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Review Article

The Relationship between Time to Surgery (TTS) and Survival in Breast Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: Curative operation is the practical and primary therapy for masses of breast cancers. In contrast, the correlation between the time interval from breast cancer diagnosis to curative surgery and survival is still uncertain.

Methods: An electronic literature search was conducted on PubMed/Medline and EMBASE (between Jan 2000 and Jan 2020). Primary endpoints were overall survival (OS) or Disease-Free Survival (DFS). The HR with 95% confidence intervals were calculated using a random-effects or fixed-effects model.

Results: The combined HR for OS was 1. 10 (95% CI 1. 08-1. 11; *P*=0. 000) by fixed-effects model, no statistically significant heterogeneity was found (*P*=1. 000; I2=0%), and this difference was statistically significant (Z=11. 99; *P*=0. 000).

Conclusion: This meta-analysis showed a significant adverse association between more prolonged time to surgery (TTS) and lower overall survival in patients with breast cancer. It is reasonable to minimize that interval between diagnosis and curative surgery.

Keywords: Breast cancer; Time to surgery; Survival; Meta-analysis

Introduction

Breast cancer is the most population malignant tumor in female patients, and it is also one of the leading causes of cancer-related death in the world currently (1). In the past few decades, we have made many advances in breast cancer treatment, and the prognosis of the breast tumor is radically improving (2). The main treatments for primary breast cancer include surgery, chemotherapy, radiation therapy, endocrine therapy, and targeted therapy (3-5). Curative operation is the practical and prior therapy for masses of breast cancers; approximately 37%-40% of breast tumor patients receive the operation (6). An early process might yield a better outcome in breast tumor treatment (7).

In comparison, time to surgery (TTS) is often delayed due to various factors (8), including greater use of preoperative highly complicated

radiological evaluation and precise bioptic technique, multidisciplinary evaluation, and reconstructive surgery coordination. Patients' social and economic factors and referral to tertiary care centers may also contribute (9-11). TTS of breast cancer has been increased steadily over the past decade (10,12,13). Though several studies have investigated the correlation between time interval from breast cancer diagnosis to curative surgery and survival, the outcome is still uncertain (14). The clinical guidelines do not specify the time interval from diagnosis to corrective surgery. Though there are no evidence-based treatments, clinicians generally agree that waiting times of less than four weeks for breast cancer operations are reasonable and responsible (15). Minimization delays of TTS are deemed to be significant because delays would confer some undesirable results (16).

To assess the relationship between TTS delays and survival in breast cancer, we undertook a systematic review and performed a quantitative meta-analysis. Our study is the first study to examine the connection between time to surgery and survival for breast cancer patients.

Materials and Methods

Data source

An electronic literature search was conducted on PubMed/Medline and EMBAS (between Jan 2000 and Jan 2020). Search terms were used such as "time to surgery", "Operative Time" or "timing to surgery", "breast neoplasm" and "survival" and "cohort studies" or "case-control studies" published in English.

The study was approved by the local institutional review board, and the requirement for informed consent was waived because of the retrospective nature of this study.

Selection criteria

Selected studies should meet the following criteria of eligibility: 1) All of the breast cancer patients underwent surgical treatment, the time from breast cancer diagnosis to surgery was documented. 2) The relationship between the time from breast cancer diagnosis to surgery and survival should be reported. 3) The end point for breast cancer patients was disease-free survival (DFS) or overall survival (OS). The hazard ratio (HR) with 95% confidence intervals (CIs) should be reported directly or sufficient data was provided to calculate them. When more than one publication was identified from the same study, only the most informative study was included. When data could not be determined, we would contact the authors. In order to avoid the effect of any publication bias, both full-text articles and meeting abstracts were included in our study.

Data extraction and quality assessment

Two experienced authors (S. Y. C and Z. X. G) independently extracted data of all eligible studies using a standardized data collection table (17). The following information from each included study was extracted: first author's name, publication year and country, study design, population characteristics, waiting time, effect estimates with corresponding 95% CIs, and covariates in the fully adjusted model.

Waiting time was defined differently in different studies, for purpose of combining the outcome of each individual study in our study, we converted the waiting time effect to a regression coefficient (β) and its standard error (SE) corresponding to the HR associated with each additional four-weeks in waiting time (18). For studies with two waiting time groups, we use the following formula to calculate β and SE,$\beta = \ln(HR)/(Xn - X_0)$, and the corresponding SE= (ln[upper of 95%CI]-ln[lower of 95%CI])/([Xn- X_0]*1. 96*2), Xn denotes exposure at group N level, and X_0 denotes exposure at reference level (19). If only a *P*-value was provided, the SE was calculated with the "test-based" method; SE=(ln[HR])/Zp, where Zp is the value of a unit-normal test (e. g. , when

P=0. 05, Zp=1. 96, 2-tailed test) (20). The value of 1. 96 might vary depending on the level of significance in each study (19,20). All time unit (day, week, or month) was converted into "week", and "N" in the Xn was defined as the number of week. The dependent variable for the regression was the log of HR, weighted by the inverse of its variance. In each of the studies, the summary HR of each four-weeks delays can be assigned as the relative risk of death for each 4-week of additional waiting for surgery, thus the summary measures presented here could be equal to $e^{\beta*4}$ (21).

We used the Newcastle–Ottawa Scale (NOS) criteria to assess the quality of all included studies (22). Any disagreements on the quality assessment and data extraction would be resolved by consensus or consultation of a third party.

Statistical analysis

The statistical analyses were performed with the software Stata 15. 0. We used the Q-test and the I^2 statistic to assess statistical heterogeneity. The fixed-effects model was used when *P*>0. 1 and I^2<50%; otherwise, the random-effects model was used (23). Funnel plots and the Begg and Egger tests were used to evaluate publication bias. Asymmetrical plot and *P*-value of Egger's test (<0. 05) suggested that there was no publication bias in all studies (24,25). For all the statistical analyses,the results was regarded as statistically significant when *P*<0. 05.

Results

The search strategy yielded 392 publications. Overall, 112 publications from PubMed/Medline, 278 publications from Embase. Fig. 1 provides an overview of the literature search and study selection. After the removal of duplicates, 283 studies remained for the screening of titles and abstracts. Of these, 245 publications were excluded based on titles or abstracts. We further excluded 29 studies that did not meet our included criteria or lack relevant information. Finally, 9 studies (8 articles) were identified as eligible for inclusion in our research, including 8 independent studies for OS (7,14,16,26-29) and 1 for DFS (28), respectively. All of those studies had good quality with a NOS score ≥of 6. Table 1 presented the characteristics of the 9 selected studies.

Included studies were conducted in the USA and Korea. The number of participants per study ranged from 2045 to 351087 for 639445 patients. The HR results from each qualified research were listed in Table 2, and the HR categories in Fig. 2A representation by surgical delay in the 8 analysis groups for overall survival was shown. The trend of HR at a different time of surgical delay was similar. Hence, we converted HR from categories to HR for a continuous representation by waiting-time (20). Figure 2B demonstrates that each HR corresponds to the relative increase in mortality with a four-week increase in waiting time. Finally, the four-fold change of each line's slope (by log converted HR) in Fig. 2B corresponding to the HR used in our study (19).

The combined HR for OS was 1. 10 (95% CI 1. 08-1. 11; *P*=0. 000) by fixed-effects model (Fig. 3). No statistically significant heterogeneity was found (*P*=1. 00; I2=0%), and this difference was statistically significant (Z=11. 99; *P*=0. 000).

To further examine our meta-analysis's reliability and robustness, we deleted 3 studies with the largest weight, and the result from the remaining studies was still consistent and statistically.

Table 1: Characteristics of studies selected for inclusion in this analysis

References	*Country*	*Median age, year*	*Sample size*	*Study quality*	*Article type*
Sachs et al. 2019	US	NA	43,970	6	Abstract
Walle et al. 2019	US	NA	11391	6	Abstract
Mansfield et al. 2015	US	NA	3932	9	Full Text
Mateo et al. 2019	US	19. 1%pts<50yr 24. 6% pts50-59y 28. 6%pts60-69y 21. 3%pts≥70y	351087	9	Full Text
Eaglehouse et al. 2019	US	54. 5 (11. 8)	9669	9	Full Text
Eriksson et al. 2018	US	58. 2 (10. 8)	7017	9	Full Text
Bleicher et al. (SEER)2016	US	75. 2 (6. 2)	94 544	8	Full Text
Bleicher et al. (NCDB)2016	US	60. 3 (13. 4)	115790	8	Full Text
Shin et al. 2013	Korea	49. 3 (10. 4	2045	9	Full Text

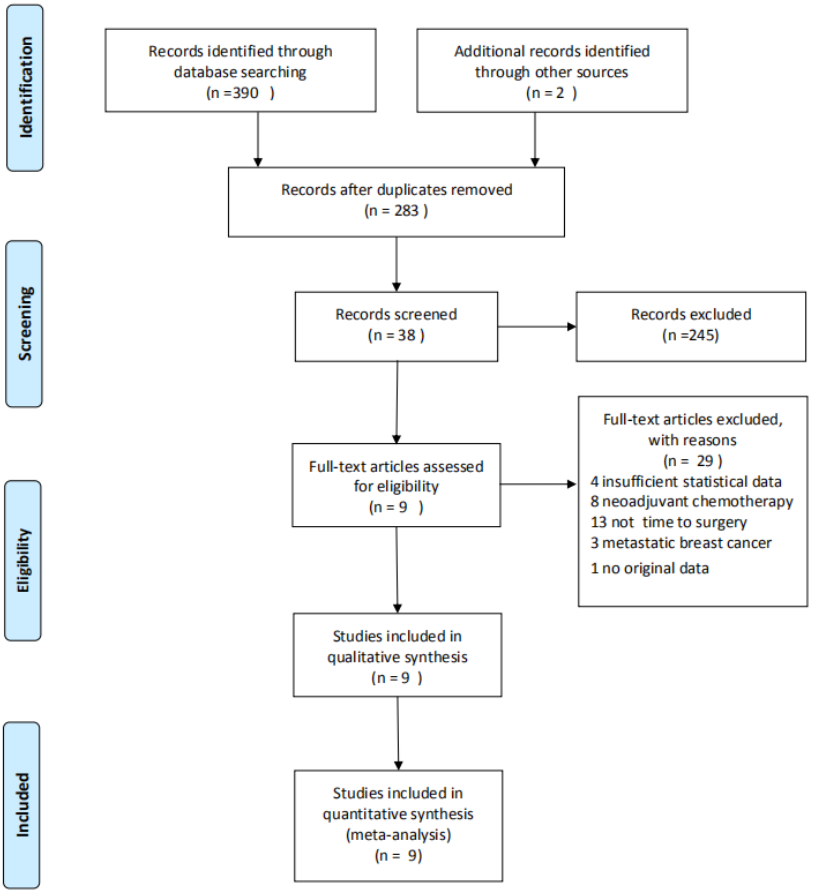

Fig. 1: Flowchart of the study selection strategy

Table 2: Outcomes reported in studies selected for inclusion in this analysis

References	*Stage*	*Wait-Time*	*HR(95 % CIs)*	
			OS	**DFS**
Sachs et al. 2019	III	12wk vs 4wk	1. 07(0. 90-1. 28)	-
Walle et al. 2019	II/III	< 3wk vs > 3wk	0. 97(0. 17-5. 65)	-
Mansfield et al. 2015	II/III	0-21d vs. 22-42 d	-	1. 588 (1. 235 -2. 043)
	-	0-21d vs. 43-63 d	-	1. 909(1. 177-3. 094)
	-	22-42 d vs. 43-63 d	-	1. 202(0. 723-1. 997)
Mateo et al. 2019	I-III	Per month of delay	1. 10(1. 08-1. 13)	-
Eaglehouse et al. 2019	I–III	≥5wk vs. < 5w	1. 07 (0. 59-1. 95)	-
Eriksson et al. 2018	NA	6wk vs. 3wk	1. 14 (0. 82-1. 59)	-
Bleicher et al. (SEER)2016	I–III	Per month of delay	1. 09 (1. 06-1. 13)	-
Bleicher et al. (NCDB)2016	I–III	Per month of delay	1. 10 (1. 07-1. 13)	-
Shin et al. 2013	NA	≥4wk vs. 4wk	1. 08(0. 69–1. 71)	-

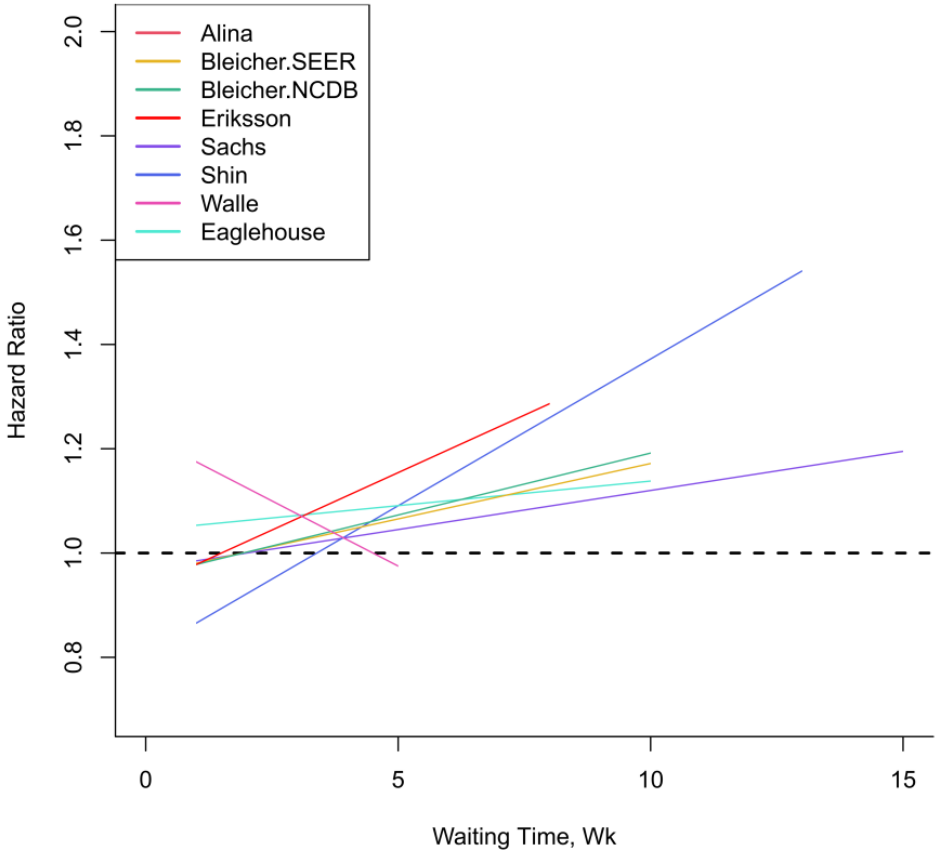

Fig. 2: Individual hazard ratio (HR) for overall survival (OS) according to waiting time categories. **A)** The relationship between OS and waiting time categories in the 8 eligible studies. The HR represents a comparison with the lowest waiting time category in each study. The first author of each study is show. **B)** Conversion of HR estimates from the original studies to an HR per week of delay. The slope of each line represents the change in the log HR per week of delay. The line for each individual study is located over the range of waiting times

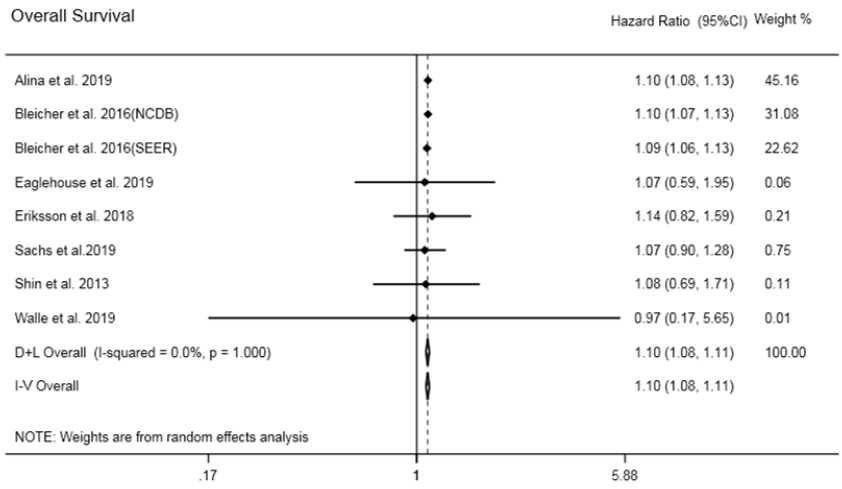

Fig. 3: The association between per 4-weeks surgical delay and overall survival

The HR after removing the study (45. 16% weight) (30), and another study (31. 08% weight) (29) was 1. 09 (95% CI 1. 06-1. 12), without evident heterogeneity either (P=1. 000, I^2=0%). Funnel plots are shown in Fig. 4A, and statistical tests showed no publication bias for OS was found in our study (Egger's P=0. 450, and Begg's P=0. 386, Fig. 4B).

Furthermore, to estimate our statistic analysis's stability, we performed a sensitivity analysis (31) (Fig. 5). The pooled HR was not affected by any individual study that demonstrated that our study results were stable and robust.

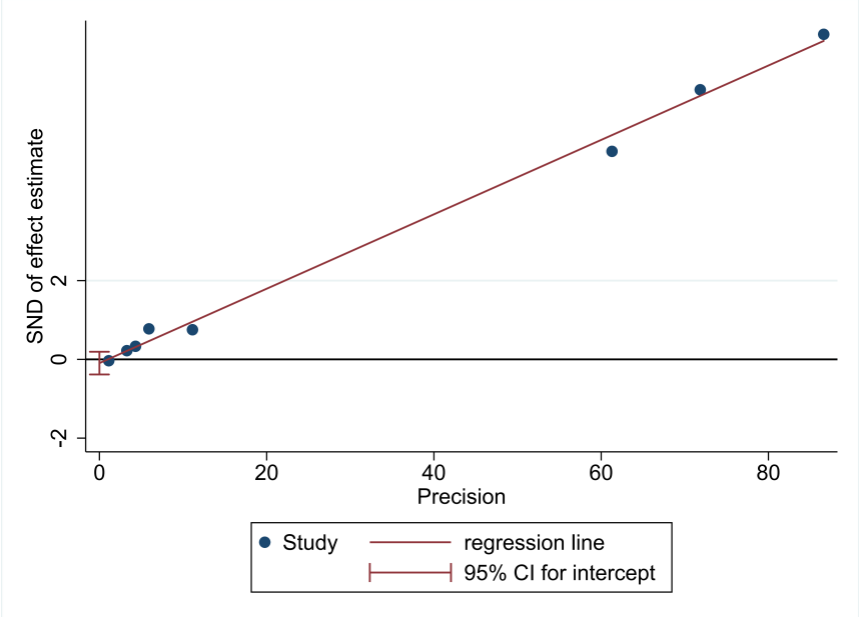

Fig. 4: A. Funnel plot of the association between TTS and OS after 3 studies with the largest weight were removed. B. Egger's funnel plot with 95% confidence limits to detect publication bias

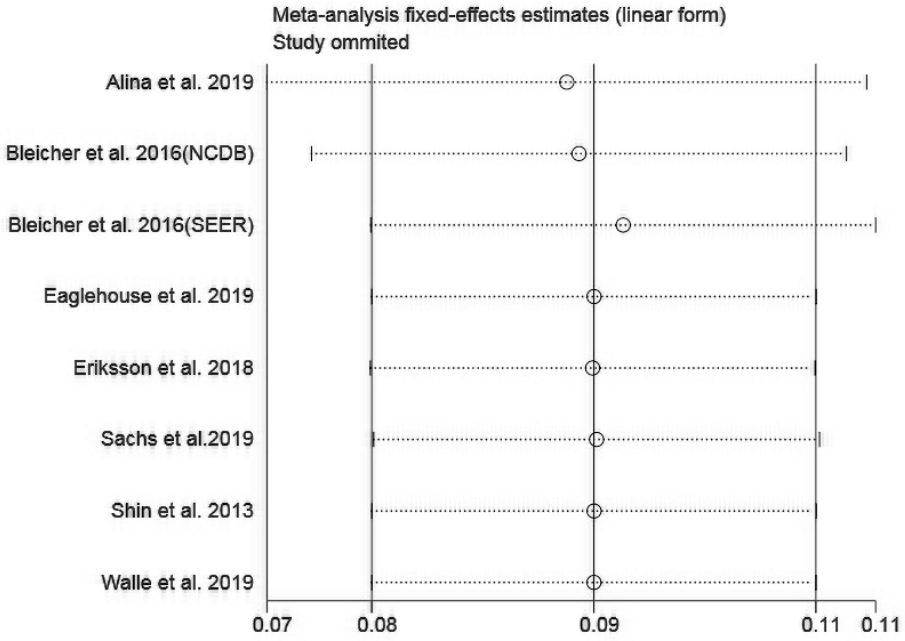

Fig. 5: Sensitivity analyses for included studies concerning OS. The vertical axis indicates the overall HR and the two vertical axes indicate its 95% CI. Every hollow round shape indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of every broken line represent the respective 95% CI

The study made by Mansfield et al. reported outcomes in terms of DFS. Table 1 showed strong associations between waiting time and the risk of DFS, the calculated HR in clinical Stage II patients was 1. 30 (95% CI 1. 17-1. 43); while in clinical Stage I patients, the HR was 0. 85(95% CI 0. 77-0. 93).

Discussion

TTS is often delayed due to various factors, including greater use of preoperative highly complicated radiological evaluation and precise bioptic technique, multidisciplinary evaluation, and reconstructive surgery coordination. Sometimes patients' social and economic reasons and referrals to tertiary care centers may also play a role in the TTS.

The finding of our meta-analysis demonstrates that there is a significant association between delays of TTS and OS in breast cancer patients. The summary HR indicated that a four-week delay in TTS is associated with a decrease in the relative risk of survival of 10% (HR=1. 10, 95%CI 1. 08-1. 11; *P*=0. 00). Our conclusion is consistent with the previously published studies, which were population-based, starting with morphological diagnosis, were limited to women who underwent an operation as the initial therapy (7,14,29).

Breast cancer phenotype has been found to relate to breast tumor behavior and patients' prognosis (32), which has been used to guide therapy. Breast cancer phenotypes were characterized as human epidermal growth factor 2 (HER2)-receptor-positive, hormone receptor (HR) positive breast tumor and triple-negative (estrogen receptor (ER), progesterone receptor (PR) negative, and HER2-negative) breast cancers (TNBC) (33). The prognosis is different between different phenotypes. In part, survival is dependent upon breast cancer phenotype

(34). Whereas, delays of TTS seem not to affect the survival of breast cancer patients with different phenotypes. In a study, the test for the interaction between TTS and tumor phenotypes demonstrated that there was no statistical difference in overall survival among all breast cancer subtypes (35). Besides, TTS delays did not differ between the three breast cancer phenotypes (30). Remarkably, while delays TTS does not vary among all phenotypes, it is reasonable to minimize that time interval between diagnosis and curative surgery.

Our study was the first study to examine the connection between TTS and OS in breast cancer patients. However, our study has some limitations. First, our results were based totally on observational studies, which should be interpreted cautiously and are insufficient evidence to alter current clinical. At the same time, it would be unethical to perform a prospective clinical trial. Second, we used the OS as the primary outcome. In terms of assessing the effects of TTS, breast cancer-specific mortality is a better outcome, while information on death's cause was insufficient in our studies. Third, due to individual information not available, subanalyses according to different features (i. e. surgery type, tumor stage, and lymph node status) failed. Fourth, the assumption used in our meta-analysis is that a log-linear relationship exists between per-week surgical delay after diagnosis and OS in patients with breast cancer. Still, the deduction may not be consistent with a practical situation. TTS more than three months were connected with an increased relative risk of death (7).

In comparison, there was no difference in survival if the patients have received surgery within three months after diagnosis (7). Hence, it might be irresponsible to use this method to reflect the surgical delay in survival. Despite these limitations, our meta-analysis still has crucial clinical directive significance. Physicians should minimize surgical delay for breast cancer patients when possible.

Conclusion

There was a significant adverse association between longer TTS and poorer overall survival in patients with breast cancer. Therefore, it is reasonable to minimize that interval between diagnosis and curative surgery, without hampering clinical diagnostic work-up and preoperative multidisciplinary evaluation.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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