Serum Albumin Levels as Predictors of Microvascular Health and Wound Healing Outcomes in Diabetic Foot Ulcers

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Abstract

Background: Diabetic foot ulcer (DFU) is a severe complication of diabetes mellitus (DM), affecting 15% of patients globally and contributing to 85% of non-traumatic lower extremity amputations. Albumin, a critical plasma protein, influences inflammation, vascularization, and tissue repair, and its deficiency (hypoalbuminemia) has been linked to poor DFU outcomes. This study aimed to investigate the association between serum albumin levels, microvascular density (MVD), and granulation tissue quality in DFU patients. Methods: A prospective observational study was conducted at Cipto Mangunkusumo General Hospital, Indonesia, from 2020 to 2022. Patients with DFU requiring surgical debridement or amputation were recruited. Baseline serum albumin levels were measured, and tissue samples were collected during procedures to evaluate granulation tissue and MVD via histological analysis. Statistical analyses, including Pearson/Spearman correlation, were performed to assess relationships between albumin levels, MVD, and granulation tissue. Results: Among 130 patients (50% male, mean age 57.66 ± 8.38 years), hypoalbuminemia was significantly associated with poorer DFU outcomes. Patients requiring amputation had lower serum albumin levels (median: 2.5 g/dL) than those undergoing debridement (median: 3.0 g/dL; $p < 0.01$). MVD was higher in the debridement group (median: 78.30 vessels/mm²) compared to the amputation group (median: 62.20 vessels/mm²; $p = 0.02$). Similarly, granulation tissue area was larger in the debridement group (median: 18.67%) than in the amputation group (median: 13.53%; $p < 0.01$). Strong positive correlations were observed between serum albumin levels and both MVD ($R = 0.89$, $p < 0.01$) and granulation tissue area ($R = 0.89$, $p < 0.01$). Conclusion: Serum albumin levels strongly correlate with MVD and granulation tissue quality, emphasizing its critical role in wound healing among DFU patients.

Keywords: Diabetic Foot Ulcers, Serum Albumin, Microvascular Density, Granulation Tissue, Wound Healing

Significance | This study deermines the critical role of serum albumin in improving vascularization and granulation tissue, reducing amputation risks in diabetic foot ulcers.

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Introduction

Diabetic foot ulcer (DFU) is a serious complication of diabetes mellitus (DM) that affects approximately 15% of patients during their lifetime. The global prevalence of DFU ranges from 6.3%, with the highest rates observed in Asia (13%) and the lowest in Europe (5.1%) (Zhang et al., 2017). DFU contributes to 85% of all non-traumatic lower extremity amputations, making it a significant global health burden (Raghav et al., 2018; Rosien et al., 2024). The pathophysiology of DFU is complex, involving mechanisms such as

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neuropathy, ischemia, and chronic infection, all of which exacerbate impaired wound healing (Falanga, 2005). Identifying factors influencing DFU healing is therefore crucial to reducing morbidity and mortality rates.

Albumin, the most abundant plasma protein with normal concentrations ranging from 3.5–5.0 g/dL, plays a pivotal role in maintaining oncotic pressure, molecular transport, and inflammatory modulation (Don & Kaysen, 2004). In DFU patients, albumin levels are often significantly reduced. A study reported that 68% of DFU patients had hypoalbuminemia, defined as serum albumin levels below 3.5 g/dL (Zhang et al., 2024). Hypoalbuminemia has been shown to increase the risk of infection by 2.5-fold and prolong wound healing by up to 50% compared to patients with normal albumin levels (Man et al., 2020). Additionally, hypoalbuminemia is strongly associated with the risk of amputation in DFU patients. One study demonstrated that the average serum albumin level in patients undergoing amputation was 2.8 g/dL, compared to 3.2 g/dL in those who healed without requiring amputation (Chang et al., 2023). Moreover, patients with hypoalbuminemia were found to have a 2.5-fold higher risk of non-healing after debridement surgery (Cheng et al., 2021). These findings underscore the importance of maintaining optimal albumin levels to reduce the need for surgical interventions.

At the tissue level, granulation tissue, which is rich in fibroblasts and new capillaries, serves as a key indicator of wound healing. Albumin has been shown to enhance collagen synthesis by fibroblasts, which is crucial for maintaining tissue integrity (Brem & Tomic-Canic, 2007). Low albumin levels not only compromise the quality of granulation tissue but also increase the risk of wound-related complications, including infection. Furthermore, MVD, a parameter reflecting the extent of angiogenesis, plays a critical role in supporting wound healing by facilitating oxygen and nutrient delivery to the affected tissues (DiPietro, 2016). Despite the importance of these indicators of microvascular health, the relationship between serum albumin levels and these parameters in DFU patients remains poorly understood.

This study aims to explore the relationship between serum albumin levels and microvascular conditions in DFU patients, specifically as reflected by MVD and granulation tissue. Understanding this relationship is expected to provide valuable insights for developing more effective interventions to improve wound healing in DFU patients.

2. Methods

2.1 Study Seing and Participants

This prospective observational study was conducted at Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, from 2020 to 2022. The study focused on DFU patients requiring either debridement or amputation, as determined by the WIfI scoring system. Patients who were admitted through the outpatient clinics or the emergency department underwent WIfI assessments, which evaluated three critical components: wound severity, ischemia, and foot infection. Wound severity was graded based on the size and depth of the ulcer, ranging from no ulcer to extensive ulcers involving the forefoot or midfoot. Ischemia was assessed using parameters such as the ankle-brachial index (ABI), toe pressure, and transcutaneous oxygen levels, with grades indicating perfusion adequacy. Foot infection was graded based on its severity, from no infection to systemic involvement characterized by signs of systemic inflammatory response syndrome (Cerqueira et al., 2019). Patients with a "high" risk of amputation according to the WIfI score within one year underwent amputation procedures.

Patients were eligible for inclusion in the study if they met the following criteria: (1) aged 18 years or older, (2) had a confirmed diagnosis of type 2 diabetes mellitus (DM), (3) presented with at least one active foot ulcer, and (4) provided consent for surgical debridement and participation in the study. Exclusion criteria included a history of malignancy in the affected area, peripheral arterial disease (PAD) with an ankle-brachial index (ABI) of ≤0.39, concurrent systemic infections (e.g., sepsis), use of immunosuppressive therapy, or any other conditions impairing wound healing, such as vasculitis, autoimmune diseases, or septic shock.

2.2 Data Collection

Demographic and clinical data were collected, including age, sex, comorbidities, HbA1c levels, and the type of procedure (amputation or non-amputation). Baseline serum albumin levels were assessed using a standardized bromocresol green assay. Microvascular conditions were represented by granulation tissue and microvascular density, which were evaluated through histological analysis, as detailed later in the section.

2.3 Tissue collection

Tissue sampling was performed in the operating room of the Central Surgery Unit (CSU) and the emergency department. The collected samples were sent to the Department of Pathology Anatomy at RSCM/FKUI for analysis of granulation tissue and tissue vascular density. The samples were obtained using the incisional biopsy method during surgical debridement procedure. Tissue was collected from the wound margin located proximal to the ulcer, with dimensions of 2 cm × 1 cm and a depth of approximately 1 cm, extending into the subcutaneous layer. The collected tissue was placed in a 5 mL Eppendorf tube prefilled with 10% formalin buffer and stored at room temperature.

2.4 Granulation tissue preparation and evaluation

Histological preparations were performed using the hematoxylin and eosin (H&E) staining method. Tissue samples were first deparaffinized with xylol, cleaned with alcohol, and rinsed with water. Hematoxylin was applied to define cell nuclei, followed by brief decolorization with hydrochloric acid and water immersion to develop the stain. Eosin was then used to highlight cytoplasmic and extracellular matrix components. After rinsing, the slides were dehydrated through graded alcohols, cleared with xylol, mounted, and labeled with a laboratory number for identification.

The stained slides were examined under a microscope to assess the distribution and extent of granulation tissue. The analysis involved a detailed observation of all visible fields, with particular attention paid to the intensity and uniformity of the staining under magnification of 100x. The quantification of granulation tissue was carried out by evaluating the extent of stained areas in the histological slides.

To ensure accuracy and consistency, two experienced pathologists independently assessed the slides. Each pathologist quantified the stained area relative to the total tissue area observed. The final granulation tissue score was determined by calculating the average of the scores provided by both pathologists.

2.4 Microvascular density

The vascularization aspect of the tissue in this study will be assessed using two approaches: the evaluation of the number of blood vessels per high-power field (HPF) and the calculation of MVD. Tissue samples will be prepared as paraffin blocks and stained with an anti-CD34 marker. Five regions with the highest vascularization ("hotspots") will be selected per low-power field (LPF) under 40x magnification. Each region will be outlined with a 200 µm box, corresponding to the field area under the microscope.

Subsequently, the blood vessels within these areas will be manually counted per high-power field (HPF) under 200x magnification using Aperio ImageScope software to determine the number of blood vessels in each region. The average number of blood vessels across the selected areas will then be calculated to determine the vessel count per HPF. Finally, this average vessel count will be divided by the area of the field of view (mm^2) to calculate the MVD value.

2.5 Statistical analysis

Data analysis was performed using SPSS software version 27 (IBM Corp., Armonk, NY). Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the data distribution, while categorical variables were presented as frequencies and percentages. The relationships between serum albumin levels, MVD, and granulation tissue quality were analyzed using Pearson or Spearman correlation coefficients, based on the normality of the data.

2.6 Ethical consideration

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from The Ethical Committee of the Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo National Hospital, with the registration number ND-599/UN2.F1/ETIK/PPM.00.02/2021.

3.Results

3.1 Patient characteristic

The study included 130 patients, with an equal distribution of males (50%) and females (50%). The mean age of the participants was 57.66 ± 8.38 years. Based on the assessment of amputation requirements using the WIfI (Wound, Ischemia, and foot Infection) score, 52 patients were identified as needing amputation procedures.

The mean age was similar across the two groups, with patients in the wound debridement group having an average age of 57.03 ± 8.05 years and those in the amputation group having an average age of 58.62 ± 8.84 years ($p = 0.30$).

Among the total cohort, hypertension was the most common comorbidity, affecting 43.08% of patients, followed by dyslipidemia (41.54%), coronary artery disease (18.46%), and chronic kidney disease (12.31%). The prevalence of comorbidities varied between the two groups. For instance, hypertension was more prevalent in the wound debridement group (60.71%) compared to the amputation group (39.29%).

Similarly, dyslipidemia was more common in the wound debridement group (64.81%) compared to the amputation group (35.19%). Notably, chronic kidney disease was more frequent among amputation patients (62.50%) compared to the wound debridement group (37.50%), although the difference was not statistically significant ($p = 0.09$).

The median HbA1c level for the total cohort was 9% (range: 4.10–20.0%), indicating suboptimal glycemic control. The HbA1c levels were comparable between the wound debridement group (median 9%; range: 4.10–13.70%) and the amputation group (median 8.98%; range: 5.2–20.0%), with no statistically significant difference ($p = 0.33$). Overall, no significant differences in age, gender distribution, comorbidities, or glycemic control were observed between the two groups, suggesting that other factors may contribute to the treatment outcomes (Table 1).

3.2 Albumin levels and local tissue microvasculature

A statistically significant difference was observed between the two groups, with a p-value of <0.01, indicates that patients in the amputation group tend to have lower serum albumin levels than those in the debridement group (Figure 1).

The condition of microvascularization was assessed through MVD and granulation tissue. Figure 2 presents a comparison between patients with well-preserved MVD and granulation tissue versus those with significantly impaired MVD and poor granulation tissue quality. The comparison of MVD and granulation area between the wound debridement group and the total amputation/limb salvage

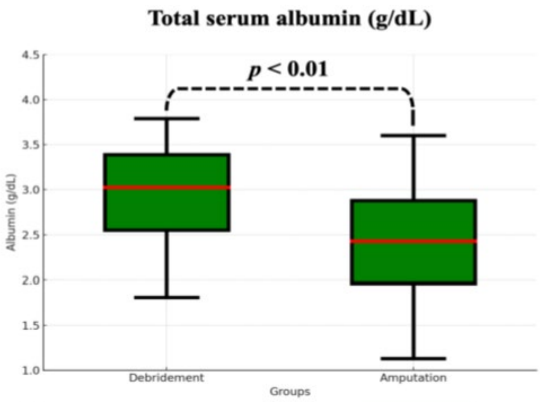

Figure 1. The boxplot compares total serum albumin levels between the debridement and amputation groups. The median albumin level is higher in the debridement group, and the difference is statistically significant (p < 0.01). This suggests that lower serum albumin levels may be associated with the need for amputation.

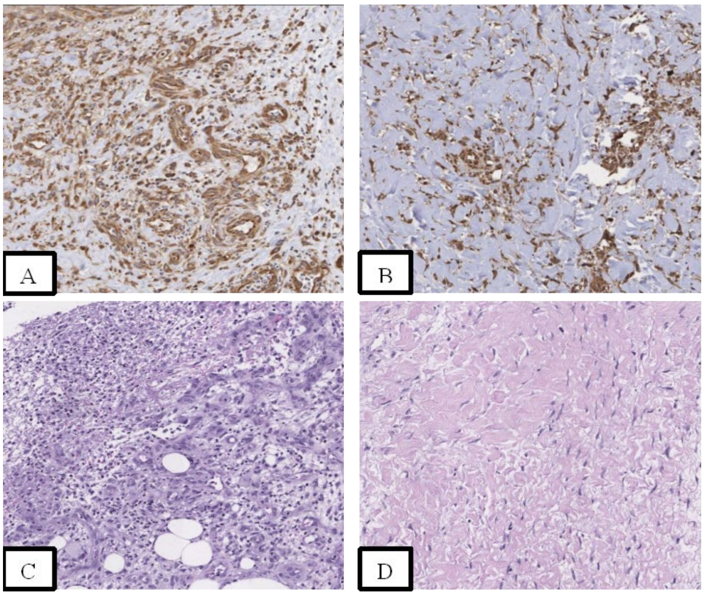

Figure 2. Representative histological images at 100x magnification. A and B: Microvascular density (MVD) stained with anti-CD34 marker. Image A shows a higher density of microvessels with tightly packed vascular structures, while image B demonstrates lower microvascular density with more sparsely distributed vessels.C and D: Granulation tissue stained with hematoxylin and eosin (H&E). Image C reveals a greater area of granulation tissue, characterized by abundant fibroblasts and capillary networks, compared to image D, which shows reduced granulation tissue and increased fibrosis.

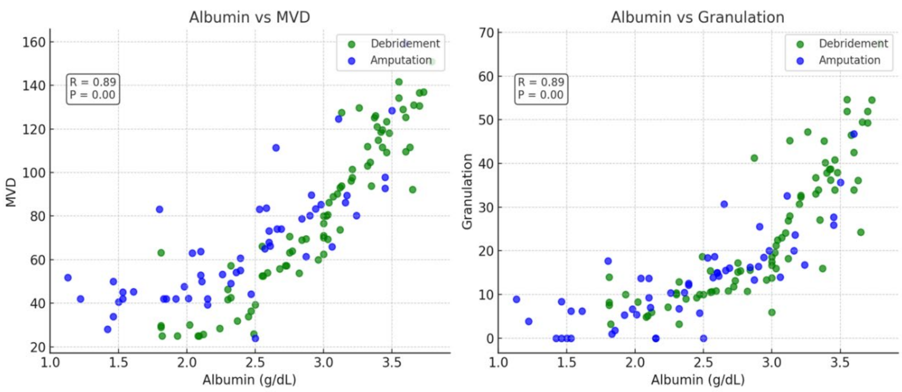

Figure 3. Scatter plots illustrating the relationship between albumin levels and microvascularization indicators. **Left panel (Albumin vs MVD)**: The plot shows a strong positive correlation (R = 0.89, p = 0.00) between albumin levels (g/dL) and microvascular density (MVD). **Right panel (Albumin vs Granulation)**: A similarly strong positive correlation (R = 0.89, p = 0.00) is observed between albumin levels and granulation area (%).

Table 1. Patient's characteristic

Variable	Total patients (n = 130)	Wound debridement only (n = 78)	Total amputation /limb salvage (n = 52)	*p* value
Age (year), mean ± SD	57.66 ± 8.38	57.03 ± 8.05	58.62 ± 8.84	0.30[a]
Gender, n (%)				
Male	65 (50.00%)	44 (56.41)	21 (40.38)	0.11[b]
Female	65 (50.00%)	34 (43.59)	31 (59.62)	
Comorbidities, n (%)				
Hypertensive disease	56 (43.08%)	34 (60.71)	22 (39.29)	1.00[b]
Chronic kidney disease	16 (12.31%)	6 (37.50)	10 (62.50)	0.09[b]
Coronary artery disease	24 (18.46%)	15 (62.50)	9 (37.50)	0.96[b]
Dyslipidaemia	54 (41.54%)	35 (64.81)	19 (35.19)	0.45[b]
HbA1c (%), median (range)	9 (4.10 – 20.0)	9 (4.10 – 13.70)	8.98 (5.2 – 20)	0.33[c]

[a] T-test; [b] Chi-square; [c] Mann-Whitney U

Table 2. Microvascular density and tissue granulation area.

Variable	Total patients (n = 130)	Wound debridement (n = 78)	Total amputation / limb salvage (n = 52)	*p* value
Microvascular density	69.50 (24.00 - 159.20)	78.30 (25.00 - 150.80)	62.20 (24.00 - 159.20)	0.02[a]
Granulation area (%)	15.58 (0.00 - 67.48)	18.67 (3.25 - 67.48)	13.53 (0.00 - 46.76)	<0.01[a]

[a] Mann-Whitney

group revealed significant differences (Table 2). The median MVD was notably higher in the wound debridement group, with a value of 78.30 (range: 25.00–150.80), compared to 62.20 (range: 24.00–159.20) in the amputation group, indicating a statistically significant difference ($p = 0.02$). Similarly, the granulation area was larger in the wound debridement group, with a median of 18.67% (range: 3.25–67.48%), compared to 13.53% (range: 0.00–46.76%) in the amputation group, which was also statistically significant ($p < 0.01$).

A strong positive correlation ($R = 0.89$, $p < 0.01$) was observed between albumin levels and MVD, indicating better vascularization in individuals with higher albumin levels. A similarly strong positive correlation ($R = 0.89$, $p = 0.00$) between albumin levels and granulation tissue area was also observed. Patients in the debridement group demonstrate larger granulation areas compared to the amputation group, reinforcing the association of higher albumin levels with improved granulation tissue formation. Together, these findings emphasize the critical role of albumin in wound healing through its positive impact on vascularization and granulation tissue quality (Figure 3).

4. Discussion

This study demonstrated a significant positive correlation between serum albumin levels and both MVD and granulation tissue area in patients with DFU. At the time of patient presentation, albumin levels were measured, and the need for amputation was assessed using the WIfI (Wound, Ischemia, and foot Infection) score. Patients requiring only debridement had higher albumin levels (median 3.0 g/dL) compared to those needing amputation (median 2.5 g/dL). This difference was also accompanied by better MVD (78.30 vessels/mm^2 vs. 62.20 vessels/mm^2) and larger granulation tissue areas (18.67% vs. 13.53%) in the debridement group ($p < 0.01$). These findings highlight the critical role of albumin in vascular health and tissue healing processes.

The relationship between hypoalbuminemia and poor wound healing has been widely reported. Irawan et al. reported that DFU patients undergoing hyperbaric oxygen therapy experienced an average increase in albumin levels of 1.2 g/dL, which significantly improved wound healing outcomes (Irawan et al., 2018). Mansoor and Modaweb found that hypoalbuminemia (<2.5 g/dL) was associated with a 3.8-fold increased risk of amputation (Mansoor & Modaweb, 2022). Cheng et al. also showed that patients with albumin levels above 3.0 g/dL had a 50% higher chance of healing without amputation compared to those with lower albumin levels (Cheng et al., 2021). These findings are consistent with our study results, reaffirming the role of albumin in influencing wound healing.

Our study also aligns with research exploring delayed healing in hypoalbuminemic patients. Soedjana et al. reported that patients with albumin levels below 2.8 g/dL had a 40% lower rate of successful skin graft uptake compared to those with albumin levels above 3.5 g/dL. Lee et al. also found that hypoalbuminemic patients required 25% longer to achieve wound closure (Lee et al., 2024). Falanga noted that low albumin levels exacerbate chronic inflammation, further slowing the healing process (Falanga, 2005). These findings support our observation that hypoalbuminemia is a major barrier to wound repair.

Nutritional status plays a critical role in DFU healing outcomes. Lee et al. reported that 78% of DFU patients had albumin levels below 3.5 g/dL, along with deficiencies in hemoglobin, zinc, and iron, all essential for wound healing (Lee et al., 2024). Moore et al. found that nutritional supplementation, including protein and micronutrients, improved healing rates by up to 30% in patients with chronic wounds (Moore et al., 2020). Porto et al. emphasized that improving nutritional status not only increased albumin levels but also reduced the risk of amputation by 40% (Da Porto et al., 2022). These findings indicate that addressing nutritional deficiencies is an essential step in DFU management.

The relationship between albumin levels and microvascular health is also critical to wound healing processes. Studies by Adhikari et al. demonstrated that interventions improving serum albumin levels increased MVD by 25% in diabetic patients (Lyttle et al., 2023). Tecilazich et al. found that albumin plays a role in enhancing endothelial function and vascular regeneration, critical components of angiogenesis (Tecilazich et al., 2013). Blakytny and Jude also associated higher albumin levels with reduced oxidative stress, which supports better vascularization and granulation tissue formation (Blakytny & Jude, 2006). These findings are consistent with our results, which show better MVD in patients with higher albumin levels.

Granulation tissue, a key indicator of wound healing, is also linked to serum albumin levels. Brem et al. reported that patients with albumin levels above 3.0 g/dL had significantly larger areas of granulation tissue compared to those with lower albumin levels (Brem & Tomic-Canic, 2007). Ravanti et al. found that hypoalbuminemia impairs fibroblast function and collagen synthesis, both critical for granulation tissue formation (Ravanti & Kahari, 2000). Our findings support these results, with patients in the debridement group showing better granulation tissue development.

The WIfI score, used in this study to assess the need for amputation, has been widely validated as a predictor of outcomes in DFU patients. Ramasamy et al. found that combining WIfI assessments with serum albumin levels provided better predictive accuracy for amputation risk than using the WIfI score alone (Ramasamy et al., 2011). Our findings support this, as lower albumin levels were associated with worse WIfI scores and an increased likelihood of amputation. Integrating albumin measurements into WIfI assessments may improve risk stratification and treatment decisions.

This cross-sectional study highlights the critical role of serum albumin levels in representing the microvascular health of DFU patients. Maintaining albumin levels above 3.0 g/dL through nutritional and therapeutic interventions may enhance vascularization and granulation tissue formation, improve healing outcomes, and reduce the risk of amputation. These findings emphasize the need for routine albumin monitoring and nutritional assessments in DFU management.

Study limitation

This study has several limitations. As a cross-sectional design, data were collected at a single time point, preventing the establishment of causal relationships between serum albumin levels, MVD, granulation tissue, and wound healing outcomes. The study also did not explore the effects of interventions aimed at increasing albumin levels, limiting its ability to provide guidance on treatment strategies. Nevertheless, these findings offer valuable insights into the relationship between serum albumin levels and the wound healing process at the tissue level, specifically describing the condition of microvascularization in patients with diabetic foot ulcers.

5. Conclusion

This study determined the critical role of serum albumin levels in diabetic foot ulcer (DFU) healing. A strong positive correlation between albumin levels, microvascular density (MVD), and granulation tissue area highlights the importance of maintaining optimal nutritional and vascular health. Patients with higher albumin levels demonstrated better wound healing outcomes, including improved granulation tissue quality and MVD, reducing the need for amputation. These findings align with previous research, emphasizing the importance of addressing hypoalbuminemia through nutritional interventions to improve DFU outcomes. Future studies should explore strategies to optimize albumin levels, ultimately enhancing patient care and reducing DFU-associated morbidity.

Author contributions

G.B.Y.S. conceptualized and designed the study. P.D. contributed to methodology development and supervised the research process. P.M.S.H., N.M.N.P., Z.N.T.E., and R.N.P. were responsible for data collection and analysis. L.R. provided critical revisions and guidance on data interpretation. G.B.Y.S. and P.M.S.H. drafted the manuscript, and all authors reviewed and approved the final version.

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Competing financial interests

The authors have no conflict of interest.

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