High expression of chaperonin-containing TCP1 subunit 3 may induce dismal prognosis in multiple myeloma

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Abstract
The prognosis role of CCT3 in MM and the possible pathways it involved were studied in our research. By analyzing ten independent datasets (including 48 healthy donors, 2220 MM, 73 MGUS, and 6 PCL), CCT3 was found to express higher in MM than healthy donors, and the expression level was gradually increased from MGUS, SMM, MM to PCL (all \( P < 0.01 \)). By analyzing three independent datasets (GSE24080, GSE2658, and GSE4204), we found that CCT3 was a significant indicator of poor prognosis (all \( P < 0.01 \)). KEGG and GSEA analysis showed that CCT3 expression was associated with JAK-STAT3 pathway, Hippo signaling pathway, and WNT signaling pathway. In addition, different expressed genes analysis revealed MYC, which was one of the downstream genes regulated by JAK-STAT3 pathway, was upregulated in MM. This confirms that JAK-STAT3 signaling pathway may promote the progress of disease which was regulated by CCT3 expression. Our study revealed that CCT3 may play a supporting role at the diagnosis of myeloid, and high expression of CCT3 suggested poor prognosis in MM. CCT3 expression may promote the progression of MM mainly by regulating MYC through JAK-STAT3 signaling pathway.

Background
Multiple myeloma (MM) is a malignant plasma cell disease, with clinical manifestations of anemia, bone pain, renal insufficiency and hemorrhage [1]. Some molecular have been conferred to be related with adverse prognosis of MM, such as RB1 and p53 related protein kinase [2, 3], but more biomarkers are still needed at present. The expressions of some molecular biomarkers are closely related to the prognosis of MM, for example, high expression of BCAR3 can predict a good prognosis in MM patients [4], overexpression of UBE2T and JAM-A predict poor prognosis [5, 6], and low serum miR-19a expression was a poor prognostic indicator in MM [7].

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Here we investigated the prognosis effect of \textit{CCT3} expression on MM.

Chaperonin-containing T-complex protein 1 (CCT) is a molecular chaperone protein, which plays a central role in assisting the folding of actin and tubulin to enhance cell migration [8, 9]. Cancer cell migration into surrounding tissues is the first step in cancer metastasis [10]. CCT has eight subunits, namely \textit{CCT1}–\textit{CCT8}, and they are irregular in different types of cancers, such as \textit{CCT8} can promote the migration and invasion of esophageal squamous carcinoma by regulating actin and tubulin, \textit{CCT6A} is a potential prognostic biomarker in glioblastoma [11]. \textit{CCT3} is one of the subunits of CCT and is widely studied in different cancers. Higher level of \textit{CCT3} expression in papillary thyroid carcinoma (PTC), and \textit{CCT3} knockdown can inhibit the proliferation of PTC cells, affect cell cycle progression and promote apoptosis [12]. \textit{CCT3} is overexpressed in gastric cancer, and \textit{CCT3} knockdown can also suppress the proliferation and induce cell apoptosis in gastric cancer [13].

Here we analyzed 2220 MM patients (2380 samples) to find out the prognosis effect of \textit{CCT3} expression on MM and its possible action pathways. All the data were collected from ten independent datasets. In our study, we found that high \textit{CCT3} expression is a dismal prognosis factor in MM patients, and its function intensity was positively correlated with the disease progression. In addition, \textit{CCT3} may mainly influence the JAK-STAT3 signaling pathway to affect the progression of MM.

\section*{Methods}

\subsection*{Patient samples}

In our study, ten independent datasets (including GSE39754 [14–16], GSE5900 [17, 18], GSE2113 [17], GSE6477 [19, 20], GSE16558 [21], GSE82307 [21], GSE38627 [22], GSE24080 [23–25], GSE2658 [17, 25–31] and GSE4204 [18]) were enrolled, and they are derived from Gene Expression Omnibus database (GEO). All the datasets include 48 healthy donors, 2220 MM patients, 73 MGUS and 6 PCL (totally 2380 samples). The expressions of \textit{CCT3} in healthy donors, MGUS patients, smoldering MM (SMM) patients, MM patients, relapsed MM (RMM) patients and PCL patients were analyzed (GSE39754, GSE5900, GSE2113, GSE6477). The differences of \textit{CCT3} expression between different cytogenetic subtypes and normal donors (GSE16558), between new patients and relapsed patients (GSE82307), between patients with beta-2 microglobulin (B2M) ≥ 3.5 mg/L and B2M < 3.5 mg/L (GSE82307), and between patients with lactate dehydrogenase (LDH) ≥ 250 U/L and LDH < 250 U/L (GSE38627) were analyzed. And the survivals between patients with high \textit{CCT3} and low \textit{CCT3} expressions were analyzed using GSE24080, GSE2658 and GSE4204 datasets.

All experiments design, quality control, and data normalization were in line with the standard Affymetrix protocols. All clinical, cytogenetic and molecular information as well as microarray data of these patients were publicly accessible at the Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo). The research was conducted in accordance International Conference on and the Declaration of Helsinki.

\subsection*{Survival analysis}

Overall survival (OS) was defined as the time from the date of diagnosis to death due to any cause. Event-free survival (EFS) defined from date of registration to the occurrence of death from any cause, disease progression or relapse, or censored at the date of last contact. Patients from datasets of GSE24080 (n = 559), GSE2658 (n = 559) and GSE4204 (n = 538) were divided into two groups according to \textit{CCT3} expression, separately. The EFS and OS were analyzed in GSE24080 dataset, and OS was analyzed in GSE2658 and GSE4204 datasets using Kaplan–Meier methods.

\subsection*{Statistical analysis}

Clinical and molecular characteristics of MM patients from the GSE24080 (n = 559) were summarized using descriptive statistics. Data sets were described with median and/or percentage. Age data were compared using Cruskal–Wallis test, categorical data were compared using Chi-square test, and numerical data were compared using Welch Two Sample t-test. Multivariate Cox proportional hazard models were constructed for EFS and OS, using a limited backward elimination procedure.

\subsection*{Pathway analysis}

KEGG pathways were analyzed by cluster-profiler package [32]. Given a ranked list of genes, gene set enrichment analysis (GSEA) determines whether predefined set of \textit{CCT3} is disproportionally overrepresented in the top or the bottom of the list instead of randomly across the list [33, 34].

\subsection*{Different expression genes analysis}

Limma package was used to identify different expression genes (DEGs) [32]. The statistical cutoff values were a fold-change of 1.0 and an adjusted \(P\) value of ≤ 0.05. All analyses were performed using R 3.5.0.
Results

The increased expression of CCT3 was associated with MM progression

We firstly analyzed the different expression of CCT3 in four independent datasets (GSE39754, GSE5900, GSE2113, and GSE6477). We found the expression of CCT3 in MM patients ($n = 170$) was significantly higher than the healthy donors ($n = 6$) (GSE39754, $P = 0.0012$) (Fig. 1a). Overexpression of CCT3 was further validated by GSE5900 dataset samples including 22 healthy donors, 44 MGUS, and 12 SMM patients, with $P < 0.001$, $P = 0.410$, $P = 0.001$, respectively (Fig. 1b). Furthermore, a third database,
including 7 MGUS, 39 MM and 6 PCL, was used for the CCT3 expression analysis (GSE2113). And it showed a significant increased expression of CCT3 in MGUS, MM and PCL gradually (P = 0.003, 0.001, 0.006, respectively) (Fig. 1c). Moreover, the expressions of CCT3 in healthy donor (n = 15), MGUS (n = 22), SMM (n = 24), MM (n = 69) and RMM (n = 28) increased gradually (GSE6477) (Fig. 1d). These results indicated that CCT3 expression level was coincidence with the myeloma progression.

We further investigate whether the expression of CCT3 was related to different types of MM. The expression of CCT3 decreased in turn in patients with t(14;16) (n = 4), t (4;14) (n = 7), RB deletion (n = 14), normal (n = 13) and t (11;14) (n = 11) karyotypes, and most of the patients have higher CCT3 expression than healthy donor except for patients with t(11;14) karyotypes (Fig. 2a). In MM patients, the expression of CCT3 was higher at relapse than at initial diagnosis (GSE82307, n = 166, P = 0.014) (Fig. 2b). In our study, we found that CCT3 expressed higher in patients with B2M ≥ 3.5 mg/L and LDH ≥ 250 U/L compared with those with B2M < 3.5 mg/L and LDH < 250 U/L (GSE38627 dataset, n = 130) (Fig. 2c, d).

**High CCT3 expression was associated with adverse outcomes in MM patients**

In the GSE24080 (n = 559) microarray dataset, CCT3high patients had a significantly shorter EFS and OS (all P < 0.001) than CCT3low patients (Fig. 3a, b). In the GSE2658 (n = 559) and GSE4204 (n = 538) datasets, the CCT3high group had markedly shorter OS compared with the CCT3low group (P < 0.001, P < 0.001 respectively) (Fig. 3c). In the GSE4204 dataset, CCT3high patients had a significantly shorter OS (P < 0.001) than CCT3low patients (Fig. 3d). All these data suggested high expression of CCT3 was a dismal prognosis factor.

**CCT3 expression related clinical and molecular characteristics**

The clinical and molecular characteristics of CCT3high and CCT3low were compared respectively (Table 1). CCT3high group had more abnormal cytogenetic, more high expression of CDK4, IDH2, and TP53 and less high expression of CCND1 and FGFR3. In addition, CCT3high group had higher B2M, CRP, LDH, ASPC, and BMCP, and lower HGB. No significant differences were found in age, gender, race, therapy, CREAT, ALB, MRI, isotype and high expression of LIG4 (Table 1).

Multivariate analysis was used to further assess the prognostic value of CCT3 (Table 2). The result indicated that high CCT3 expression, high B2M and high LDH were independent unfavorable prognostic factors for OS (P = 0.001, 0.039, and P < 0.001, respectively). High CCT3 expression, high LDH, and HGB were independent risk factors for EFS (P = 0.028, 0.004, and 0.038, respectively).

**CCT3 expression related signaling pathways in MM**

We utilized the KEGG and GSEA enrichment analysis to investigate the possible regulation mechanisms of CCT3 expression in the process of MM. KEGG pathway analysis indicated that the CCT3 targeted genes were involved in JAK-STAT3 signaling pathway, WNT signaling pathway and two pathways centralizing in leukemia related terms (namely acute myeloid leukemia and chronic myeloid leukemia) (Fig. 4a). Consistent with the KEGG finding, GSEA of gene sets differentially regulated in CCT3high and CCT3low groups revealed that the leukocyte migration, regulation of leukocyte migration, IL6/JAK/STAT3 signaling and regulation of STAT cascade gene sets were significantly upregulated in CCT3high group. These finding indicated that high expression of CCT3 was related to the leukemia and JAK-STAT3 signaling pathway.

**Associations between genome-wide expression profiles and CCT3 expression**

By analyzing the GSE24080 dataset (n = 559), 18 different expression genes (DEGs) were identified between CCT3high (n = 280) and CCT3low (n = 279), including 8 upregulated genes and 10 downregulated genes that were significantly associated with CCT3 expression (logFCI > 1, P value < 0.05) (Fig. 5a). The upregulated genes included CCT3, MYC, NBL, FABP5, MATR3, NUF2, LAMP5, and MEIS2. The downregulated genes included CCND1, BASP1, PF4, PPBP, MDK, SLC2A10, CD163, VCAM1, SLC46A3, and CTSW.

For further, the different expressed genes were in a protein–protein interaction (PPI) network analysis. CCT3 can directly function with FABP5, CCND1 and MATR3, and CCT3 can regulate MYC through FABP5 (Fig. 5b). The different expression values were validated in the heatmaps of the 18 DEGs in GSE24080 (Fig. 5c).

**Discussion**

In our present study, by performing different gene expression analysis, survival analysis, and other bioinformatics analytical methods using ten independent GEO datasets, we identified high CCT3 was an adverse progression of MM. And CCT3 was significantly over-expressed in MM patients compared with healthy donors in our study (Fig. 1), indicating that it may be a carcinogenic protein.
Previous research has proved that the abnormal expression of \textit{CCT3} can affect the migration of cancer cells and the prognosis of cancer patients. Altered expression of \textit{CCT3} was found in many cancers, such as hepatocellular carcinoma (HCC), gastric cancer, liver cancer and colorectal cancer [8, 9, 35, 36], and overexpression of \textit{CCT3} was not only associated with lymph-node metastasis of gastric cancer [35] but also can indicate a poor prognosis in HCC patients [37, 38]. And in line with the above findings, high expression of \textit{CCT3} was an adverse prognosis factor in our

**Fig. 2** The expression level of \textit{CCT3} was related to different types of MM. \textbf{a} The expression of \textit{CCT3} decreased in turn in patients with t (14;16) \((n = 4)\), t(4;14) \((n = 7)\), RB deletion \((n = 14)\), normal \((n = 13)\) and t(11;14) \((n = 11)\) karyotypes. \textbf{b} The expression of \textit{CCT3} was higher at relapse than at initial diagnosis \((n = 33)\). \textbf{c} The expression of \textit{CCT3} was higher in patients with B2M \(\geq 3.5\) mg/L \((n = 59)\) compared with those with B2M < 3.5 mg/L \((n = 71)\). \textbf{d} The expression of \textit{CCT3} was higher in patients with LDH \(\geq 250\) U/L \((n = 16)\) compared with those with LDH < 250 U/L \((n = 114)\).
The expression level of CCT3 increased gradually with the progress of disease from MGUS, SMM, MM to RMM and PCL (Fig. 1b–d). With the malignancy of the disease, the expression of CCT3 also increased gradually (Fig. 1c). Different karyotypes of MM also predict different prognosis. In our study, MM with adverse abnormality translocations (including t(14;16), t(4;14) and RB deletion) have higher CCT3 expression, and MM with favorable abnormality translocations of t(11;14) have relatively lower CCT3 expression (Fig. 2a). And CCT3 was highly expressed in relapse than in detection of MM patients (Fig. 2b). In addition, serum beta-2 microglobulin (B2M) < 3.5 mg/L and serum LDH ≤ the upper limit of normal are used to define the stage I of MM (Guideline). Furthermore, high CCT3 expression was proved to be a bad survival predictor by analyzing three independent datasets (Fig. 2c, d). These finding indicated that high expression of CCT3 may serve as an indicator in diagnosis and prognosis of MM patients.

Clinical and characters of high and low CCT3 expression groups were analyzed in our study. CCT3high group had higher B2M and LDH. These characters were proved to be strong predictors for MM patients [39, 40]. And in multivariate analysis, CCT3, B2M and LDH were proved to be independent negative prognosis factors for OS in MM patients. This result confirmed the inferior effect of CCT3 on MM for further.

CCT3 affects the progression of HCC by activating signal transducer and activator of transcription (STAT)3/ STAT3 [37, 41]. STAT3 is the major factor in JAK-STAT3 pathway signaling, which plays an important role in many

Fig. 3 High CCT3 expression was associated with adverse outcomes in MM patients. a In GSE24080 (n = 559) dataset, CCT3high patients had a significantly shorter EFS (P < 0.001) than CCT3low patients. b In GSE24080 dataset, CCT3high patients had a significantly shorter OS (P < 0.001) than CCT3low patients. c In GSE2658 (n = 559) dataset, CCT3high patients had a significantly shorter OS (P < 0.001) than CCT3low patients. d In GSE4204 (n = 538) dataset, CCT3high patients had a significantly shorter OS (P < 0.001) than CCT3low patients.
aspects of tumorigenesis [42]. By binding specific enhancers, STAT dimers can regulate the transcription of target genes [43]. The activation of STAT dimers in nucleus can be affected by mitogen-activated protein kinase (MAPK), AKT/mammalian target of rapamycin (mTOR) and JAK [44], and a recent study disclosed that mTORC, which is a multi-protein signaling complex of mTOR, assembly and signaling can be affected by eukaryotic chaperonin CCT [45].

In our study, high CCT3 expression was associated with JAK-STAT3 rather than mTOR pathway by KEGG and GSEA analysis (Fig. 4). And through different expression gene analysis and PPI analysis, we found that MYC was highly expressed in CCT3 high group. c-MYC, as a target gene in cancer, has been proved to be implicated in STATs [46].

Here we studied the possible mechanism pathways of CCT3 in MM. In our study, high CCT3 expression was associated with JAK-STAT3 rather than mTOR pathway by KEGG and GSEA analysis (Fig. 4). And through different expression gene analysis and PPI analysis, we found that MYC was highly expressed in CCT3 high group. c-MYC, as a target gene in cancer, has been proved to be implicated in STATs [46]. And in our study, MYC was upregulated in

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**Table 1** Patients’ characteristics of 559 MM patients according to CCT3 expression levels in GSE24080.

|                | CCT3low, n = 279 | CCT3high, n = 280 | P value |
|----------------|------------------|------------------|---------|
| AGE, mean (range) | 57.41 (24.83–76.50) | 58.57 (29.70–75.94) | 0.160a |
| Gender (%)       |                  |                  |         |
| Female           | 101 (36.2)       | 121 (43.21)      | 0.108b  |
| Male             | 178 (63.8)       | 159 (56.79)      |         |
| Race (%)         |                  |                  |         |
| Other            | 31 (11.11)       | 31 (11.07)       | 1.000b  |
| White            | 248 (88.89)      | 249 (88.93)      |         |
| Cytogenetic abnormality (%) |        |                  |         |
| No              | 209 (74.91)      | 143 (51.07)      | <0.001b |
| Yes             | 70 (25.09)       | 137 (48.93)      |         |
| Therapy (%)      |                  |                  |         |
| TT2             | 166 (59.5)       | 179 (63.93)      | 0.323b  |
| TT3             | 113 (40.5)       | 101 (36.07)      |         |
| B2M (mean (SD)) | 4.098 (4.835)    | 5.363 (5.785)    | 0.005c  |
| CRP (mean (SD)) | 9.364 (15.627)   | 13.888 (28.221)  | 0.019c  |
| CREAT (mean (SD)) | 1.24 (1.131)   | 1.405 (1.391)    | 0.125c  |
| LDH (mean (SD)) | 157.921 (52.804) | 185.982 (74.308) | <0.001c |
| ALB (mean (SD)) | 4.082 (0.554)    | 4.015 (0.608)    | 0.173c  |
| HGB (mean (SD)) | 11.574 (1.725)   | 10.934 (1.842)   | <0.001c |
| ASPC (mean (SD)) | 39.426 (23.353) | 45.913 (23.683)  | 0.001c  |
| BMPC (mean (SD)) | 43.243 (25.552) | 49.475 (25.919)  | 0.004c  |
| MRI (mean (SD)) | 10.431 (14.485)  | 11.637 (13.591)  | 0.310c  |
| ISOTYPE (%)      |                  |                  |         |
| FLC              | 45 (16.13)       | 39 (13.93)       | 0.632b  |
| IgA              | 59 (21.15)       | 74 (26.43)       |         |
| IgG              | 160 (57.35)      | 153 (54.64)      |         |
| High CCND1, no (%) | 166 (59.5)     | 114 (40.71)      | 0.008b  |
| High CDK4, no (%) | 102 (36.56)     | 178 (63.57)      | 0.001b  |
| High LIG4, no (%) | 150 (53.76)     | 130 (46.43)      | 0.730b  |
| High FGFR3, no (%) | 157 (56.27)    | 123 (43.93)      | 0.002b  |
| High IDH2, no (%) | 125 (44.8)      | 155 (55.36)      | 0.028b  |
| High TP53, no (%) | 115 (41.22)     | 165 (58.93)      | 0.001b  |

AGE age at registration (years), Cytogenetic abnormality an indicator of the detection of cytogenetic abnormalities, B2M beta-2 microglobulin, mg/l, CRP C-reactive protein, mg/l, CREAT creatinine, mg/dl, LDH lactate dehydrogenase, U/l, ALB albumin, g/l, HGB hemoglobin, g/dl, ASPC aspirate plasma cells (%), BMPC bone marrow biopsy plasma cells (%), MRI number of magnetic resonance imaging (MRI)-defined focal lesions (skull, spine, pelvis), SD standard deviation, no number of patients

aCruskal–Wallis test
bChi-square test
cWelch Two Sample t-test
MM patients with high CCT3 expression (Fig. 5a) and was connected with CCT3 through FABP5 (Fig. 5b). All these findings indicated that high CCT3 can affect the progression of MM through JAK-STAT3 signaling pathway. In addition, CCT3 expression was also related to the Hippo signaling pathway and WNT signaling pathway (Fig. 4a), which are closely related to carcinogenesis [47–49]. Therefore, CCT3 expression may influence the progress of MM through these three signaling pathways, and mainly by JAK-STAT3 signaling pathway.

In conclusion, increased expression level of CCT3 was more likely to express in dangerous MM patients and can independently predict an adverse prognosis for MM patients. High expression of CCT3 may be a potential candidate biomarker for the molecular diagnosis and prognosis of MM patients. Otherwise, CCT3 expression was associated with Hippo signaling pathway, WNT signaling pathway, and JAK-STAT3 signaling pathway. Over-expression of CCT3 may influence the MM progress mainly through JAK-STAT3 signaling pathway, and CCT3 can be used as a potential therapy target in MM in the future.

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### Table 2 Multivariate analysis for EFS and OS.

| Variables            | EFS          | OS           |
|----------------------|--------------|--------------|
|                      | EFS (95%CI)  | P value      | OS (95%CI)   | P value      |
| CCT3 (High vs. Low)  | 1.49 (1.04–2.13) | 0.028        | 1.87 (1.31–2.67) | 0.001        |
| B2M                  | 1.15 (0.79–1.69) | 0.461        | 1.50 (1.02–2.21) | 0.039        |
| CRP                  | 0.83 (0.59–1.17) | 0.282        | 1.24 (0.90–1.72) | 0.192        |
| LDH                  | 2.11 (1.27–3.50) | 0.004        | 2.46 (1.62–3.73) | <0.001       |
| HGB                  | 0.68 (0.47–0.98) | 0.038        | 0.95 (0.66–1.35) | 0.760        |
| ASPC                 | 0.97 (0.66–1.44) | 0.887        | 1.32 (0.89–1.96) | 0.173        |
| BMPC                 | 1.53 (1.00–2.34) | 0.052        | 1.28 (0.83–1.98) | 0.267        |
| CCND1 (High vs. Low) | 0.77 (0.56–1.08) | 0.126        | 0.93 (0.67–1.28) | 0.645        |
| CDK4 (High vs. Low)  | 1.01 (0.73–1.41) | 0.951        | 1.19 (0.85–1.65) | 0.312        |
| FGFR3 (High vs. Low) | 1.07 (0.78–1.48) | 0.663        | 0.99 (0.72–1.35) | 0.925        |
| MYC (High vs. Low)   | 0.83 (0.59–1.18) | 0.305        | 0.84 (0.59–1.17) | 0.299        |
| TP53 (High vs. Low)  | 1.03 (0.74–1.44) | 0.869        | 0.78 (0.56–1.08) | 0.139        |

EFS event-free survival, OS overall survival, HR hazard ratio, CI confidence interval, B2M Beta-2microglobulin, mg/l, CRP C-reactive protein, mg/l, LDH lactate dehydrogenase, U/l, HGB hemoglobin, g/dl, ASPC aspirate plasma cells (%), BMPC bone marrow biopsy plasma cells (%)

Fig. 4 CCT3 expression related signaling pathways in MM. a KEGG analysis revealed that CCT3 targeted genes were involved in JAK-STAT3 signaling pathway, Thyroid hormone signaling pathway, Hippo signaling pathway, WNT signaling pathway and two pathways centralizing in leukemia related terms (namely acute myeloid leukemia and chronic myeloid leukemia). b GSEA analysis revealed that CCT3 high expression was associated with upregulated pathways of leukocyte migration, regulation of leukocyte migration, IL6/JAK/STAT3 signaling and regulation of STAT cascade.
Fig. 5 Different expression genes (DEGs) between CCT3high and CCT3low group in MM patients. a Volcano plots of DEGs between CCT3high and CCT3low group. From GSE24080 dataset (n = 559), 18 DEGs were identified between CCT3high (n = 280) and CCT3low (n = 279), including 8 upregulated genes (purple dots) and 10 downregulated genes (green dots) that were significantly associated with CCT3 expression (logFC| > 1, P < 0.05). b PPI network of the DEGs. The red points represent upregulated genes and green points represent downregulated genes. c Heatmaps showed that 18 DEGs between CCT3high and CCT3low group of GSE24080.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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