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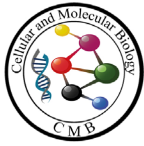

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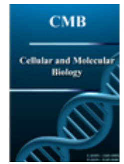

Original Article

IL-38 attenuates renal ischemia/reperfusion injury through suppressing inflammation in mice

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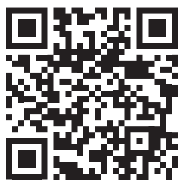

Abstract

Inflammation plays an important role in the pathogenesis of renal ischemia/reperfusion injury (IRI). Interleukin-38 (IL-38) is an emerging cytokine with multiple functions involved in infection and immunity. The present study aimed to determine whether IL-38 attenuates renal IR injury in an animal model and to identify the underlying mechanisms. For this purpose, the renal IRI model was induced by left renal pedicle clamping for 45 min and right nephrectomy in mice. All mice were intraperitoneally injected with vehicle or IL-38. Renal histology, function, apoptosis and inflammatory cytokines were assessed. mRNAs were detected by Real-time PCR. The proteins were measured by Western blot. Results showed that the expression of IL-38 mRNA and protein in kidney tissue was significantly increased at 6 h and reached a peak at 24 h after renal IRI, along with the kidney dysfunction. IL-38 significantly decreased renal IRI, as reflected by the attenuation of renal dysfunction, tubular damage and cellular apoptosis. Thus, IL-38 markedly ameliorated the survival rate after renal IRI. In addition, IL-38 significantly increased the level of cytoplasmic IκB-α and suppressed the nuclear translocation of NF-κB, which inhibited the expression and release of inflammatory cytokines. In conclusion, IL-38 significantly protects against renal IRI probably by inhibiting pro-inflammatory reactions.

Keywords: Renal ischemia/reperfusion injury, IL-38; Inflammation, NF-κB.

1. Introduction

Acute kidney injury (AKI) is a major clinical problem that can result from renal ischemia/reperfusion injury (IRI), leading to acute kidney failure with increased morbidity and mortality in critically ill adults [1]. Renal IRI is inevitable during various types of operations including renal transplantation, surgical revascularization of the renal artery and treatment of suprarenal aortic aneurysms et al [2-4]. Due to a sudden transient reduction of blood flow, reperfusion of renal tissue initiates a series of cellular events leading to renal cell death. It is recognized that inflammation is perhaps the most crucial pathophysiological process involved in the propagation of renal IRI [5]. Therefore, the regulation of inflammation is an important strategy for preventing renal IRI.

The inflammatory response mediated by neutrophils and macrophages has been regarded as the main role in the pathogenesis of renal injury following IRI [6]. Several studies have shown that an attenuation of the inflammatory process at the early phase could be a possible way to prevent renal IRI [7, 8]. Research on interleukin-38 (IL-38) has highlighted its role as an anti-inflammatory cytokine within the IL-1 family. IL-38 has been shown to modulate immune responses, potentially reducing the production of pro-inflammatory cytokines [9]. Studies have indicated its involvement in conditions such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus et al [10]. IL-38 could bind to the IL-1 receptor accessory protein-like 1 (IL-1RAPL1), affecting the inflammatory pathways [10]. Ongoing research is exploring its therapeutic potential in various inflammatory and autoimmune diseases. However, the role and mechanism of IL-38 in renal IRI remain unclear. The aims of the present study were three fold: (1) to examine whether IL-38 participates in the process of renal IRI; (2) to determine whether IL-38 alleviates kidney damage after IRI; and (3) to determine whether renoprotection is associated with anti-inflammation induced by IL-38.

2. Materials and methods

2.1. Animals

Male C57BL/6 mice (7-8 weeks old; weight, 23-25g) were purchased from Nanjing Medical University (Nanjing, China). The animal protocol was approved by the Animal Care and Use Committee. All male mice were housed in temperature-controlled cages with free access to food and water.

2.2. Experimental protocal

The mice were randomly divided into three groups:

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a sham-operated group (Sham); an ischemia/reperfusion group (IR); and an IR plus IL-38-treated group (IR+IL-38). All mice were subjected to renal IRI as previously described [11]. The right kidney was exposed and removed. Then, the left renal pedicle was clamped for 45 min by a nontraumatic microvascular clip to induce ischemia. After renal ischemia, vascular clamp was removed to allow reperfusion. IL-38 was dissolved in phosphate-buffered saline (PBS). Animals were blindly randomized 5 min before renal ischemia to receive 0.5 μg of recombinant mouse IL-38 (Sigma-Aldrich, St. Louis, MO, USA) or the same volume of vehicle intraperitoneally.

2.3. Real-time PCR

Total RNA was extracted from kidneys using Trizol reagent (Invitrogen, California, USA) according to the manufacturer's instructions. One microgram of total RNA was isolated to produce cDNA in a reverse transcription reaction by using PrimeScript RT Master Mix (TaKaRa, Dalian, China). The following primers used were as follows: forward primer 5'- CCT GGC GTG TGT AAA GAC AA -3' and reverse primer 5'- CAG ATC CCA AGC TTC TCT GG -3' for IL-38; forward primer 5'- CAG GCG GTG CCT ATG TCT C -3' and reverse primer 5'- CCA TTT GGG AAC TTC TCA TCC CTT -3' for TNF-α; forward primer 5'- GCT ACC AAA CTG GAT ATA ATC AGG A -3' and reverse primer 5'- CCA GGT AGC TAT GGT ACT CCA GAA -3' for IL-6; forward primer 5'- ACT GCA CCC ACT TCC CAG T -3' and reverse primer 5'- TGT CCA GCT GGT CCT TTG TT-3' for IL-10; forward primer 5'- ACC ACA GTC CAT GCC ATC AC -3' and reverse primer 5'- CAC CAC CCT GTT GCT GTA GCC -3' for GAPDH. Real-time PCR was done using a QuantiFast SYBR Green PCR kit (Qiagen, Hilden, Germany) on a StepOne Real-time PCR System (Applied Biosystems, California, USA). Relative gene expression was calculated by the $2^{-\Delta\Delta CT}$ method, with GAPDH serving as an internal control.

2.4. Measurement of renal function

After 24 h of reperfusion, blood samples were collected for the measurement. Renal function was monitored by measuring the levels of blood urea nitrogen (BUN) and creatinine (Cr) using commercial kits (Jiancheng Bioengineering Institute, Nanjing, China) according to the instructions.

2.5. Histological evaluation

The kidney tissues were fixed in 4% paraformaldehyde 24 hours after reperfusion, and then processed into paraffin sections. The kidney tissues were stained with hematoxylin-eosin as previously described [11]. Ten high-magnification (×400) fields of the cortex and the outer stripe of the outer medulla were randomly selected. Histological assessment of renal damage was determined by semi-quantitative analysis of tubular injury including the presence of tubular cell necrosis, loss of brush border, vacuolization, tubule dilation or cast formation. These factors were scored as follows: no injury (0); mild: less than 25% (1); moderate: less than 50% (2); severe: less than 75% (3); and very severe: more than 75% (4).

2.6. Measurement of Tissue TNF-α, IL-6, IL-10 and MPO

Renal tissue homogenate collected 24 hours after reperfusion were used to measure the concentrations of TNF-α, IL-6 and IL-10 by the ELISA method using a commercially available assay kit (Neoscience Inc, Beijing, China) according to the instructions. MPO activity in the kidney tissue 24 h after reperfusion was measured according to manufacturer instructions (Jiancheng Bioengineering Institute, Nanjing, China).

2.7. Western blot analysis

As described [11], proteins were extracted from kidney tissue 24 hours after reperfusion. After treatments, samples (40 μg per lane) were loaded and then separated on an SDS-PAGE (10% gels) and electrotransferred to PVDF membranes. The membranes were incubated with the following primary antibodies: IL-38, Bax, Bcl-2, IκB-α, and NF-κB (Abcam, Cambridge, UK) 1:1000, Cleaved Caspase-3 (Cell Signaling Technology, Danvers, USA) at 4°C overnight. Following extensive washing, the primary antibody bindings were detected with a secondary antibody (Cell Signaling Technology, Danvers, USA) 1:5000. The immunoreactive bands were visualized and photographed by using an EC3 Imaging System (UVP Inc., USA).

2.8. Statistical analysis

All values were expressed as mean ± SD. Comparisons across more than two groups involved use of one-way ANOVA and the Student-Newman-Keuls test. Animal survival differences between groups were determined using the log-rank test. $P \leq 0.05$ was set as the significance level.

3. Results

3.1. Changes of tissue IL-38 expression and function after renal IRI

The expression of IL-38 mRNA and protein in kidney tissue at 6, 12, 24 and 48 h were higher than it at 0 h, and peaked at 24 h during reperfusion (Fig. 1A-C, $P < 0.05$). Similarly, the rise in the concentration of tissue TNF-α began at 6 h and peaked at 24 h during reperfusion (Fig. 1D, $P < 0.05$). After renal IRI, the increase in the concentration of blood BUN and Cr reflecting the damaged degree of kidney function began to increase at 12 h (Fig. 1E and F, $P < 0.05$).

3.2. IL-38 attenuated mortality and renal injury after renal IRI

Fig. 2A shows that by day 7 after renal ischemia-reper-

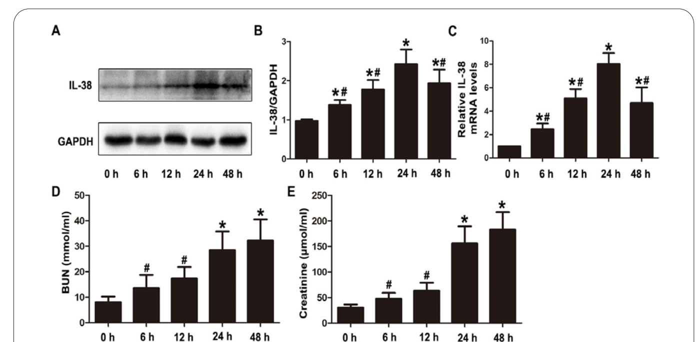

Fig. 1. Changes of tissue IL-38 expression and function after renal IRI. (A-B) Western blot band and bar graph of IL-38 (n=5); (C) Quantitative real-time reverse transcription polymerase chain reaction analysis of IL-38 mRNAs (n=5); (D) The concentrations of TNF-α in kidneys (n=5); (E-F) Circulating levels of BUN and Cr (n=5). * $P < 0.05$ compared with 0 h; # $P < 0.05$ compared with 24 h.

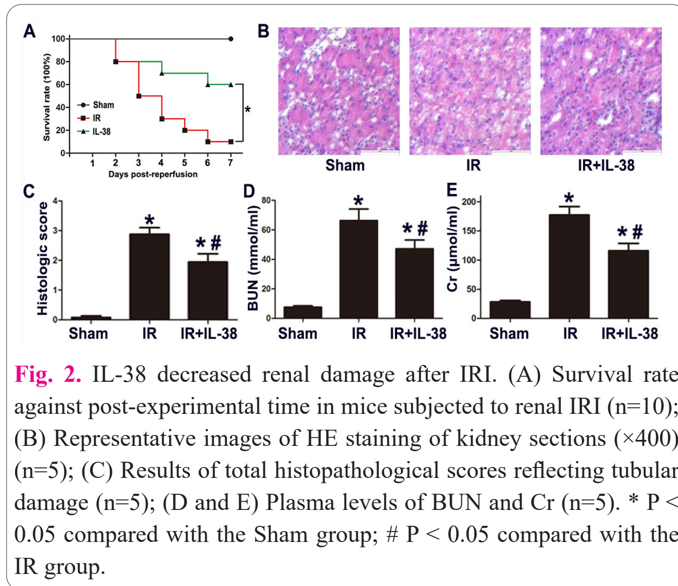

Fig. 2. IL-38 decreased renal damage after IRI. (A) Survival rate against post-experimental time in mice subjected to renal IRI (n=10); (B) Representative images of HE staining of kidney sections (×400) (n=5); (C) Results of total histopathological scores reflecting tubular damage (n=5); (D and E) Plasma levels of BUN and Cr (n=5). * P < 0.05 compared with the Sham group; # P < 0.05 compared with the IR group.

fusion injury (IRI), 90% of the mice had died, meaning 9 out of 10 mice. Importantly, IL-38 markedly improved the survival rate, with 4 out of 10 mice dead (P < 0.05).

The renal morphological change was assessed by H&E staining (Fig. 2B). Histological kidney injury, including necrotic tubules, loss of brush border, vacuolar degeneration and cast formation, were observed after renal IRI. The injury score in the IR group was markedly increased compared with the Sham group (Fig. 2C, P < 0.05). Then, the injury score in the IR+IL-38 group was significantly lowered compared with the IR group (P < 0.05). The concentration of plasma BUN and Cr reflecting the kidney function was measured by commercial kits (Fig. 2D and E). IL-38 reduced the elevation of BUN and Cr levels after renal IRI compared with the IR group (P < 0.05).

3.3. IL-38 decreased renal apoptosis after IRI

Because activation of Caspase-3 plays an important role in apoptotic process, we analyzed their expression in the kidney tissue. As shown in Fig. 3A and B, the active level of Caspase-3 in the IR+IL-38 group was significantly reduced when compared with the IR group (P < 0.05).

To further study the mechanism by which IL-38 attenuated renal cell apoptosis, Bax and Bcl-2 expressions were analyzed by Western blot (Fig. 3A and C-E). The Bax expression in the IR group was significantly increased compared with the Sham group, while the Bcl-2 expression was decreased (P < 0.05). However, IL-38 reduced the Bax expression and enlarged the Bcl-2 expression in the kidney tissue when compared with the IR group (P < 0.05). Importantly, we found that the Bax/Bcl-2 ratio was extremely attenuated in the IR+IL-38 group when compared with the IR group (P < 0.05).

3.4. IL-38 suppressed nuclear factor- κB (NF-κB) activation

After the renal IRI, the nuclear translocation of NF-κB was increased and the level of cytoplasmic IκB-α was decreased as shown in Fig. 4A-C. However, IL-38 significantly suppressed the nuclear translocation of NF-κB and elevated the level of cytoplasmic IκB-α compared with the IR group (P < 0.05).

3.5. IL-38 decreased pro-inflammatory cytokines and MPO activity in the kidney after IRI

As shown in Fig. 5A-F, ELISA and Real-time PCR detection heightened the levels of inflammatory cytokines, including TNF-α and IL-6, and the anti-inflammatory

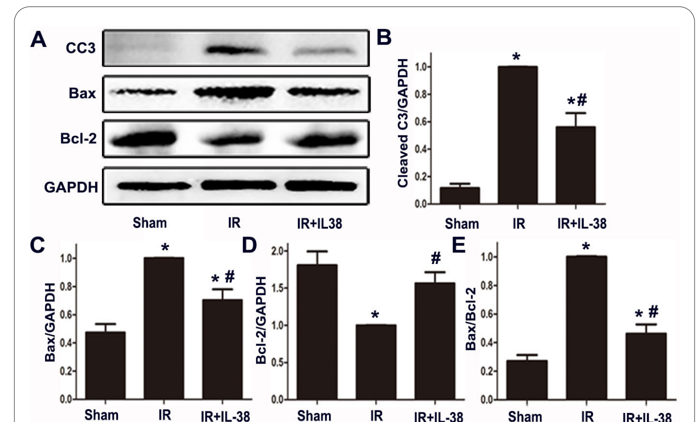

Fig. 3. IL-38 decreased renal apoptosis after IRI. (A) Western blot band of CC3, Bax and Bcl-2 (n=5); (B-E) Bar graphs of CC3, Bax and Bcl-2, Cleaved Caspase3 (CC3) (n=5). * P < 0.05 compared with the Sham group; # P < 0.05 compared with the IR group.

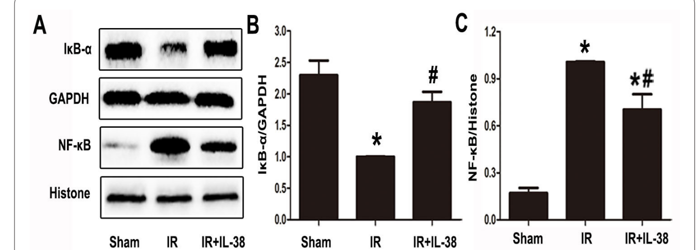

Fig. 4. Effects of IL-38 on NF-κB activation in the kidney after IRI. (A) Western blot band of NF-κB and IκB-α (n=5); (B and C) Bar graphs of NF-κB and IκB-α (n=5). * P < 0.05, compared with the Sham group; # P < 0.05, compared with the IR group.

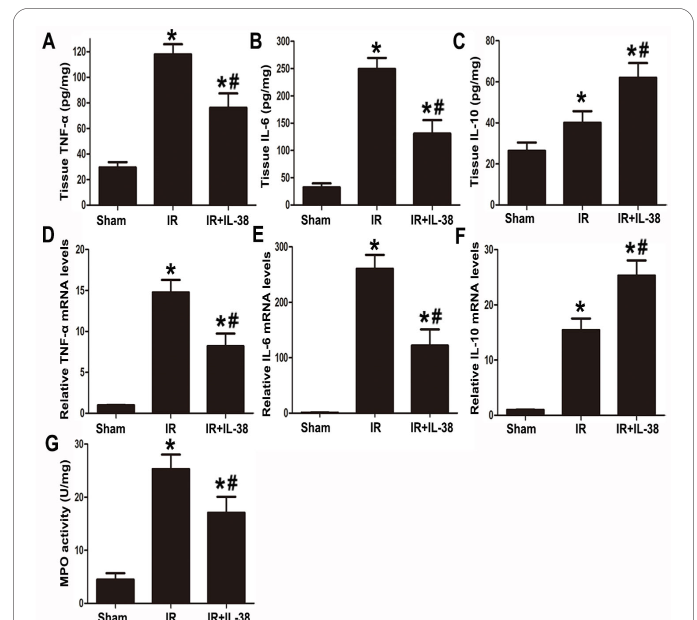

Fig. 5. Effects of IL-38 on pro-inflammatory cytokines in the kidney after IRI. (A-C) ELISA of IL-6, TNF-α and IL-10 production in kidney (n=5); (D-F) Quantitative real-time reverse transcription polymerase chain reaction analysis of IL-6, TNF-α and IL-10 mRNAs (n=5); (G) MPO activity in renal tissues (n=5). * P < 0.05, compared with the Sham group; # P < 0.05, compared with the IR group.

cytokine IL-10 in the IR group compared with the Sham group ($P < 0.05$). IL-38 significantly decreased the levels of TNF-α and IL-6 as well as further increased the level of IL-10 compared with that in the IR group ($P < 0.05$). MPO activity reflecting neutrophil infiltration levels in the kidney was measured by a kit. After renal IRI, MPO activity in the kidney tissue was increased. As shown in Fig. 5G, IL-38 significantly decreased MPO activity compared with that in the IR group ($P < 0.05$).

4. Discussion

Renal IRI is a common cause of AKI and can lead to irreversible kidney damage and high mortality. Therefore, interventions after renal IRI will be beneficial, such as anti-inflammation [12, 13] and anti-oxidation [14] et al. In this study, we showed that IL-38 prevented the deterioration of renal function in the renal IRI model. The renoprotection probably relied on the anti-inflammatory and anti-apoptotic capabilities because IL-38 markedly suppressed neutrophils activation, pro-inflammatory factors generation and the ratio of Bax to Bcl-2. Furthermore, IL-38 inhibited nuclear factor NF-κB activation.

IL-38 also referred to as IL1F10, is a member of the IL-1 family. The human IL1F10 exhibits significant sequence similarity to receptor antagonists of IL-1 and IL-36 [15]. Its structural and sequence features suggest that it may play a role in modulating both adaptive and innate immune responses. It is extensively expressed in a range of tissues, such as the brain, heart, kidney, spleen, placenta, and tonsils. IL-38 shows promise as a clinical biomarker for predicting acute myocardial infarction [16]. It reduces myocardial ischemia-reperfusion injury by suppressing inflammation in macrophages [17]. IL-38 reduces mortality by alleviating inflammatory responses and increasing bacterial clearance in septic mice [18]. It mitigates the inflammatory response in sepsis by reducing macrophage apoptosis and activating the NLRP3 inflammasome [19]. After the occurrence of shock or sepsis, kidney is often the first organ with inflammatory response. However, the expression and role of IL-38 following renal IRI remain unclear. In our study, the expressions of IL-38 mRNA and protein after renal IRI started to increase 6 h, peaked at 24 h and maintained at a high level. It was indicated that IL-38 participated in the early stage of inflammatory response after renal IRI. In the early phase of renal IRI, TNF-α level increases and stimulates the expression of other cytokines and chemokines for further promoting inflammation, which leads to tissue damage [20]. In our study, the change of TNF-α expression after renal IRI was similar to the IL-38 expression. Meanwhile, IRI led to the deterioration of renal function reflected by the plasma BUN and Cr accumulation. It indicated that our model was reliable and reproducible. Our results indicated that the inflammatory response participated in the development of kidney dysfunction after IRI. More importantly, IL-38 could be related to the inflammatory response to renal IRI.

To explore the effect of IL-38 in renal IRI was treated after renal ischemia in mice. Our results showed that IL-38 administration protected against renal IRI: increasing the survival ratio, decreasing the morphological score and ameliorating the renal function. It demonstrated that IL-38 played an important role in the pathogenesis of renal IRI. Therefore, our study indicated that IL-38 inhibition could attenuate kidney damage after IRI.

Many investigators believe that apoptosis significantly contributes to ischemic renal dysfunction [21, 22]. To investigate the effect of IL-38 in renal cell apoptosis, Bax and Bcl-2 protein levels were measured by Western blot. During apoptosis, the Bcl-2 protein family integrates life and death signals [23]. Our results indicated that IL-38 treatment can decrease pro-apoptotic protein Bax and increase anti-apoptotic protein Bcl-2 expression. A previous study indicated that the ratio of Bax to Bcl-2 determines whether apoptosis is induced or inhibited [24]. Therefore, IL-38 treatment can decrease the ratio of Bax to Bcl-2 to attenuate cellular apoptosis after renal IRI, which was confirmed by measuring TUNEL-positive cells and cleaved Caspase-3 protein. Because the intrinsic and extrinsic apoptotic pathways converge at the activation of Caspase-3, we measured renal-cleaved Caspase-3 reflecting its apoptotic degree after IRI. Therefore, our results demonstrated that IL-38 significantly reduced renal apoptotic cells by decreasing Bax and increasing Bcl-2 protein expression after IRI.

The mechanisms by which IL-38 protects against renal IRI remain unclear. The inflammatory cascade is a major component in the pathogenesis of renal IRI, causing kidney tissue damage by releasing several mediators [25]. The previous study indicated that IL-38 mediated the activation of neutrophils and monocytes, and may have a predominant role in inflammatory responses [26]. Therefore, we speculated that the anti-inflammatory effect could play an important role in the renoprotection induced by IL-38. As demonstrated by ELISA and Real-time PCR analysis, IL-38 treatment reduced IRI-induced production of pro-inflammatory cytokines, such as TNF-α and IL-6, and increased the anti-inflammatory cytokine IL-10. The NF-κB family of transcription factors regulates the expression of numerous genes that play a key role in the inflammatory response, including cytokines, adhesion molecules and chemokines, such as TNF-α and IL-6. In our study, IL-38 treatment effectively increased the level of cytoplasmic IκB-α to suppress the nuclear translocation of NF-κB. Neutrophil recruitment and activation can cause tissue damage that contributes to the pathogenesis of renal IRI [27]. MPO activity is considered to be an indicator of neutrophil infiltration. Our results demonstrated that IL-38 treatment could inhibit neutrophil recruitment and activation reflected by the decrease in the MPO activity. Therefore, our results were consistent with the previous hypothesis that IL-38 treatment prevented renal IRI by suppressing the inflammatory response.

There are some limitations in this study. We found that IL-38 treatment can protect against renal IR injury in the early stage, but it is still unknown whether it could induce renoprotective effects in the chronic stage. In addition, further research is needed for a better understanding of the specific mechanism of renoprotection induced by IL-38.

5. Conclusion

In summary, our findings showed that IL-38 mediated anti-inflammatory effects in a model of renal IRI. In our study, IL-38 mitigated kidney injury by inhibiting pro-inflammatory cytokine production and neutrophil infiltration. Taken together, these data suggest that IL-38 may represent a potential new therapeutic approach for the treatment of renal IRI.

Authors' contributions

Conceived and designed the experiments: DL. Performed the experiments: DL, LD. Analyzed the data: LL. Contributed to the discussion and wrote the paper: HS, DL.

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Conflicts of interest

None to declare.

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