]

This study is limited by its retrospective nature and small sample size. However, the use of real-world data from a community practice provides valuable insight into the practical application of these tools outside controlled clinical trials. Given the retrospective nature of the study, we are unable to quantify the number of patients tested during the 2023 to 2024 study period, nor the reasons for omissions in testing. Cost of the test was rarely a factor, as it has been well covered by insurance in our experience. Potential bias is introduced by which patients are chosen for BCI testing. Some clinicians avoid testing small, low-grade tumors or large tumors that are lymph node positive. Furthermore, age and factors such as patient tolerance and bone density may influence clinicians or patients to discontinue therapy independent of BCI testing. However, Table 1 shows that a wide variety of stages and ages were included.

The lack of outcomes data that are statistically significant limits our ability to draw conclusions regarding the better tool to provide recommendations that translate to patient benefit. In addition, the relatively short time frame (approximately 2 to 3 years from testing to the current time) does not allow all recurrences to be captured. Therefore, this study is hypothesis-generating rather than practice-changing.

CONCLUSION

While the CTS5 (prognostic tool) and BCI (prognostic and predictive tool) demonstrate good overall concordance in low-risk disease, they diverge significantly in higher-risk and intermediate-risk populations. In the overall population, there was a non-statistically significant concordance. BCI may provide additional predictive insights for patients with grade 2 tumors and those with discordance between clinical features and genomic biology.

Integrating BCI into the decision-making framework may allow decisions regarding EET that would not be possible using a prognostic tool such as CTS5 alone, especially in clinically low-risk patients with high genomic risk and in clinically high-risk patients with low genomic benefit. Further studies with larger sample sizes and extended follow-up will allow analysis of the utility of BCI vs CTS5 for decision-making.

ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Board (IRB) of Henry Ford Hospital. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee. Patient consent was waived due to the retrospective nature of the study.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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AI DISCLOSURE

AI-assisted tools were used for bibliographic formatting support. The authors reviewed and approved all manuscript content and take full responsibility for the final version.

AUTHOR CONTRIBUTION

MQ: Formal analysis, Visualization, Writing – original draft. YA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology. QA: Data curation, Investigation, Writing – original draft. GDB: Formal analysis. SEL: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

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