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RESEARCH ARTICLE

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Noninvasive high-intensity focused ultrasound for skin brightening efficacy using a topical agent containing glutathione and hyaluronic acid

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ABSTRACT

Background: High-intensity focused ultrasound (HIFU) is well-documented for skin rejuvenation, lifting, and tightening. However, its synergistic effects with topical agents, enhanced by HIFU-induced vibration and heat, remain underexplored.

Objective: To evaluate clinical and photographic outcomes of HIFU combined with a topical agent versus the topical agent alone.

Method: This non-randomized controlled trial involved 20 female volunteers (ages 30–55) divided into two groups. Group A ($n=10$) received two HIFU sessions combined with a topical agent containing glutathione and hyaluronic acid. Group B ($n=10$) received the topical agent alone. Outcomes were assessed using digital photography, patient satisfaction surveys, and the A-One Smart™ system for fine wrinkles, hyperpigmentation, and hydration. Skin brightening was evaluated with the Global Esthetic Improvement Scale (GAIS).

Results: Group A showed significant reductions in fine wrinkles (6.25 ± 2.00 mm to 3.10 ± 1.62 mm), improved hyperpigmentation (3.50 ± 0.80 to 2.10 ± 1.05), and increased hydration (28 ± 10 to 55 ± 11) (all $p<0.05$). Over two-thirds of Group A reported significant improvements, with no complications. Group B showed minimal, non-significant changes ($p>0.05$), with only 30% reporting noticeable improvements.

Conclusion: Combining HIFU with a topical agent significantly enhances skin quality and brightness without adverse effects.

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KEYWORDS
high-intensity focused ultrasound (HIFU); glutathione; hyaluronic acid; facial rejuvenation; skin brightening

Introduction

High-intensity focused ultrasound (HIFU) treatment has established itself as a safe and effective noninvasive method for facial lifting and tightening (1). Clinical studies have documented significant benefits associated with HIFU, including reductions in fine lines and hyperpigmentation, as well as improvements in skin elasticity, rejuvenation, and lifting effects (2, 3). These outcomes underscore HIFU's role as a reliable method for skin rejuvenation and tightening.

To further enhance the clinical outcomes of HIFU, practitioners have increasingly integrated combination treatments with other modalities such as laser and radio frequency (RF) (4). Despite the established efficacy of these combined approaches, there is a lack of research investigating the synergistic effects of HIFU and topical agents. Specifically, the impact of HIFU-induced vibration and heat on the absorption and efficacy of topical agents remains unexplored. This study aims to address this gap by evaluating the clinical and photographic changes following two treatment sessions of a topical agent containing glutathione and hyaluronic acid (HA), with and without the adjunctive use of HIFU. The goal is to determine whether HIFU enhances the potential for skin brightening and overall skin quality improvement when used in conjunction with the topical agent.

Material and methods

Patients

Twenty Asian female volunteers, aged 30–55 years with Fitzpatrick skin types II–III, participated in this study. Participants provided written informed consent, and the study adhered to the 1975 Declaration of Helsinki guidelines. Exclusion criteria included pregnancy, breastfeeding, electrical implants, open wounds, skin infections, autoimmune diseases, and bleeding disorders. Participants were advised to avoid anti-aging skin therapies for six weeks prior to and during the study period to ensure uniformity in treatment outcomes.

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Study design

This study is a randomized controlled trial designed to evaluate the effects of HIFU combined with a topical agent versus the topical agent alone. Participants were randomly assigned to either Group A or Group B.

Treatment protocol

Group A ($n = 10$) received two HIFU treatments combined with the application of a topical agent containing glutathione and hyaluronic acid. The topical agent was applied manually by a single operator every two weeks. The HIFU treatment was performed using the ULTRAFORMER MPT device (CLASSYS Inc., South Korea), with a 1.5 mm cartridge delivering 500 shots (0.2–0.3 joules) over the full face. Each session lasted approximately 7 min and was repeated at 14-day intervals. Figure 1 illustrates the HIFU treatment areas marked in green for Group A.

Group B ($n = 10$) received two applications of the topical agent alone, manually applied by a single operator every two weeks.

Measurement and evaluation

Fine wrinkles, hyperpigmentation, and hydration were assessed using the A-One Smart™ system (A-One, Inc., South Korea), which employs advanced digital analysis to quantify these skin parameters. Wrinkle and hyperpigmentation measurements were obtained both through the A-One Smart™ system and manually by a single operator. Hydration was quantified using the same system.

Skin brightening effects were evaluated using the Global Esthetic Improvement Scale (GAIS). The GAIS categorizes improvements as follows: 1: Very Much Improved, 2: Much Improved, 3: Improved, 4: No Change, 5: Worse. Assessments were conducted by three blinded physicians, and the mean GAIS score from the three evaluators was used for analysis.

Figure 1. High-intensity focused ultrasound treatment areas marked in green in Group A.

Statistical analysis

Data were analyzed using descriptive statistics, with means and standard deviations calculated using Microsoft Excel (version 2016, 16.0.6741.2048). Comparative analysis between Group A and Group B was performed using t-tests, with statistical significance set at $p < 0.05$. Figure 2 shows the study diagram illustrating the treatment protocols and procedures for Group A and Group B.

Results

The study assessed the efficacy of High-Intensity Focused Ultrasound (HIFU) combined with a topical agent versus the topical agent alone. In Group A, which received two HIFU treatments along with the topical agent containing glutathione and hyaluronic acid, significant improvements were observed. Fine wrinkles decreased from 6.25 ± 2.00 to 3.10 ± 1.62, and hyperpigmentation improved from 3.5 ± 0.80 to 2.10 ± 1.05. Hydration increased notably from 28 ± 10 to 55 ± 11, as shown in Table 1. These changes were documented using the A-One Smart™ system, which captured the before (A) and after (B) effects of the treatment (Figure 3). Additionally, patient self-assessment results from Group A, following ULTRAFORMER MPT treatment combined with topical agents, reflected perceived improvements in skin condition (Figure 4).

In contrast, Group B, which received only the topical agent applied bi-weekly, showed minimal changes. The improvements were slight and not statistically significant (p-value > 0.05), as detailed in Table 2. Patient self-assessment results from Group B, following the application of topical agents alone, indicated less pronounced changes in skin condition compared to Group A (Figure 5). According to the Global Esthetic Improvement Scale (GAIS), assessed by three blinded physicians, 70% of participants in Group A were rated as 'very much improved' or 'much improved'

Table 1. Effects of HIFU treatment combined with topical agents (Group A).

Skin parameter	Pretreatment mean (± SD)	Post-treatment mean (± SD)	Difference (mean change)	p-value
Fine wrinkles	6.25 ± 2.00	3.10 ± 1.62	−3.15	< 0.05
Hyperpigmentation	3.5 ± 0.80	2.10 ± 1.05	−1.40	< 0.05
Hydration	28 ± 10	55 ± 11	+27	< 0.05

This table presents the quantitative measurements of fine wrinkles, hyperpigmentation, and hydration in Group A before and after two sessions of HIFU treatment combined with topical agents containing glutathione and hyaluronic acid. The table includes pretreatment and post-treatment mean values (± standard deviations), the mean change observed, and the statistical significance (p-value) for each skin parameter.

Table 2. Effects of topical agents alone (Group B).

Skin parameter	Pretreatment mean (± SD)	Post-treatment mean (± SD)	Difference (mean change)	p-value
Fine wrinkles	6.30 ± 2.10	5.90 ± 2.00	−0.40	> 0.05
Hyperpigmentation	3.60 ± 0.85	3.50 ± 0.80	−0.10	> 0.05
Hydration	30 ± 12	32 ± 11	+2	> 0.05

This table shows the quantitative measurements of fine wrinkles, hyperpigmentation, and hydration in Group B, which received topical agents alone. It includes pretreatment and post-treatment mean values (± standard deviations), the mean change observed, and the statistical significance (p-value) for each skin parameter.

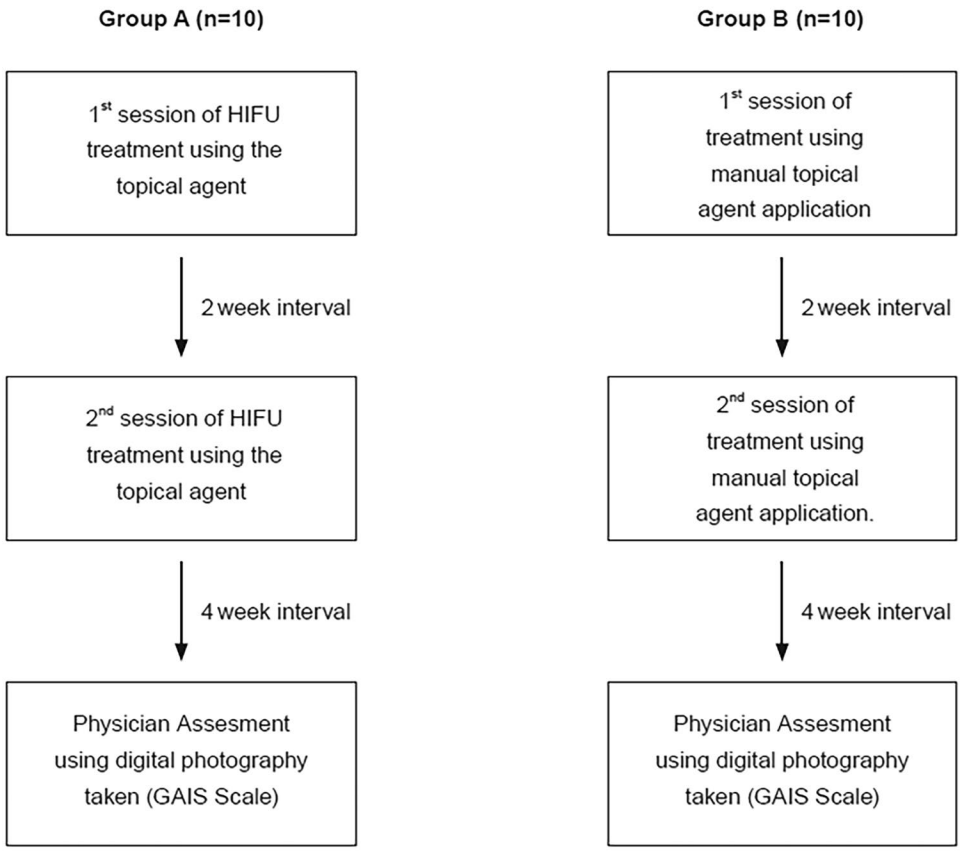

Figure 2. Study diagram illustrating the treatment protocols and procedures for Group A and Group B.

(Figure 6). Conversely, only 30% of participants in Group B achieved similar ratings.

Discussion

The quest for clear, smooth, and youthful skin has spurred the advancement of various skin rejuvenation technologies, including radiofrequency, laser ablation, low-level lasers, and non-thermal ultrasound (5, 6).

HIFU has gained prominence as a noninvasive treatment for skin rejuvenation and tightening. While HIFU is widely used and considered a gold standard in esthetic medicine, the clinical effectiveness of combining HIFU with topical agents, particularly in terms of enhancing the absorption of active ingredients through ultrasound-induced vibration and heat, remains underexplored (7–10).

In this study, we evaluated the effects of combining HIFU with a topical agent containing glutathione and hyaluronic acid. Group A received HIFU treatment delivered using a circular hand-piece movement alongside the application of the topical agent. The HIFU procedure induced a warming sensation and vibration, which is hypothesized to enhance the absorption of the topical agent. Glutathione, a potent antioxidant, is known for its skin-whitening properties and anti-melanogenic effects, which impact melanin production (10–12). Hyaluronic acid, with its biodegradability and non-toxicity, functions primarily as a hydrating agent by binding water to tissue, thus improving skin hydration (6, 9, 13).

Our findings demonstrate that two sessions of HIFU combined with the topical agent resulted in significant improvements in skin quality. Specifically, fine wrinkles decreased from 6.25 ± 2.00 to 3.10 ± 1.62, hyperpigmentation reduced from 3.5 ± 0.80 to 2.10 ± 1.05, and hydration increased from 28 ± 10 to 55 ± 11 in Group A. These changes were statistically significant ($p < 0.05$). Patient self-assessments and GAIS ratings further supported these results, indicating noticeable enhancements in skin attributes.

In contrast, Group B, which received only the topical agent, exhibited minimal changes in skin parameters. The lack of statistically significant improvements in fine wrinkles, hyperpigmentation, and hydration ($p > 0.05$) highlights the added benefit of combining HIFU with topical agents.

One limitation of our study is the design; while we conducted a randomized controlled trial, a split-face study would have provided a more direct comparison within the same patient. Such a design could have controlled for individual variability and offered a more precise assessment of the relative efficacy of the combined treatment versus the topical agent alone.

Despite this limitation, our study confirms the efficacy and safety of combining HIFU with topical agents. No adverse effects, such as scarring, pigmentation issues, or texture abnormalities, were observed, reinforcing the safety profile of the combined treatment approach.

In conclusion, integrating HIFU treatment with a topical agent containing glutathione and hyaluronic acid significantly improves skin quality and brightness compared to using topical agents alone. These findings suggest that the combination treatment is effective and safe, providing a promising approach for enhancing skin rejuvenation. Future research, ideally using a split-face design, could further elucidate the benefits and optimize treatment protocols.

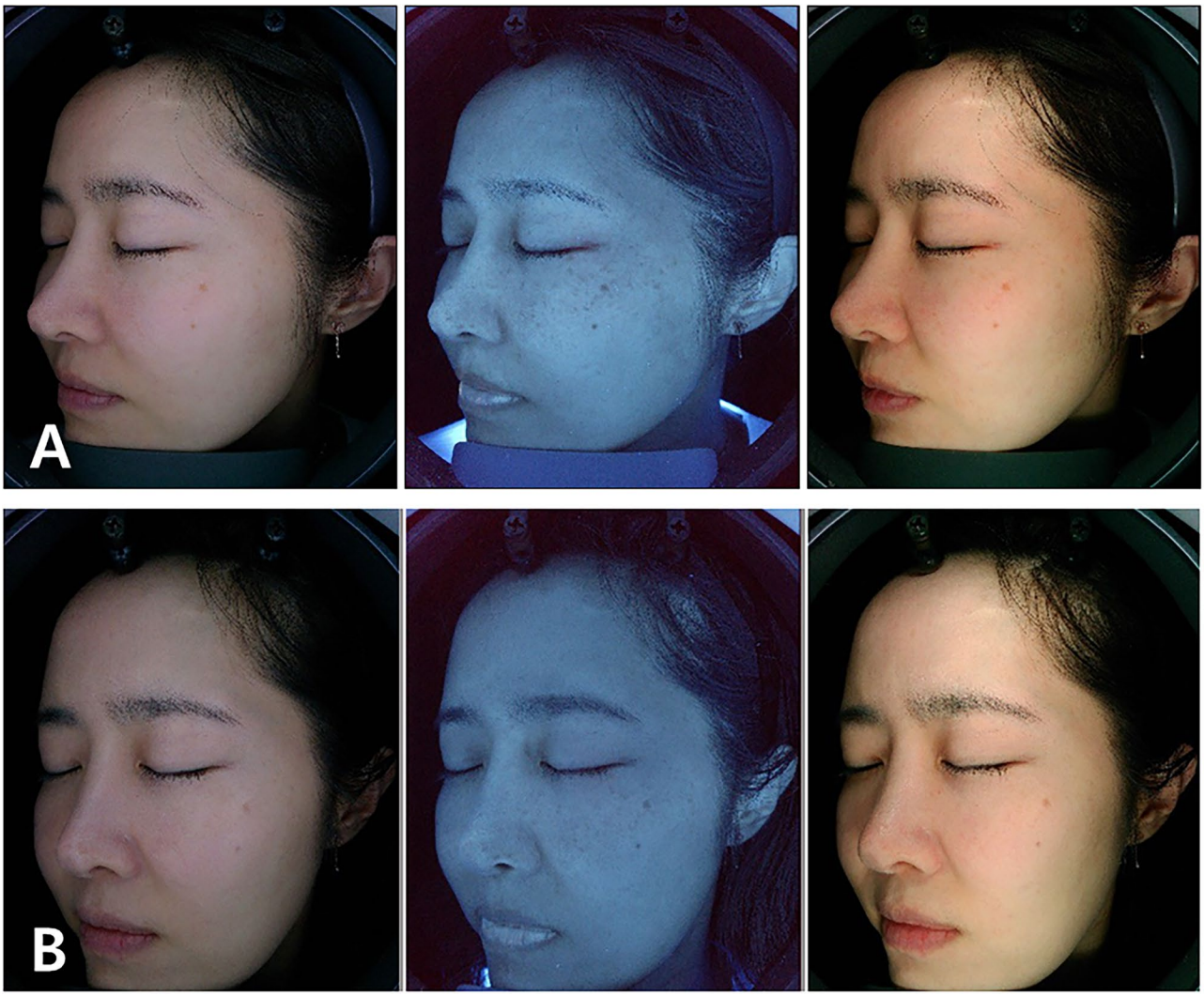

Figure 3. Fine lines, hyperpigmentation, and hydration observed prior to and following a series of high-intensity focused ultrasound treatment using the topical agent with the multi-functional imaging system. The before (A) and after the treatment (B).

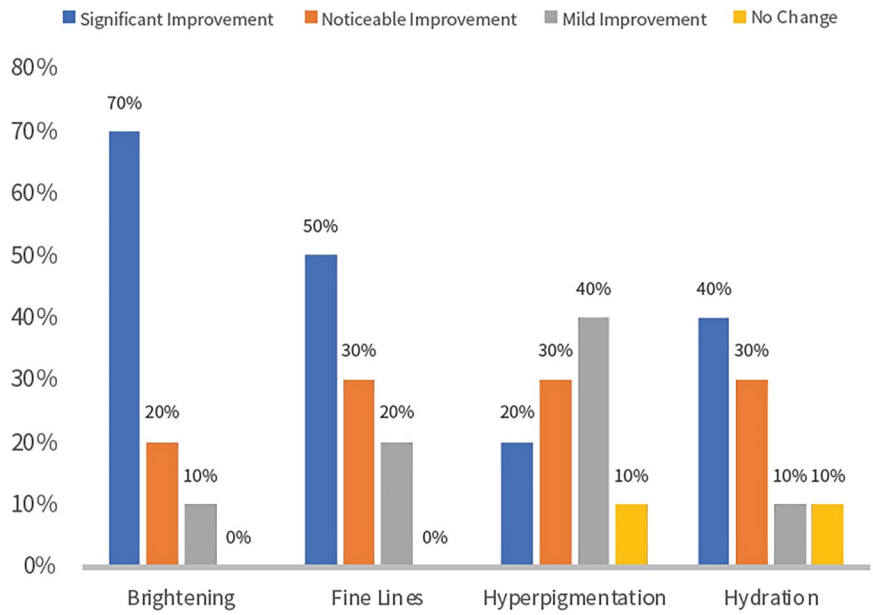

Figure 4. Patient self-assessment results from Group A following ULTRAFORMER MPT treatment combined with topical agents, reflecting perceived changes in skin condition.

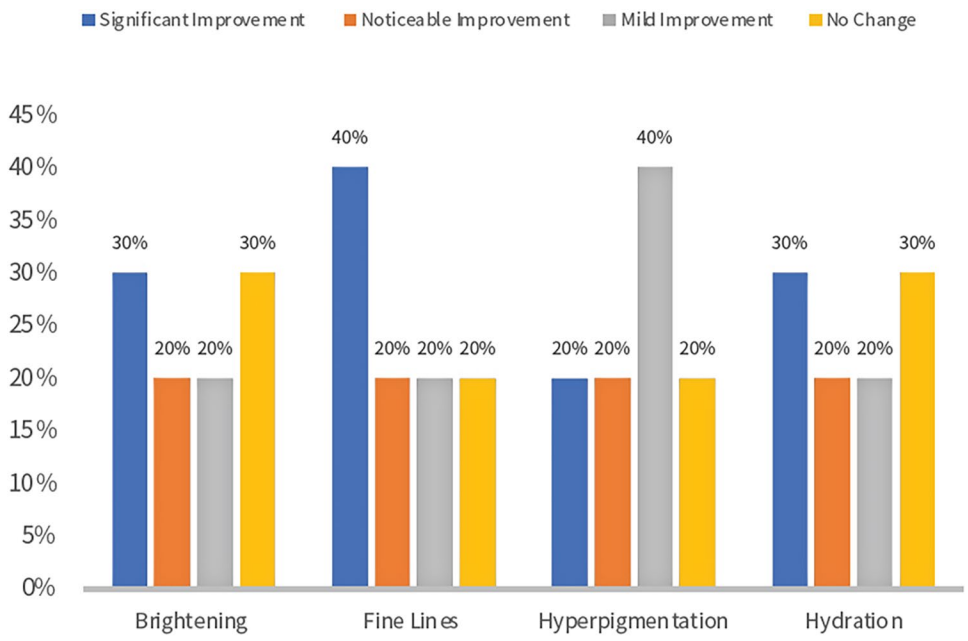

Figure 5. Patient self-assessment results from Group B following application of topical agents alone, showing perceived changes in skin condition.

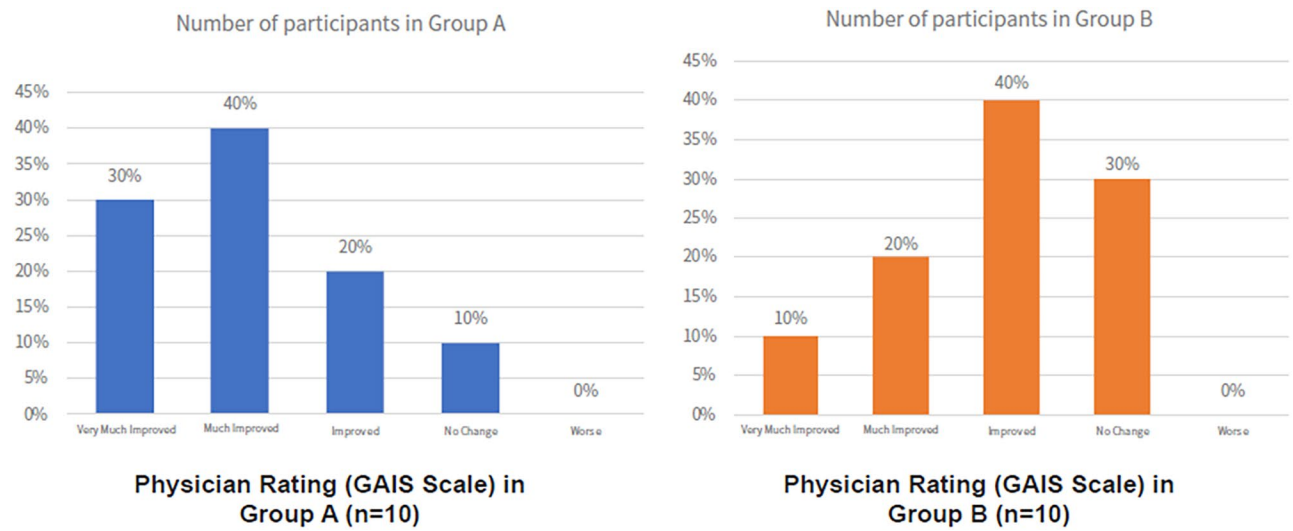

Figure 6. Global Esthetic Improvement Scale (GAIS) ratings by physicians evaluating the skin brightening effects in both treatment groups.

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This study was conducted in compliance with the Declaration of Helsinki.

Author contributions

All authors have reviewed and approved the article for submission.

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Visualization, Kyu-Ho Yi, Jovian Wan, Angela Wai Kay Lee, Sophie Pei-Hsuan Lu, Hsien Li Peter Peng.

Supervision, Kyu-Ho Yi, Po Han Patrick Huang.

Disclosure statement

I acknowledge that I have considered the conflict of interest statement included in the 'Author Guidelines'. I hereby certify that, to the best of my knowledge, that no aspect of my current personal or professional situation might reasonably be expected to significantly affect my views on the subject I am presenting.

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