ORIGINAL RESEARCH

Clinical Predictors of Bacteremia Outcome After Initial Empirical Antimicrobial Therapy in Patients with Hematological Malignancies: A Retrospective Analysis

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Objective: We performed a retrospective analysis to investigate the clinical predictors of bacteremia outcome involving *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae (K. pneumoniae)* after initial empirical antimicrobial therapy among hematological malignancy cases.

Methods: This retrospective study was conducted between April 2018 and April 2023. All bloodstream infections (BSIs) caused by *E. coli* and *K. pneumoniae* in hospitalized hematological malignancy (HM) patients were identified. Data on patient demographics, clinical characteristics, empirical antimicrobial treatment, outcomes and the antimicrobial susceptibility were collected from medical records. Multivariate analyses were utilized to assess the risk factors for all-cause mortality within 28 days and carbapenem resistance. Optimal cutoffs for continuous predictive variables were evaluated by receiver operating characteristic (ROC) curve analysis.

Results: Among 61 individuals diagnosed with bacteremia, 39 cases were caused by *E. coli* bacteremia, while the remaining 22 were identified as *K. pneumoniae* bacteremia. Out of these, there were 10 cases of carbapenem-resistant Enterobacteriaceae (CRE) and 12 cases resulted in all-cause mortality within 28 days. Analysis indicated that Pitt score was an independent risk factor for mortality and a cut-off of 2.5 was a reliable predictor with 83.3% sensitivity and 85.7% specificity, respectively. Impaired mental status and elevated body temperature exceeding 38.6°C as well as a procalcitonin (PCT) level over 8.24 ng/mL on the third day (d3) after antimicrobial treatment were identified as independent risk factors for predicting carbapenem resistance.

Conclusion: We found that Pitt score with a cut-off of 2.5 was a reliable predictor for mortality within 28 days in HM bacteremia cases. Impaired mental status and elevated temperature exceeding 38.6°C as well as a procalcitonin (PCT) level over 8.24 ng/mL on d3 after antimicrobial treatment were identified as predictive risk factors to carbapenem resistance.

Keywords: antimicrobial resistance, mortality, risk factors, initial clinical response

Introduction

Individuals diagnosed with hematological malignancies who have received numerous rounds of chemotherapy are highly susceptible to the development of bloodstream infections (BSIs). Gram-negative bacilli are the primary etiological agents responsible for bloodstream infections (BSIs) in immunocompromised hosts.[1] Carbapenem-resistant Enterobacteriaceae (CRE) bacteremia poses a significant mortality risk and is emerging as a critical concern for individuals with hematological malignancies who are undergoing aggressive chemotherapy regimens or stem cell transplantation (SCT).[2] However, the identification of the specific pathogen in patients with febrile neutropenia often poses challenges. In order to improve sensitivity, it is essential to conduct repeated blood cultures, despite the potential drawbacks of time consumption and relatively low positive culture rates (<20%).[3] Moreover, drug susceptibility reports typically require a few days for completion.

Currently, there is limited research on predicting the bacteremia outcome and speculating antimicrobial resistance based on the initial clinical response indicators. Therefore, a retrospective study was conducted to investigate the predictors for carbapenem resistance as well as overall prognosis in cases of bacteremia involving *E. coli* or *K. pneumoniae* among patients with HMs.

Materials and Methods

Study Setting and Patient Population

This is a single-center, retrospective, and observational study conducted in hematology department of Peking University Third Hospital, Beijing, China. Adults who were hospitalized with monomicrobial *E. coli* or *K. pneumoniae* bacteremia between April 2018 and April 2023 were included. Clinical and demographic data were collected from electronic medical records including the malignancy diagnosis, disease status, comorbidities, exposure of previous chemotherapy, empirical antibiotics administered, vital sign trends, laboratory data, the duration of neutropenia, presentation with septic shock, mental status alteration, mechanical ventilation, microbiological data and all-cause 28-day mortality. Only the first isolate was included during a single clinical episode occurring within 4 weeks, and duplicates from the same patient were excluded.

Definition

Bacteremia was defined as the isolation of organisms from at least one bottle of blood culture specimen from patients with compatible clinical signs or symptoms. BSI onset was defined as the collection date of the first positive blood culture. Carbapenem resistance was defined as resistance to one or more of meropenem (MEM), imipenem (IPM), and ertapenem. Neutropenia and severe neutropenia were defined as an absolute neutrophil count (ANC) of < 500 cells/mm^3 and <100 cells/mm^{3,} respectively. The Pitt bacteremia score (PBS) including values of temperature, blood pressure, mental status, and the presence or absence of mechanical ventilation and cardiac arrest[4] was calculated within 48h from the day of BSI onset, and the highest score was recorded. The diagnosis of septic shock followed the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) clinical criteria.[5]

Identification and Drug Susceptibility Testing

For bacterial identification, the VITEK2 Compact automatic microbial analysis system manufactured by Mérieux, France, and the BD-Bruker MALDI Biotyper microbial spectrometry rapid identification system by Bruker, Germany, were utilized. For the assessment of antimicrobial susceptibility, the VITEK2 Compact, a completely automated microbiological analyzer, was utilized to ascertain the minimum inhibitory concentration (MIC) of commonly used antimicrobial drugs, via an automated methodology. Drug susceptibility is assessed based on the guidelines provided by the American Clinical Laboratory Standardization Institute (CLSI) and categorized as sensitive (S), intermediate drug resistance (I), and drug resistance (R).[6] Another method used for drug sensitivity assessment is Kerby-Bauer disk diffusion and AGAR dilution method for confirmation of results or when dealing with atypical bacterial strains, in accordance with the protocols established by the CLSI.

Statistical Analysis

The software SPSS, version 27.0, was adapted for statistical analysis. Continuous variables with normal distributions are presented as means $\pm$ the standard deviation (SD), and those with non-normal distributions are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and proportions. Statistical significance was calculated using the chi-square (χ^2) test for categorical variables, independent sample *t*-test or Mann–Whitney *U*-test was used for continuous variables. To identify risk factors for CRE or mortality, all significant variables with $p < 0.1$ along with other variables of clinical importance, were included in a multivariate logistic regression model. Odds ratios (ORs) and their 95% confidential intervals (CIs) were calculated. All p values were two tailed, and $p < 0.05$ was considered statistically significant. A further ROC analysis was carried out to search for a possible cut-off value, and the corresponding ROC curve was traced with related area under curve (AUC) values. For these cut-off values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

Demographic and Clinical Characteristics

During the study period over consecutive 5 years, a total of 145 strains of *E. coli* (n=77) and *K. pneumoniae* (n=68) were identified from blood cultures. Out of these, only the first isolates during a single clinical episode of 61 cases were included (Supplement Figure 1). The clinical characteristics of these cases are summarized in Table 1. Among them, 39 cases were attributed to *Escherichia coli* bacteremia and the remaining 22 cases to *Klebsiella pneumoniae* bacteremia. The median age of the patient population was 54.0 (31.5–63.5) years, with 65.6% being male. Among these patients, 39 were diagnosed with aggressive lymphoma, accounting for the majority (63.9%) of HM cases. The median number of

Table 1 Clinical Characteristics of Cases with Escherichia Coli or Klebsiella Pneumoniae Bacteremia

General and Clinical Characteristics	N=61
Age years, median (range)	54 (31.5,63.5)
Gender male/female	40 (65.6)
Klebsiella pneumoniae bacteremia	22 (36.1)
Escherichia coli bacteremia	39 (63.9)
Underlying hematological disorders	
Acute leukemia	16
Chronic myelomonocytic leukemia (CMML)	1
Multiple myeloma/plasma cell leukemia	5
Aggressive lymphoma	39
No. of previous chemotherapy lines	5 (2–8)
Evaluation of the effectiveness of previous chemotherapy	
Untreated	8
Relapse/refractory	22
Partial remission	5
Complete remission	22
Stable disease	2
Not evaluated	2
Comorbidities	
Coronary heart disease	3
Diabetes mellitus	5
Arrhythmia	3
Peptic ulcer	2
Interstitial lung disease	4
Invasive pulmonary fungal disease	5
Autogenetic peripheral blood stem cell transplantation	12 (19.7)
Allogeneic hematopoietic stem cell transplantation	6 (9.8%)
Systemic corticosteroids	22 (36.1)
Central venous catheter insertion	18 (29.5)
Peripheral catheter insertion	39 (63.9)
GI tract or perianal infection	26 (42.6)
Fever °C degree, median (range) when BSI onset	39.5 (37–42)
ANC < 500 (cells/mm3) when BSI onset	49 (80.3)
ANC < 100 (cells/mm3) when BSI onset	47 (77.0)
Days of ANC < 500 (cells/mm3)	9 (5–13)
Initial empirical application of carbapenems	59 (96.7)
CRE	10 (16.4)
Septic shock	14 (23.0)
Mechanical ventilation	4 (6.5)
Overall 28-day mortality	12 (19.7)

Abbreviation: GI, gastrointestinal.

previous chemotherapy lines was 5, with 22 (36.1%) cases being relapse and refractory. At the onset of BSIs, 18 (29.5%) patients were undergoing hematopoietic stem cell transplantation (HSCT), including 12 cases of autologous SCT and 6 cases of allogeneic SCT. At the BSI onset, 49 (80.3%) cases presented with neutropenia, and 47 (77.0%) had severe neutropenia. Of all the patients, 14 (23.0%) experienced septic shock, and 4 (6.6%) required mechanical ventilation. Carbapenems were administered as the principal empirical antimicrobial treatment in almost all cases (n=59, 96.7%). There were 10 (16.4%) cases of carbapenem-resistant Enterobacteriaceae (CRE) and 12 (19.7%) cases of all-cause mortality within 28 days.

Risk Factors for 28-Day Mortality

We analyzed clinical data of *E. coli* or *K. pneumoniae* BSI in HM patients (Table 2). Variables with P < 0.1 were included in the multivariable logistic regression analysis. The results showed that Pitt score (OR 2.605 95% CI 1.602–4.235, p<0.001) was an independent risk factors for 28-day mortality. ROC curve analysis indicated that a PBS cut-off of 2.5 was a good predictor for mortality, with an AUC of 0.889 (95% CI 0.752–1.000), sensitivity of 83.3%, and specificity of 85.7% (Figure 1). Notably, the mortality rate among those with CRE was found to be significantly higher compared to non-CRE cases.

Comparison of Clinical Characteristics of Early Response Between Carbapenem Susceptible and Resistant Groups and Risk Factor for Carbapenem Resistance

Comparison of clinical characteristics of initial response between cases with and without CRE infections was presented in Table 3. Various factors such as higher maximum temperature on the third day (d3) after antimicrobial treatment, disturbance of consciousness, septic shock within 72 hours following onset of BSI, need for mechanical ventilation, higher Pitt score, and higher PCT level on d3 were more frequently observed in patients with CRE and showed statistically significant differences. Variables with a significance level of P<0.1 were chosen for the multivariate logistic regression model for antimicrobial resistance. The multivariate analysis revealed that impaired mental status (OR, 6.117; 95% CI, 3.149–16.630; P = 0.003) and elevated temperature on the third day after antimicrobial treatment (OR, 3.325; 95% CI, 1.084–9.592; P =0.035) were independent risk factors for CRE infections.

In addition, we determined a potential threshold value for PCT and peak temperature on day 3 as a predictor of CRE after performing an ROC analysis. The optimal threshold for PCT on day 3 was found to be 8.24ng/mL, with an AUC of

Table 2 Analysis of 28-Day Mortality in *E. Coli* or *K. Pneumoniae* BSI Cases

|	Non-survivors (n=12)	Survivors (n=49)	χ2/Z value	P values	Multivariate Regression	
					OR (95% CI)	P value
Age, years	60.5 (52–66)	45.0 (30–62)	−1.706	0.088		
Male	8/12	33/49	0.002	1.000		
K. pneumoniae	5	17	0.203	0.652		
Escherichia coli	7	32				
Underlying hematological disorders						
Leukemia	4	14	1.857	0.349		
lymphoma	6	33				
MM/plasma cell leukemia	2	3				
No. of previous chemotherapy lines	5 (5–9)	8 (3–8)	−0.055	0.956		
Relapse/refractory	6/12	16/49	1.258	0.432		
ANC < 500 (cells/mm3)	7	42	4.573	0.047		
ANC < 100 (cells/mm3)	6	41	6.181	0.022		
Days of ANC < 500 (cells/mm3)	6 (0.75–13.25)	10 (6–14)	−1.165	0.244		
CRE	6	4	12.31	0.002		
Pitt score	5.0 (3.25–6.0)	1.0 (0.0–1.5)	−4.31	<0.001	2.605 (1.602–4.235)	<0.001

ROC curve of Pitt score
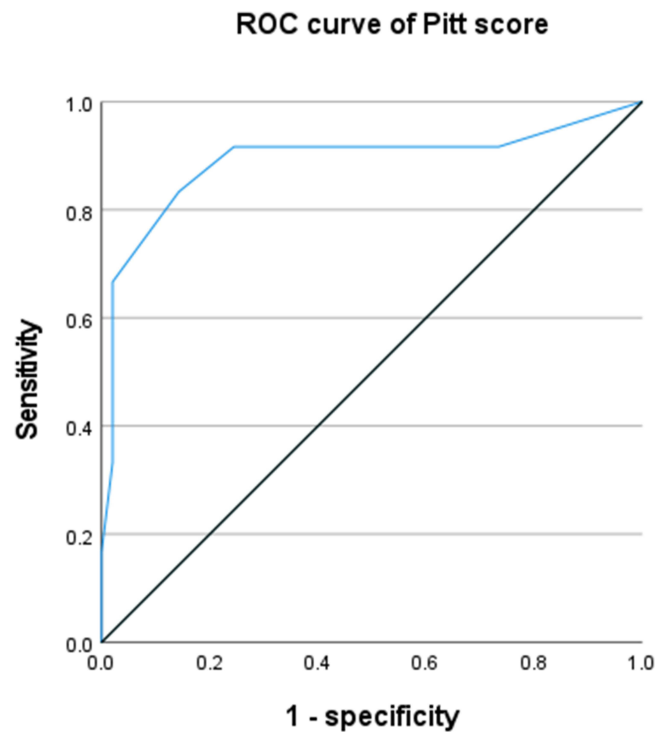
Figure I Receiver operating characteristic (ROC) curve of Pitt bacteremia score (PBS).

0.861. The positive predictive value (PPV) and negative predictive value (NPV) were 85.3% and 81.1%, respectively, with a sensitivity of 80.0% and specificity of 86.3%. For the peak temperature on day 3, the optimal threshold was 38.6 °C, with a PPV of 91.1% and NPV of 82.2%, along with a sensitivity of 80.0% and specificity of 92.2%. The AUC was determined to be 0.878 (Figure 2).

Table 3 Clinical Characteristics of Early Response and Risk Factors for CRE

	Resistant Group (n=10)	Susceptible Group (n=51)	χ2/Z value	P value	Multivariate Regression	
					OR	P value
Age, years	61.5 (47–66)	51.0 (31–62)	−1.277	0.202		
Male	7	33	0.104	1.000		
K. pneumoniae	7	15	5.973	0.027		
Escherichia coli	3	36				
GI or perianal infection	4	22	0.034	1.000		
HSCT	2	16	0.52	0.732		
K. pneumoniae in HSCT	2	1	1.94	0.467		
Escherichia coli in HSCT	0	15	2.03	0.419		
Peak temperature on d3	39.0 (38.3–39.6)	37 (36.6–37.8)	−3.769	<0.001	3.325 (1.084–9.592)	0.035
Impaired mental status	8	3	31.07	<0.001	6.117 (3.149–16.630)	0.003
Septic shock within 72h of onset of BSI	7	7	14.97	<0.001		
Mechanical ventilation	4	0	21.83	<0.001		
Pitt score	5 (2.8–6.0)	1 (0.0–2.0)	−3.645	<0.001		
PCT on d3	23.29 (6.72–32.58)	0.75 (0.23–2.68)	71.0	<0.001		
Time to first positive by sterility blood culture (hours)	9.1 (5.7–12.1)	8.8 (7.3–10.6)	−0.214	0.830		
Time to get susceptibility reports (days)	3.0 (3.0–5.0)	3.0 (2.0–4.0)	−0.475	0.635		

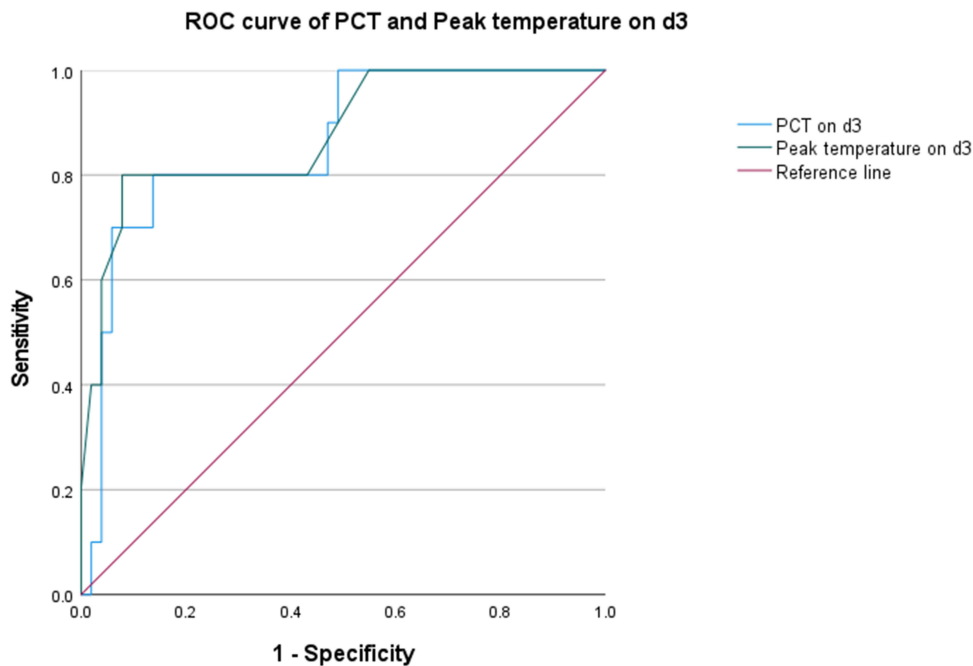ROC curve of PCT and Peak temperature on d3

Figure 2 ROC curve of maximum temperature and PCT level on d3 after empirical antimicrobial therapy.

Discussion

Due to immunodeficiency, mucosal barrier destruction, and neutropenia caused by cytotoxic chemotherapy, patients with HMs are at a higher risk for BSIs. It is estimated that 11–38% of HM patients develop BSIs while undergoing chemotherapy,[7–9] resulting in a mortality rate of 12–42%.[10,11] Previous studies have shown that Gram-negative bacteria (GN-bacteria) are the main pathogens for BSIs in HM patients.[12] The most frequently isolated Gram-negative bacteria were *Escherichia coli* (24.2%) followed by *Klebsiella spp.* (16.3%)[13] which were the primary focus of our investigation.

In clinical practice, hematologists usually employ de-escalation therapy in the early stages of BSIs, and carbapenems are frequently administered as initial empirical therapy for febrile neutropenia due to their broad antibacterial spectrum and high efficacy.[14] However, as medication usage increases, drug resistance becomes more prevalent. According to the China Antimicrobial Resistance Surveillance System (CARSS) statistics, the resistance rates of *K. pneumoniae* to IPM and MEM increased from 3.0% and 2.9% in 2005 to 25.0% and 26.3% in 2018.[15] The mortality rate of CRE BSIs in immunocompromised hosts is remarkably high, ranging from 45%-100% in HM patients,[2] with the majority of patients dying within 14 days. Patients with HMs along with HSCT recipients, are more prone to CRE infections due to extended hospital stays, compromised immunity, and intensive chemotherapy.[16] Preemptive identification of CRE infection has shown to be one of the most important factors in improving clinical outcome.[2,17]

Existing literature suggests that individuals who are rectal carriers of CRE, particularly cases with antecedent chemotherapy or radiotherapy and those suffering from recurrent GI tract mucositis or perianal infections are at an elevated risk for the development of CRE infections.[18,19] The recurrent use of broad-spectrum antibiotics could potentially alter the intestinal flora and promote the growth of carbapenem-resistant organisms in the intestinal microbiota.[20] Disruption of the normal intestinal barrier and translocation through the gastrointestinal tract could lead to endogenous bacteremia. In our study, we noted that 26 (42.6%) patients suffered from gastrointestinal or perianal infections. However, there was no significant difference between the carbapenem resistant and susceptible groups. The absence of significant finding may be attributed to the limited sample size of our analysis.

Blood cultures are considered as the gold standard for diagnosing infections but they often take 3–5 days and have a low positive rate, limiting their use for early diagnosis.[3] Typical symptoms of infection include fever, chills, and hypotension. According to our study, the effectiveness of initial antimicrobial therapy could be evaluated within 3 days based on the patient's early clinical response indicators. Resolution of fever and other infectious signs, along with

improved general condition, indicate appropriate antimicrobial therapy. However, persistent high fever, deteriorating general condition, early onset of septic shock, impaired consciousness, and alterations in PCT levels could serve as early indicators of antimicrobial resistance.

PCT serves as a stable indicator of infections which remains unaffected by neutropenia, immune deficiency, and glucocorticoid application.[21] In healthy individuals, its expression is minimal (< 0.05 μg/L), or even undetectable.[22] However, during infection, PCT can be swiftly produced and released into the bloodstream due to inflammatory factors or bacterial toxins. Serum PCT level demonstrates good sensitivity and specificity for early sepsis diagnosis.[23] In our study, a maximum temperature beyond 38.6°C on the d3 post anti-infection treatment, along with a PCT level exceeding 8.24 ng/mL, indicated a high probability of CRE infection. The current literature lacks sufficient similar studies on early clinical response indicators within 72 hours. Our research offers hematologists new insights into early warning signals after empirical antimicrobial treatment.

If the clinical response is suboptimal, early identification of high-risk patients for CRE infections and prompt transition to novel antimicrobial agents such as Ceftazidime-Avibactam (CAZ/AVI) may contribute to reducing mortality rates.[17,24] Specifically, CAZ/AVI demonstrated significant efficacy in the treatment of carbapenem-resistant *Klebsiella pneumoniae*, achieving an 85% success rate for clinical outcomes within 30 days according to literature.[25] However, data from the China Antimicrobial Surveillance Network (www.chinets.com) indicated that in 2023, among 16,125 strains of carbapenem-resistant *K. pneumoniae*, there was still an observed resistance rate of 11% to CAZ/AVI. Alternative antimicrobial options for CRE infections such as colistin, tigecycline, and meropenem/vaborbactam could be considered.[26]

Regarding prognostic indicators for therapeutic results, Pitt score serves as a widely used acute illness severity index in infectious disease research, with a score ≥ 4 commonly utilized to indicate severe illness and high mortality risk.[27] Past literature has highlighted higher Pitt scores as an independent risk factor for mortality in CRE BSIs.[2,28] This study similarly found an independent association between a higher Pitt score and mortality, consistent with previous findings. The study identified a Pitt score cut-off of 2.5 as a reliable predictor of mortality. Additionally, over 36% of patients in this study were in a relapsed or refractory state, indicative of the complexity and severity of underlying hematological disorders, which is speculated to be one of reasons contributing to the relatively high mortality rate.

This study is subject to various limitations. First, its retrospective nature and the relatively small sample size from a single center may lead to results that differ from those in other regions due to sample size, accuracy of medical records, data integrity, and selection bias. Combining data from multiple centers or conducting prospective studies will address the aforementioned limitations, which will be the focus of our next work.

Conclusion

The study's analysis revealed that the Pitt score with a cut-off of 2.5 independently correlated with the risk of mortality within 28 days. Impaired mental status and elevated body temperature beyond 38.6°C, along with a procalcitonin (PCT) level over 8.24 ng/mL on the third day after antibiotic treatment were established as independent risk factors for carbapenem resistance.

Ethics Declarations

This retrospective study was carried out using the opt-out method for the case series in our hospital. The study was approved by Peking University Third Hospital Medical Science Research Ethics Committee (approval NO. 706–01) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was waived by our Institutional Review Board because of the retrospective nature of our study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; We all have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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