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ORIGINAL RESEARCH

Characteristics of Immunocytes and Cytokines in Patients with Bloodstream Infections Caused by Carbapenem-Resistant *Klebsiella pneumoniae* in China

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Objective: To evaluate the characteristics of immunocytes and cytokines associated with bloodstream infections (BSIs) caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP).

Methods: Patients with BSIs *K. pneumoniae* (BSIs-Kpn) were enrolled in our hospital between 2015 and 2022. Whole blood and serum samples were collected on the first day after diagnosis. Immunocytes and cytokines profiles were assessed using multicolor flow cytometry and multiplex immunoassays, respectively. The test cytokines included interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2, IL-4, IL-6, IL-10, and IL-17A.

Results: A total of 313 patients had BSIs-Kpn, including 145 with CRKP, 43 with extended-spectrum β-lactamases (ESBL) producing Kpn (ESBL-Kpn) and 125 with non-CRKP or non-ESBL-Kpn (susceptible Kpn, S-Kpn). Absolute number of leukomonocyte (CD45+) in CRKP, ESBL-Kpn and S-Kpn were 280.0 (138.0–523.0) cells/μL, 354.5 (150.3–737.3) cells/μL, and 637.0 (245.0–996.5) cells/μL, respectively. Compared with S-Kpn group, the absolute numbers of leukomonocyte (including T lymphocytes, B lymphocytes and natural killer cells) in patients with CRKP were significantly lower than that in patients with S-Kpn ($P < 0.01$). The levels of cytokines IL-2 and IL-17A were significantly higher in patients with S-Kpn than in those patients with CRKP ($P<0.05$). The area under receiver operating curve (AUC) of IL-2, IL-4, and IL-17A for S-Kpn was 0.576, 0.513, and 0.561, respectively, whereas that for the combination of these three cytokines with immunocytes was 0.804.

Conclusion: Patients with BSIs-CRKP had lower leukomonocyte counts. High levels of IL-2 and IL-17A combined with immunocyte subpopulations showed relatively high diagnostic value for BSIs-S-Kpn from BSIs-CRKP.

Keywords: *Klebsiella pneumoniae*, immunocytes, IL-2, IL-4, IL-17A

Introduction

Bloodstream infections (BSIs) caused by *Klebsiella pneumoniae* (BSIs-Kpn), especially carbapenem-resistant Kpn (CRKP), are potentially life threatening to public health.[1–3] BSIs-Kpn are responsible for 7.2% and 8.8% of community- and hospital-onset BSIs.[2] Between 2014 and 2019, the number of BSIs-CRKP in China increased substantially from 7.0% to 19.6%.[3] Previous studies have indicated that BSIs-CRKP are associated with increased morbidity and mortality.[4–6] Recent data reported that the age-standardized mortality rate of BSIs-Kpn was 3.5% of all deaths caused

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by 33 bacterial pathogens in 2019.[7] However, in China, the mortality rate of BSIs-CRKP has increased from 33.3% in 2012 to 42.8% in 2019.[8]

Owing to the lack of appropriate antibiotic options, BSIs-CRKP have become a great challenge for clinicians.[4,5] Fortunately, the development of novel antibiotics has opened new prospects for combating BSI-CRKP. However, resistance to novel β-lactam/β-lactamase inhibitor combinations has been reported.[9] Therefore, it is important to explore the interactions between the host and the CRKP proteins. Most evidence has shown that CRKP can hide its pathogen-associated molecular patterns and induce adaptive costs to regulate immune evasion, resulting in CRKP with long-term survival in the host.[10–12] In addition, cytokines play a key role in the immune response to Kpn.[13] Herein, we conducted integrated immunology and microbiology analyses to investigate the differences in the inflammatory response among CRKP, extended-spectrum β-lactamases (ESBL) producing Kpn (ESBL-Kpn), and non-CRKP or non-ESBL-Kpn (susceptible Kpn, S-Kpn).

Methods

Study Population

This study was an observational analysis. The clinical diagnosis of BSIs-Kpn among adult patients was screened by positive blood culture at The First Affiliated Hospital, Zhejiang University School of Medicine, from 2015 to 2022. The patients with fungal, viral or mixed bacterial co-infection were excluded. The medical records of patients included demographics, and laboratory examination.

Whole blood and serum samples were collected on the first day after diagnosis. Antibiotic susceptibility tests were performed using standard biochemical methods with VITEK® 2 Compact (bioMérieux, France). Carbapenem resistance was defined as resistance to imipenem, meropenem, or ertapenem according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[14]

Analysis of Immunocytes Subpopulations with Flow Cytometry

Peripheral blood samples (7 mL) were drawn from the venous circulation of the BSIs-Kpn. Red blood cells were lysed in whole blood. The absolute counts or percentages of each immunocyte in whole blood were determined using multicolor flow cytometry (TBNK Kit - 6 Color Immunophenotyping Kit, Agilent Technology, United States) with a BD FACS Canto II flow cytometer (BD Biosciences, New Jersey, USA), and the results were analyzed using DIVA software and FlowJo 10.0. Immunocyte subpopulations included mature peripheral T lymphocytes (CD3+), helper T lymphocytes (CD3+CD4+), cytotoxic T lymphocytes (CD3+CD8+), B lymphocytes (CD3-CD19+), and natural killer cells (CD3-CD16+CD56+).

Cytokines Assay

Serum cytokines levels were measured using the Human Th1/Th2 Cytometric Bead Array (CBA) Kit II (Becton Dickinson, CA, USA). Levels of 7 cytokines were measured: interferon-gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-2, IL-4, IL-6, IL-10, and IL-17A. All samples were assayed according to the manufacturer's instructions. The fluorescence intensity of the beads was measured using a BD FACSCanto II flow cytometer (BD Biosciences). Heat maps of cytokines profile were analyzed using TBtools.[15]

Statistical Analysis

The abnormal distribution of continuous variables was expressed as median (interquartile range). Cytokines were log10-transformed for statistical analysis. The chi-square test was used for comparisons between different groups. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of different cytokines alone or in combination with immunocyte subpopulations in terms of area under the ROC curve (AUC). Statistical significance was defined as a two-tailed P-value of < 0.05. SPSS 23.0, for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad version 8 (San Diego, California, USA) were used to analyze the data.

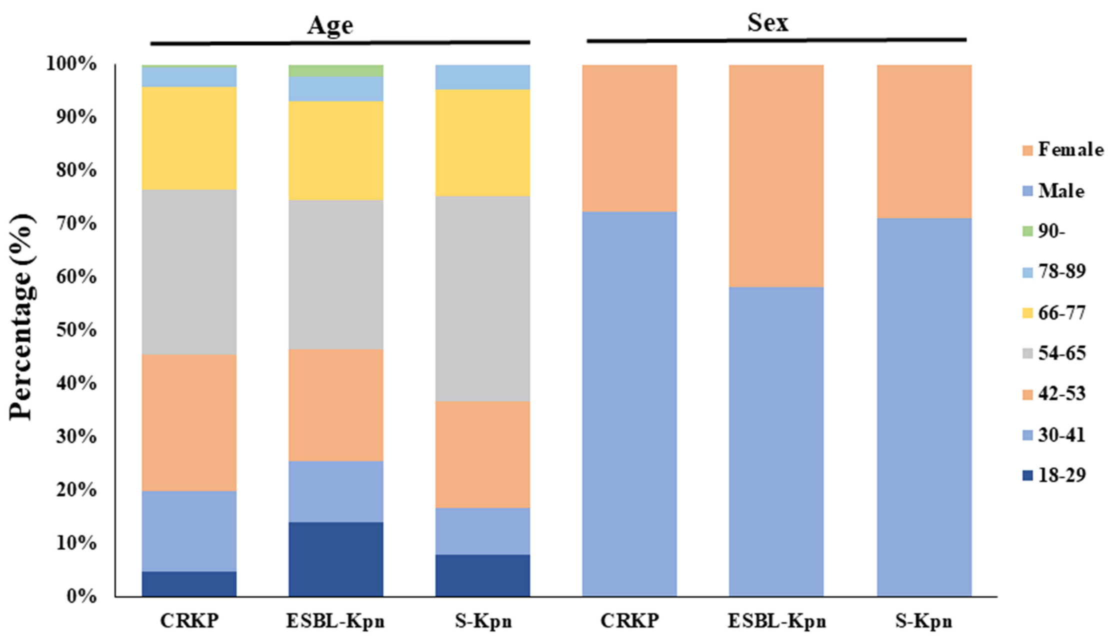

Figure 1 Demographic characteristics of included patients with BSIs-Kpn. CRKP, Carbapenem-resistant *K. pneumoniae*; ESBL-Kpn, extended-spectrum β-lactamases producing *K. pneumoniae*; S-Kpn, non-CRKP or non-ESBL-Kpn.

Results

Study Population

In total, 313 patients with BSIs-Kpn were enrolled in this study. Among these patients, 145 had CRKP, 43 had ESBL-Kpn, and 125 had S-Kpn infections.

A comparison of the demographic characteristics is presented in Figure 1. The BSI-CRKP group consisted of 105 men and 40 women with a mean age of 54±15 years, ranging 18 from 91 years. There were no significant differences in gender, age, tumor incidence rate, white blood cell and hypersensitivity C reactive protein, among CRKP, ESBL-Kpn and S-Kpn groups (P>0.05) (Supplementary Table 1). The level of procalcitonin in patients with CRKP was lower than ESBL-Kpn and S-Kpn (P=0.041).

The most common departments of the included BSIs patients with CRKP, ESBL-Kpn, and S-Kpn were hepatobiliary and pancreatic surgery, nephrology, and infectious disease, respectively (Supplementary Figure 1).

Subpopulations of Immunocyte

Immunocyte subpopulations were detected in 237 patients, including 111 with CRKP, 36 with ESBL-Kpn, and 90 with S-Kpn. Absolute number of leukomonocyte (CD45+) in CRKP, ESBL-Kpn and S-Kpn were 280.0 (138.0–523.0) cells/μL, 354.5 (150.3–737.3) cells/μL, and 637.0 (245.0–996.5) cells/μL, respectively (Table 1). Compared with S-Kpn group, the

Table 1 Absolute Numbers of Immunocyte Subpopulations in Patients with BSIs-Kpn

Subpopulations of Immunocyte (Cells/μL)	CRKP	ESBL-Kpn	S-Kpn	P value
Leukomonocyte (CD45+)	280.0 (138.0–523.0)	354.5 (150.3–737.3)	637.0 (245.0–996.5)	0.000
Mature peripheral T lymphocytes (CD3+)	197.0 (81.0–407.0)	237.0 (73.8–563.8)	398.0 (143.5–758.5)	0.005
Helper T lymphocytes (CD3+CD4+)	98.0 (36.0–237.0)	131.5 (33.5–287.8)	180.0 (72.5–424.0)	0.002
Cytotoxic T lymphocytes (CD3+CD8+)	74.0 (23.0–131.0)	83.5 (33.0–232.2)	138.0 (50.0–250.5)	0.003
Natural killer cells (CD3-CD16+CD56+)	25.0 (8.0–62.0)	35.0 (8.0–53.3)	58.0 (23.0–128.5)	0.000
B lymphocytes (CD3-CD19+)	45.0 (10.0–101.0)	35.5 (16.8–86.0)	86.0 (44.5–150.5)	0.000

Abbreviations: BSIs-Kpn, bloodstream infections caused by *K. pneumoniae*; CRKP, Carbapenem-resistant *K. pneumoniae*; ESBL-Kpn, extended-spectrum β-lactamases producing *K. pneumoniae*; S-Kpn, non-CRKP or non-ESBL-Kpn.

absolute numbers of mature peripheral T lymphocytes (CD3+), helper T lymphocytes (CD3+CD4+), cytotoxic T lymphocytes (CD3+CD8+), B lymphocytes (CD3-CD19+), natural killer cells (CD3-CD16+CD56+) in patients with CRKP were significantly lower ($P < 0.01$) (Figure 2).

Cytokines Profile Among the Patient Groups

The concentrations of IFN-γ, TNF-α, IL-2, IL-4, IL-6, IL-10, and IL-17A were assayed in the 145 patients (Figure 3). The levels of cytokines IL-2 and IL-17A were significantly higher in patients with S-Kpn than in those with CRKP ($P<0.05$) (Table 2). Although no significant difference was found among the three groups regarding the level of IL-6 ($P=0.891$), the IL-6 level of 113.25 (23.84–419.10) pg/mL in patients with CRKP was higher than that of 57.04 (31.40–297.09) pg/mL in patients with S-Kpn. There was no statistical difference in IL-4 among CRKP, ESBL-Kpn and S-Kpn groups ($P=0.121$), while the level of IL-4 in S-Kpn group was higher than that in CRKP group ($P=0.048$). The AUCs of IL-2, IL-4, and IL-17A for S-Kpn were 0.576 (95% CI:0.430–0.721), 0.513 (95% CI:0.368–0.658), and 0.561 (95% CI:0.416–0.705), whereas the AUC for the combination of these three cytokines with immunocytes was 0.804 (95% CI:0.686–0.921) (Supplementary Figure 2).

Discussion

The mortality rate of BSIs-CRKP is as high as 42.8%.[8] In the past few decades, novel antibiotics have been used to treat CRKP.[16] However, resistance to novel antibiotics has been reported in CRKP.[9,17] Several studies have indicated that inflammation plays an important role in the clearance.[10–12,18] To date, the correlation between immunocyte subpopulations, cytokines, and CRKP, especially for BSIs, remains unknown. In this study, we examined the levels of five immunocyte subpopulations and seven cytokines in patients with BSI-Kpn. The levels of IL-2 and IL-17A were higher in patients with S-Kpn than in those with CRKP. Additionally, levels of immunocyte subpopulations in patients with CRKP were lower than those in patients with CRKP.

Available research has demonstrated that Kpn can frustrate normal immune responses and capitalize on immunocompromised states, resulting in high mortality.[19] Our data indicated that the absolute numbers of immunocyte subpopulations in patients with CRKP were significantly lower than those in patients with S-Kpn. There are two

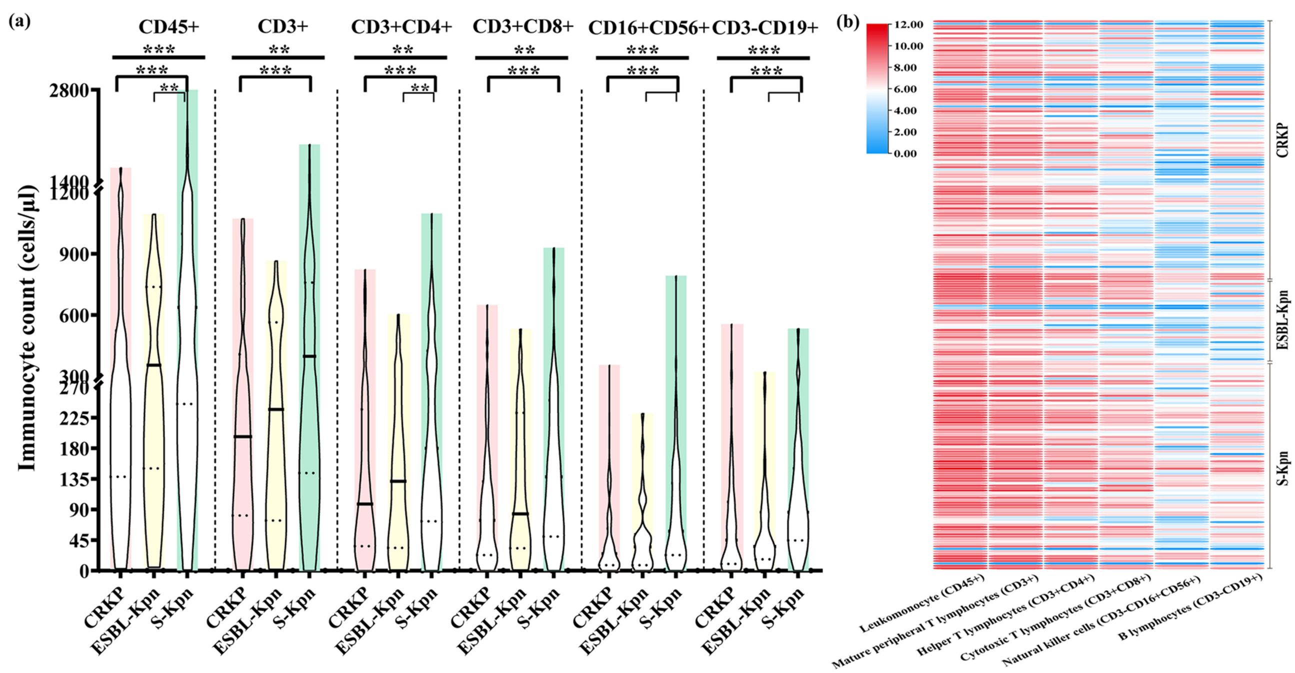

Figure 2 Immunocyte subpopulations in patients with BSIs-Kpn. (**a**) The absolute numbers of immunocyte subpopulations. (**b**) Heat map of immunocyte for each patient. Solid line represents median, dotted lines represent quartiles. P scales of<0.001 (***), <0.05 (**).

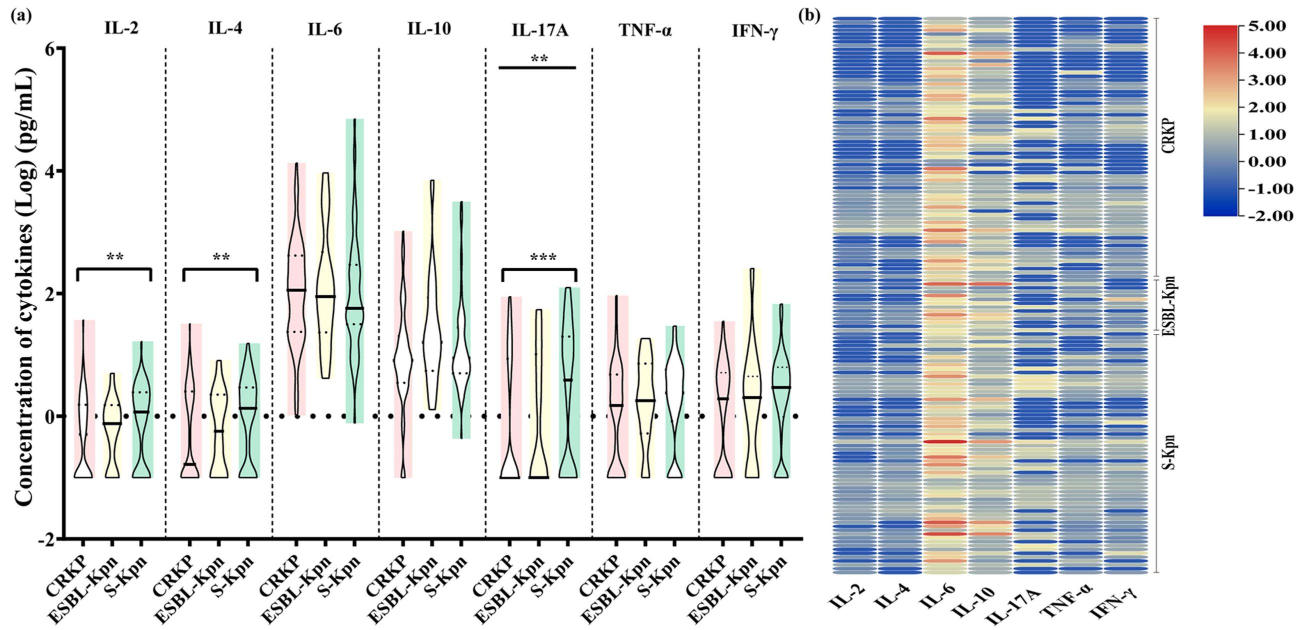

Figure 3 Cytokines concentrations in patients with BSIs-Kpn. (**a**) The concentration of IL-2, IL-4, IL-6, IL-10, IL-17A, IFN-γ, and TNF-α. (**b**) Heat map of cytokines concentrations for each patient. Solid line represents median, dotted lines represent quartiles. P scales of<0.01 (***), <0.05 (**).

potential reasons for this observation. First, CRKP, isolated from BSIs, can establish protected reservoirs in the host to prevent eradication.[19,20] A second possible reason is variations in host immunological defenses against BSIs-Kpn. A recent study showed that decreased complement pathway function is associated with lower survival, more BSIs, and impaired in vitro serum killing of CRKP during critical illness.[21,22] Although Kpn possesses several adaptations to evade immunocytes killing, the degree of success of immune evasion differs among CRKP, ESBL-Kpn, and S-Kpn. However, the specific mechanisms involved in this remain unclear. Large-scale clinical studies are needed to explore common and unique strategies for immune evasion among diverse isolates of CRKP, ESBL-Kpn, and S-Kpn to develop novel therapeutic options against BSIs-Kpn.

Cytokines play key roles in both the innate and adaptive immune responses.[23] In this study, BSIs-CRKP showed higher IL-6 levels than S-Kpn, although no statistical differences were found. Notably, IL-2, IL-17A and procalcitonin were significantly higher in BSIs patients with S-Kpn than in those with CRKP. Additionally, the AUC for the combination of these three cytokines with immunocytes increased. Consistent with our results, previous studies have shown that S-Kpn infection leads to increased IL-17 levels.[24,25] In animal models with Kpn infections, Th17 or IL-17A deficiency could decrease in neutrophil recruitment and result in increased systemic disseminated infection and death.[26–28] Therefore, Th17 and IL-17A may have a role in augmenting host defense against S-Kpn.[24,28–30] However, research on the differences

Table 2 Cytokines Profile of Patients with BSIs-Kpn

Cytokines (pg/mL)	CRKP	ESBL-Kpn	S-Kpn	P value
IL-2	0.51 (0.10–1.56)	0.76 (0.10–1.54)	1.17 (0.10–2.44)	0.075
IL-4	0.17 (0.10–2.53)	0.63 (0.10–2.26)	1.36 (0.10–2.98)	0.121
IL-6	113.25 (23.84–419.10)	90.61 (25.35–817.70)	57.04 (31.40–297.09)	0.891
IL-10	8.02 (3.47–18.65)	16.34 (5.64–90.13)	9.01 (4.97–27.87)	0.230
TNF-α	1.50 (0.10–4.83)	1.78 (0.53–7.25)	2.42 (0.83–5.73)	0.140
IFN-γ	1.94 (0.1–5.18)	2.06 (0.10–4.71)	2.97 (0.97–6.32)	0.224
IL-17A	0.10 (0.10–8.69)	0.10 (0.10–10.33)	3.90 (0.10–20.08)	0.026

Abbreviations: BSIs-Kpn, bloodstream infections caused by *K. pneumoniae*; CRKP, Carbapenem-resistant *K. pneumoniae*; ESBL-Kpn, extended-spectrum β-lactamases producing *K. pneumoniae*; S-Kpn, non-CRKP or non-ESBL-Kpn.

between CRKP- and S-Kpn-induced IL-17 production is limited. Therefore, dynamic studies of immunocytes and cytokines profiles would be valuable for understanding the interaction between BSIs-Kpn and immune responses.

This study had several limitations. First, the immunocytes and cytokines profiles of the inflammatory response induced by BSIs-CRKP are not dynamic. In addition, there are difficulties in recruiting patients due to bacterial identification and antimicrobial susceptibility testing with certain hysteresis. Therefore, the sample size of this study was limited. However, the results of the present study contribute to the understanding of inflammatory markers in BSIs-Kpn, particularly CRKP.

Conclusions

In conclusion, patients with BSIs-CRKP have low immunity. High expression levels of IL-2 and IL-17A, combined with immunocyte subpopulations, could be used as biomarkers for the diagnosis of BSIs-S-Kpn.

Ethical Approval

The work was in accordance with the Declaration of Helsinki. This study was approved by the recommendations of the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine with written informed consent from all subjects (Reference Number: 2022337).

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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