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ORIGINAL RESEARCH

Interaction of Acute Respiratory Failure and Acute Kidney Injury on in-Hospital Mortality of Patients with Acute Exacerbation COPD

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Purpose: Both acute respiratory failure (ARF) and acute kidney injury (AKI) are two common complications in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Moreover, both ARF and AKI are reported as increasing the risk of mortality of patients with AECOPD. However, the interaction of ARF and AKI on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on in-hospital mortality in AECOPD patients.

Patients and Methods: We performed a retrospective, observational cohort study of data from Nanjing First Hospital. The effect of AKI and ARF on in-hospital mortality was assessed using a multivariate logistic regression model. Additive interaction was assessed with the relative excess risk due to interaction.

Results: A total of 1647 participants were enrolled. ARF and AKI occurred in 515 (31.3%) and 357 (21.7%) patients, respectively. Overall, in-hospital mortality was 5.7%. The in-hospital mortality of the neither ARF nor AKI group, the ARF only group, the AKI only group, and both the ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively. After multivariate logistic regression analysis, the independent factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83–0.93, $P < 0.001$), ARF only (OR 8.53, 95% CI 3.64–19.99, $P < 0.001$), AKI only (OR 8.99, 95% CI 3.58–22.55, $P < 0.001$), and both ARF and AKI (OR 39.13, 95% CI 17.02–89.97, $P < 0.001$). The relative excess risk due to interaction was 22.62 (95% CI, 0.31 to 44.93), the attributable proportion due to interaction was 0.59 (95% CI, 0.36 to 0.79), and the synergy index was 2.46 (95% CI, 1.44 to 4.20), indicating ARF and AKI had a significant synergic effect on in-hospital mortality.

Conclusion: ARF and AKI had a synergistic effect on in-hospital mortality in AECOPD patients.

Keywords: acute respiratory failure, acute kidney injury, in-hospital mortality, acute exacerbation chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 400 million people and is already the third leading cause of death in the world, which the World Health Organization predicted would not occur until 2030.[1] In China, the prevalence of COPD in people aged 20 years or older is 8.6% (nearly 100 million Chinese adults), and more than 1 million people die and more than 5 million people be disabled due to COPD each year.[2] Acute exacerbation of COPD (AECOPD) is an important factor of the death in patients with COPD,[3] and is also the main expenditure portion of medical expenses for patients with COPD.[4]

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Both acute respiratory failure (ARF) and acute kidney injury (AKI) are two common complications in patients with AECOPD.[5,6] AECOPD is the third most common etiology in medical patients hospitalized because of ARF,[7] and AKI occurs in patients with AECOPD ranging from 1.9% to 21.3%.[6,8,9] Moreover, both ARF and AKI are reported as increasing the risk of mortality of patients with AECOPD.[10] However, the interaction of ARF and AKI on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on mortality in AECOPD patients.

Materials and Methods

Study Design

The study was approved by the Ethics Committee of Nanjing First Hospital. Because of the retrospective study, this study was performed with an approved waiver of informed consent. We conducted a retrospective review of consecutive patients with AECOPD admitted to Nanjing First Hospital from January 2014 to January 2017. The diagnostic criteria for AECOPD were as follows: (i) history of COPD (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 at the clinical stable state) and (ii) an acute worsening of respiratory symptoms (such as dyspnea, cough, or sputum purulence) and warrant hospital admission.[11] Inclusion criterion: patients with COPD exacerbation required hospitalization. Exclusion criteria: patients without full medical records, patients with a urinary-tract infection, patients with a history of stage 5 chronic kidney disease (CKD), and those undergoing dialysis prior to hospital admission.

Definitions of ARF and AKI

ARF defined by an arterial oxygen tension (PaO_2) <60 mmHg in acute state.[12] AKI was defined as a serum creatinine (SCr) change that met the 2012 Kidney Disease Improving Global Outcomes criteria: an increase in the SCr level by ≥0.3 mg/dL within 48 h or ≥1.5-fold from the baseline within 7 days.[13] Urine output data were not obtained and were not used for AKI.[13] The baseline level of SCr was defined as the lowest one during hospitalization.

Data Collection

Data were collected from the medical records: gender, age, comorbid conditions (hypertension, anemia, diabetes mellitus, coronary artery disease, chronic cor pulmonale, atrial fibrillation, and cerebrovascular diseases), laboratory tests (albumin, neutrophil ratio, platelet count, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein), and complications (ARF and AKI).

Statistical Analysis

The statistical analysis was performed using statistical software SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as percentages and were analyzed by the chi-squared test or Fisher's exact test where appropriate. Continuous variables were shown to be the mean and standard deviation (SD) for normally distributed data, or the median and interquartile range (IQR) for non-normally distributed data. Continuous variables with normal distribution were compared using a Student's *t*-test, while continuous variables with non-normal distribution were assessed by Mann–Whitney *U*-tests. All subjects were categorized into four subgroups according to the complications of ARF and AKI. All variables were initially estimated through univariate logistic regression analysis, and only statistically significant variables were incorporated into the multivariable logistic regression model. $P < 0.05$ was considered as statistically significant. To examine the interaction between ARF and AKI on in-hospital death in AECOPD patients, multivariable logistic regression analysis was used to obtain the covariance matrix and regression coefficients.[14] Microsoft Excel sheet was used to calculate three measures: the relative excess risk due to interaction (RERI); the attributable proportion due to interaction (AP); and the synergy index (SI).[15,16]

Results

Study Population

A total of 1823 patients were hospitalized with AECOPD, and 176 (9.7%) patients were excluded due to exclusion criteria. Finally, 1647 participants were enrolled for analysis. For the study population, most (77%) patients were male, and the median age of the overall cohort was 78 years (IQR: 71–84). ARF occurred in 515 (31.3%) patients, and 357 (21.7%) patients developed AKI. In particular, 157 (9.5%) had ARF and AKI, 358 (21.7%) had ARF without AKI, 200 (12.2%) did not have ARF but developed AKI, and 932 (56.6%) had neither ARF nor AKI. Overall, in-hospital mortality was 5.7% (94/1647). Table 1 shows the demographic, comorbid conditions, laboratory tests and in-hospital mortality of participants categorized by ARF and AKI. The in-hospital mortality of the neither ARF nor AKI group, the ARF only

Table 1 Characteristics of Participants Categorized by ARF and AKI

Variables	Neither ARF nor AKI (n = 932)	ARF Only (n = 358)	AKI Only (n = 200)	Both ARF and AKI (n = 157)	*P* value
Demographics					
Gender (male), n (%)	722 (77.5)	265 (74.0)	157 (78.5)	117 (74.5)	0.476
Age (years)	77 (70–83)	78 (69–83)	82 (76–85)	80 (76–86)	<0.001
Comorbid conditions, n (%)					
Hypertension	480 (51.5)	176 (49.2)	126 (63.0)	90 (57.3)	0.007
Anemia	237 (25.4)	115 (32.1)	85 (42.5)	67 (42.7)	<0.001
Diabetes mellitus	138 (14.8)	60 (16.8)	38 (19.0)	28 (17.8)	0.412
Coronary artery disease	244 (26.2)	78 (21.8)	85 (42.5)	65 (41.4)	<0.001
Chronic cor pulmonale	288 (30.9)	214 (59.8)	85 (42.5)	84 (53.5)	<0.001
Atrial fibrillation	92 (9.9)	25 (7.0)	35 (17.5)	22 (14.0)	0.001
Cerebrovascular diseases	187 (20.1)	63 (17.6)	84 (27.0)	40 (25.5)	0.026
Laboratory tests					
Albumin (g/L)	35.7 (33.1–38.3)	34.4 (32.1–37.2)	34.9 (32.1–37.7)	32.5 (29.0–35.4)	<0.001
Neutrophil ratio (%)	74.8 (66.6–82.8)	81.2 (72.8–88.2)	80.1 (73.0–88.4)	86.8 (80.1–91.0)	<0.001
Platelet count (10^9/L)	188 (147–228)	177 (135–222)	181 (146–216)	155 (121–203)	<0.001
Triglyceride (mmol/L)	0.80 (0.62–1.11)	0.82 (0.66–1.07)	0.88 (0.67–1.18)	0.91 (0.70–1.16)	0.125
Total cholesterol (mmol/L)	3.96 (3.35–4.65)	3.94 (3.39–4.65)	3.94 (3.30–4.77)	3.54 (2.97–4.49)	0.005
High density lipoprotein (mmol/L)	1.18 (0.97–1.39)	1.16 (0.94–1.40)	1.11 (0.90–1.36)	1.03 (0.80–1.25)	<0.001
Low density lipoprotein (mmol/L)	2.35 (1.82–2.94)	2.34 (1.92–2.95)	2.42 (1.84–2.96)	2.05 (1.49–2.77)	0.124
Outcome					
In-hospital mortality, n (%)	7 (0.8)	25 (7.0)	15 (7.5)	47 (29.9)	<0.001

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury.

group, the AKI only group, and both the ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively.

Characteristics of in-Hospital Death in AECOPD Patients

Table 2 shows the differences between the survival group and the death group. Compared with the survival group, patients in the death group were of advanced age (81years versus 78 years, $P < 0.001$). Patients in the death group were more likely to have the comorbidities of anemia (43.6% versus 29.8%, $P = 0.005$), coronary artery disease (41.5% versus 27.9%, $P = 0.005$), and chronic cor pulmonale (54.3 versus 39.9, $P = 0.006$). Patients in the death group had a higher neutrophil ratio (86.0% versus 77.9%, $P < 0.001$), and triglyceride (0.95 versus 0.82, $P = 0.030$), while they had lower platelet counts (161 versus 184, $P = 0.007$), high-density lipoprotein (1.06 versus 1.16, $P = 0.014$), low-density lipoprotein (2.10 versus 2.35, $P = 0.012$), and albumin (31.7 versus 35.2, $P < 0.001$). In addition, comparison with the neither ARF nor AKI group, the ARF only group (OR 9.92, 95% CI 4.25–23.15, $P < 0.001$), the AKI only group (OR 10.71, 95% CI 4.31–26.64, $P < 0.001$), and both the ARF and AKI group (OR 56.46, 95% CI 24.91–127.98, $P < 0.001$) had significantly increased in-hospital death risk.

Independent Factors for in-Hospital Death in AECOPD Patients

After multivariate logistic regression analysis, the independent factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83–0.93, $P < 0.001$), ARF only (OR 8.53, 95% CI 3.64–19.99, $P < 0.001$), AKI only (OR 8.99, 95% CI 3.58–22.55, $P < 0.001$), and both ARF and AKI (OR 39.13, 95% CI 17.02–89.97, $P < 0.001$) (Table 3).

Biological Interaction of ARF and AKI on in-Hospital Death in AECOPD Patients

Figure 1 shows the excess risks due to ARF, AKI, and their interaction in an analysis of in-hospital mortality adjusted for all risk factors. As shown in Table 4, we found a statistically significant synergistic interaction between ARF and AKI on in-hospital death. The estimated RERI was 22.62 (95% CI 0.31–44.93), indicating that there would be 22.62 relative excess risks due to the

Table 2 Univariate Logistic Analysis of Risk Factors for in-Hospital Death in Patients with AECOPD

Variables	All Patients (n=1647)	Survival Group (n=1553)	Death Group (n=94)	*P* value
Demographics				
Gender (male)	1261 (76.6)	1192 (76.8)	69 (73.4)	0.456
Age (years)	78 (71–84)	78 (70–83)	81 (78–86)	<0.001
Comorbid conditions, n (%)				
Hypertension	872 (52.9)	824 (53.1)	48 (51.1)	0.707
Anemia	504 (30.6)	463 (29.8)	41 (43.6)	0.005
Diabetes mellitus	264 (16.0)	246 (15.8)	18 (19.1)	0.396
Coronary artery disease	472 (28.7)	433 (27.9)	39 (41.5)	0.005
Chronic cor pulmonale	671 (40.7)	620 (39.9)	51 (54.3)	0.006
Atrial fibrillation	174 (10.6)	160 (10.3)	14 (14.9)	0.160
Cerebrovascular diseases	344 (20.9)	321 (20.7)	23 (24.5)	0.379
Laboratory tests				
Albumin (g/L)	35.0 (32.4–37.8)	35.2 (32.6–37.9)	31.7 (27.8–35.1)	<0.001
Neutrophil ratio (%)	78.4 (69.6–86.0)	77.9 (69.0–85.5)	86.0 (79.6–90.8)	<0.001
Platelet count (10^9/L)	182 (141–224)	184 (142–225)	161 (124–209)	0.007
Triglyceride (mmol/L)	0.82 (0.64–1.12)	0.82 (0.64–1.11)	0.95 (0.68–1.21)	0.030
Total cholesterol (mmol/L)	3.93 (3.31–4.63)	3.94 (3.32–4.63)	3.75 (3.08–4.59)	0.110
High density lipoprotein (mmol/L)	1.15 (0.94–1.38)	1.16 (0.94–1.38)	1.06 (0.83–1.32)	0.014
Low density lipoprotein (mmol/L)	2.32 (1.81–2.93)	2.35 (1.82–2.93)	2.10 (1.64–2.65)	0.012
Complications of ARF and AKI, n (%)				
Neither ARF nor AKI	932 (56.6)	925 (59.6)	7 (7.4)	
ARF only	358 (21.7)	333 (21.4)	25 (26.6)	<0.001
AKI only	200 (12.1)	185 (11.9)	15 (16.0)	<0.001
Both ARF and AKI	157 (9.5)	110 (7.1)	47 (50.0)	<0.001

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Table 3 Multivariate Logistic Analysis of Risk Factors for in-Hospital Death in Patients with AECOPD

Variables	Mortality (%)	OR	95% CI	*P* value
Albumin	–	0.88	0.83–0.93	<0.001
Complications of ARF and AKI				
Neither ARF nor AKI	0.8% (7/932)	Reference	Reference	
ARF only	7.0% (25/358)	8.53	3.64–19.99	<0.001
AKI only	7.5% (15/200)	8.99	3.58–22.55	<0.001
Both ARF and AKI	29.9% (47/157)	39.13	17.02–89.97	<0.001

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

additive interaction between ARF and AKI. AP revealed that 59% of the total odds of in-hospital death were attributed to the interaction between ARF and AKI. In addition, SI was 2.46 (95% CI, 1.44–4.20), suggesting that the risk of in-hospital death in both ARF and AKI patients was 2.46 times as high as the sum of risks in patients presenting only one single complication.

Discussion

Both ARF and AKI were two common complications in AECOPD patients.[5,6] Although previous studies had reported that development of a single complication (ARF or AKI) was associated with an increased risk of mortality in patients with AECOPD,[10] the effect of the addition of two complications (ARF and AKI) on in-hospital mortality

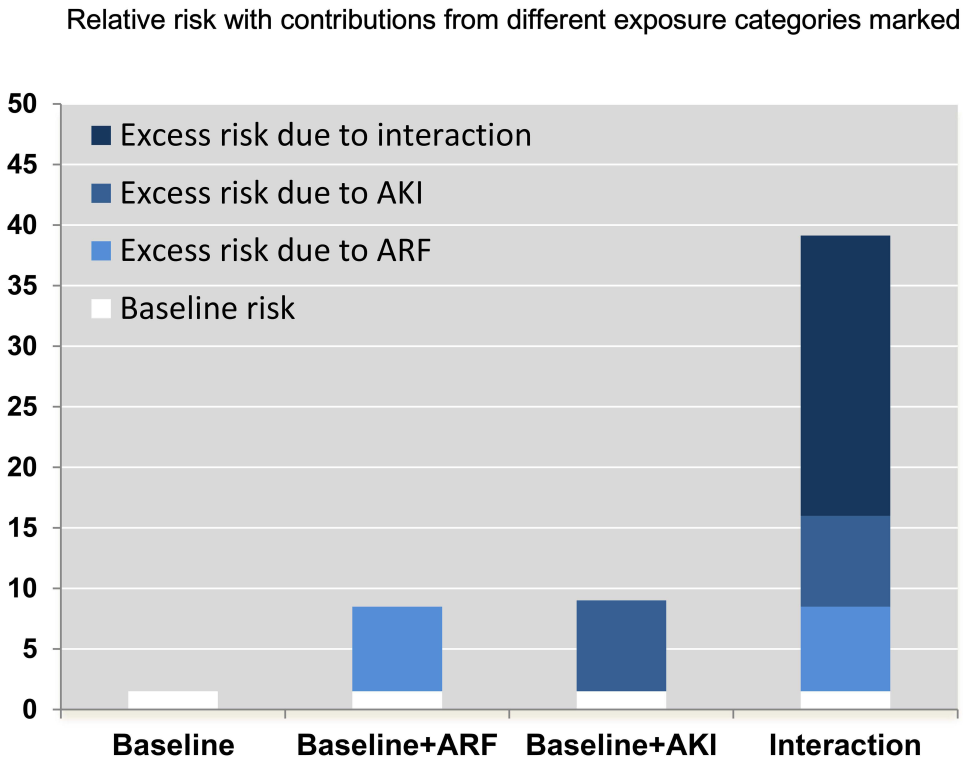

Figure 1 Relative risk with contributions from ARF, AKI, or a combination of both.
Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury.

was still unknown. In this study, we explored the interactive effect of ARF and AKI on the in-hospital death of patients with AECOPD.

After multivariate logistic regression analysis, we found that albumin, ARF only, AKI only, and both ARF and AKI were independently associated with in-hospital death in AECOPD patients. Serum albumin level was part of the acute-phase protein response, and low level of serum albumin may reflect a persistent inflammation or worsening clinical status during AECOPD.[17,18] Previous studies had also reported that low level of serum albumin was not only related to prolong hospital stay, but also increase mortality in AECOPD patients.[19,20] Our results also indicated that low level of serum albumin could increase in-hospital mortality in AECOPD patients. We found that patients with ARF and AKI had increased 8.53-fold and 8.99-fold in-hospital death risk, respectively. However, once patients coexisted with ARF and AKI, the in-hospital death risk was increased to 39.13-fold. Furthermore, after interaction analysis, we found a statistically significant synergistic interaction between ARF and AKI on in-hospital death of patients with AECOPD. Similarly, compared to patients without ARF and AKI, Kim et al reported that patients undergoing high-risk intraabdominal general surgery procedures with ARF and AKI had 14.2 times and 10.8 times risk for postoperative mortality, respectively.[21] Moreover, patients undergoing high-risk intraabdominal general surgery procedures coexisted with ARF and AKI, and the postoperative death risk was increased to 65.2 times.[21] In addition, the development of ARF and AKI also showed significant positive additive interactions to further increase the risk of mortality.[21] The estimated RERI was 22.62, indicating that there would be 22.62 relative excess risk due to the additive interaction between ARF and AKI. AP revealed that 59% of the total odds of in-hospital death were attributed to the interaction between ARF and AKI. In addition, SI was 2.46, suggesting that the risk of in-hospital death in both ARF and AKI patients

Table 4 Measures for Estimation of Biological Interaction Between ARF and AKI for the Risk of in-Hospital Death in Patients with AECOPD

Measures of Biological Interaction	Estimate	95% CI
RERI	22.62	0.31–44.93
AP	0.59	0.36–0.79
SI	2.46	1.44–4.20

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RERI, relative excess risk due to interaction; AP, attributable proportion; SI, synergy index; CI, confidence interval.

was 2.46 times higher than the sum of risks in patients presenting only one single complication. Hence, it is important to improve the prognosis of AECOPD to avoid the development of AKI and ARF.

However, our study was epidemiologic in nature and did not provide direct evidence for the exact mechanisms underlying this synergism. Recent years, the lungs-kidneys crosstalk had been focused on the critically ill patients.[22,23] ARF may induce renal damage via the following mechanisms: (1) hypoxia was known to be able to reduce the renal blood flow and contribute to decrease the glomerular filtration;[23] correspondingly, hypercapnia reduced renal blood flow directly by activating renal vasoconstriction and indirectly by systemic vasodilation secondary to high $PaCO_2$.[23–25] (2) Systemic pro-inflammatory mediators were released from the injured lungs, and were associated with AKI.[26,27] More specifically, increased levels of interleukin-6, plasminogen activator inhibitor-1, and soluble tumor necrosis factor receptors I and II in ARF were associated with the development of AKI.[27] (3) COPD could increase intra-abdominal pressure, and then caused renal edema because of diminished venous drainage, which led to a vicious cycle that further increased intra-abdominal pressure.[23] (4) Mechanical ventilation that had improved lung function in ARF had undesirable effects on decreased renal function, which could be induced by hemodynamic and blood gas disturbances, neurohumoral negative effects, and bio-trauma.[23,25,28] On the other hand, AKI may induce lung injury via the following mechanisms: (1) AKI may lead to lung injury by increasing production of inflammatory mediators.[29,30] (2) AKI caused a significantly decreased expression in the pulmonary predominant water channel, aquaporin 5, possibly contributing to lung injury.[31] Therefore, it was important to determine the exact mechanisms between ARF and AKI, which could improve the prognosis of AECOPD patients.

There are several limitations in our study. First, it is a single-centered retrospective study. A prospective multicenter study is needed to confirm our conclusions. Second, the data set lacks of data on other organ systems (such as the heart, liver or gut), which might have affected in-hospital mortality of AECOPD patients. Third, as urine output is not monitored in most of the patients, this study does not use the urine output standard to diagnose AKI.

Conclusion

We present epidemiologic evidence that ARF and AKI independently increase the risk of in-hospital death in patients with AECOPD. More importantly, we find that the simultaneous development of ARF and AKI demonstrate positive additive interactions, which imply that the two complications interact synergistically to further increase the risk of in-hospital mortality above and beyond what would be expected with one complication alone. Our observations underline the importance of understanding the clinical implications of altered organ system function and the recognition that these two complications may have far-reaching effects when ARF combines with AKI simultaneously. Further studies will be required to determine the complex mechanism behind the synergistic effect and to explore the best therapeutic targets for the prevention of the interactive injury between lungs and kidneys.

Abbreviations

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARF, acute respiratory failure; AKI, acute kidney injury; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CKD, chronic kidney disease; PaO_2, arterial oxygen tension; SCr, serum creatinine; SD, standard deviation; IQR, interquartile range; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index; OR, odds ratio; CI, confidence interval; $PaCO_2$, arterial carbon dioxide pressure.

Data Sharing Statement

Datasets are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study protocol was approved by the Nanjing First Hospital Institutional Review Board. Individual patient consent was waived on condition that all patient data were de-identified before evaluation because this study was a retrospective analysis. Confidentiality and the protection of data will be respected at all times. This study was conducted in accordance with the Declaration of Helsinki.

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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 for the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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