Concomitant chest trauma and traumatic brain injury, biomarkers correlate with worse outcomes

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BACKGROUND: Clinical data are lacking on the influence of chest trauma on the secondary injury process after traumatic brain injury (TBI), with some data suggesting that multiple trauma may worsens brain injury. Blunt chest trauma and TBI represent the two major single injury entities with the highest risk of complications and are potential biomarker targets.

METHODS: Trauma patients with severe TBI were enrolled. Serum biomarker levels were obtained every 6 hours for 72 hours. Baseline, 6 hours and 24 hours CT head scans were evaluated. Neurologic worsening was defined as increased contusions, ischemia, compression of basal cisterns, and/or midline shift. The TBI patients with chest injury (Abbreviated Injury Scale chest score ≥1) and those without chest injury were compared. Wilcoxon rank sum test, univariate logistic regression and receiver operating characteristic were reported.

RESULTS: Fifty-seven patients. Mean age of 40.5 years. Median motor Glasgow Coma Scale score at admission and 24 hours was 3 (interquartile range, 1–5) and 5 (interquartile range, 3–5). Of the patients enrolled, 12.2% patients underwent craniotomy within 6 hours from the time of admission and 22.8% within 12 hours. Patients with chest trauma, 24.5% had a chest Abbreviated Injury Scale score of 3 or greater, and 73.6% sustained blunt chest trauma. Stratifying TBI patients with and without chest injury revealed higher mean levels of IL-4, IL-5, IL-8, and IL-10 and lower mean IFN-γ and IL-7 levels in patient with chest injury. IL-7 levels adjusted for chest injury predicted neurological worsening with area under the receiver operating characteristic of 0.59 (p value = 0.011). The TBI and chest trauma patients' IL-4 and neuron-specific enolase levels were predictive of mortality (area under the receiver operating characteristic of 0.67 and 0.63, p = 0.0001, 0.003), respectively.

CONCLUSION: Utilizing biomarkers for early identification of patients with TBI and chest trauma has the capability of modifying adverse factors affecting morbidity and mortality in this subset of TBI patients. (*J Trauma Acute Care Surg.* 2019;87: S146–S151.

LEVEL OF EVIDENCE: Level III.

KEY WORDS: TBI; biomarkers; cytokines; critical care; chest trauma.

Traumatic brain injury (TBI) is a common pathology seen in adult trauma patients. It remains a major cause of mortality and morbidity.[1] In the military, TBI has been a signature injury of the conflicts in the Middle East.[2,3] A variety of complications that often occur after TBI, including hypotension and hypoxia, can contribute to secondary brain injury and are associated with worse functional outcomes.[4–6] The complex cascade of molecular and cellular events cause secondary injury that follows can aggravate the initial TBI insult. This cascade of events reduces the chances of functional recovery but could, at least theoretically, be counteracted.[7,8]

In the study, we proposed that prediction of the development of secondary injury and neurological worsening (NW) could expedite care of the critically injured and may improve patient outcomes. The purpose of this study is to determine whether we can predict development of events ahead of time so that clinicians can proactively manage adverse intracranial events. Our previous work has demonstrated that this is possible with the use of continuously monitored physiological data. The addition of serum biomarkers to these algorithms may make these predictions more robust. However, biomarkers and physiological data are influenced by more than just TBI. The effect of concomitant injuries may confound the ability to predict specific intracranial events, such as intracranial hypertension (ICH) or cerebral hypoperfusion (CH).

The role of an initial and repeat brain CT scans is well established in the management of TBI. Serial CT scans in head trauma are obtained for early capture of NW that can lead to early medical and surgical interventions prior to the development of clinical symptoms.[9] Others have recommended relying on clinical examination to analyze the need for a repeat head CT.[10–13] This strategy is especially practical in the rural areas, developing countries, and combat situations with limited resources.

Chest trauma has particular relevance on outcome after severe trauma with clinically impaired lung function typically occurring within 72 hours after trauma. The majority of severe chest traumas are associated with significant concomitant injuries, such as TBI.[14] In TBI with concomitant chest trauma, the posttraumatic course and outcomes may be significantly influenced by thoracic injuries, which can account for up to 25% of trauma-related deaths.[15,16] Indicating chest trauma may represent a leading determinant of adverse outcome after multiple

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injuries.[7,8,17,18] In particular, pulmonary contusions (PCs) are independently associated with posttraumatic complications, such as acute respiratory distress syndrome and multiple-organ dysfunction syndrome.[18–22] In addition to the direct impact of chest trauma on pulmonary function, the lung has been described as an indirect target organ for secondary damage that is caused by the inflammatory response after trauma.[21]

We studied and analyzed biomarkers that may provide insight into the local and systemic effects of TBI with thoracic trauma. Clinical data are lacking on the influence of chest trauma on the secondary injury process after TBI, with some data suggesting that multiple injuries may lead to systemic inflammation that affects the neuroinflammatory response of TBI and worsens brain injury. The clinical course and outcomes of multiple injuries patients is largely determined by the severity and pattern of injuries sustained. Blunt chest trauma and TBI represent the two major single injury entities with the highest risk of complications[23] and are potentially detectable by biomarkers, reflecting the systemic response to multiple injuries. The specific aim is to evaluate the differences between biomarkers in patients with TBI and concomitant chest trauma compared with patients with TBI alone and to determine the effect of these concomitant injuries on predicting mortality and NW.

METHODS

This is a single-center, prospective, observational study conducted at the R Adams Cowley Shock Trauma Center (STC) at the University of Maryland Medical Center. Study approval was obtained by the Institutional Review Board (IRB) from the University of Maryland School of Medicine. Informed consent was obtained from legally authorized representatives.

The study included adult trauma patients (age, ≥18 years), admitted to STC within 6 hours of injury with a severe TBI as defined by head Abbreviated Injury Scale (AIS) score greater than 2 and postresuscitation motor Glasgow Coma Scale (mGCS) score less than 6, and admission to the intensive care unit for continuous physiologic monitoring. Included patients had intracranial pressure (ICP) monitors; either intraventricular catheters or intraparenchymal pressure monitors (Camino; Integra LifeSciences) placed within 6 hours of admission. Transferred patients, active cardiac arrest, or mortality within 24 hours of trauma center arrival were excluded from the study. Further exclusions were patients with nonsurvivable brain injury and TBI who did not require ICP monitoring.

The management of patients with TBI at STC is protocolized using an institutional algorithm based on the BTF Guidelines.[24] These guidelines outline clinical management strategies to maintain an ICP less than 20 mm Hg and cerebral perfusion pressure greater than 60 mm Hg, including sedation, analgesia, mechanical ventilation to maintain $PaCO_2$ of 35 mm Hg to 40 mm Hg, head elevation (30°–45°), and maintenance of normal oxygenation, blood pressure, and volume status. First-tier therapies for treatment of ICH include insertion of an intraventricular catheter, increasing sedation and/or hyperosmolar therapy. Intractable ICH is treated with moderate hyperventilation ($PaCO_2$ < 35 mmHg), induction of barbiturate coma, and/or decompressive craniectomy.[14,25]

Fifteen serum cytokine (CYT) levels were obtained on admission and every 6 hours for 72 hours. Specimens were obtained via in-dwelling arterial line or peripheral phlebotomy. Blood was drawn into standard 5-mL serum collection tubes, centrifuged to remove any cellular debris and then frozen at minus 80°C until batch processing. Specimens were analyzed using the Luminex (Luminex Corp., Austin, TX) system and Millipore (Millipore, Billerica, MA) assay kits. The CYT measured included interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF- α), interleukin (IL)-2, IL-4, IL-10, IL-18, IL-6, IL-8, granulocyte macrophage colony stimulating factor, IL-12p70, IL-13, IL-5, IL-7, neuron-specific enolase (NSE), and S100 calcium-binding protein B (S-100b). All samples were run in duplicate.

Standard of care head CT scans at admission, 6-hour and 24-hour CT scans were reviewed. Neurologic worsening was defined by CT imaging findings of increased contusions, ischemia, compression of basal cisterns, and/or midline shift. Patients were stratified by TBI with chest injury, defined as chest AIS score of 1 or greater, and TBI without chest injury. Wilcoxon rank sum test was used to compare biomarkers between the two groups. Neurologic worsening was diagnosed at 24-hours after admission, biomarker levels measured between 18 hours and 24 hours were analyzed for their association with NW and mortality, by using logistic regression. Area under the receiver operating characteristic (AUROC) was used to measure the association between the CYT level and the outcomes. *p* value less than 0.05 was considered as statistically significant.

RESULTS

The study screened 875 patients from December 2013– to November 2016 with severe TBI, of whom 178 met all study eligibility criteria. The study population included 57 patients (Fig. 1) prospectively enrolled. The mean age of the enrolled patients was 40.5 years (standard deviation [SD], ± 22.0 years), 78.9% of patients were male. The Median admission Injury Severity Score was 25 (interquartile range [IQR]. 15–35). Included patients had a median mGCS at admission and 24 hours of 3 (IQR, 1–5) and 4 (IQR, 3–5), respectively. The study patient

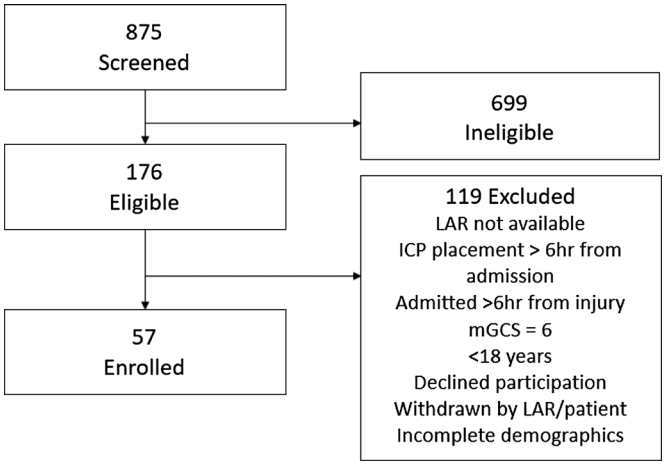

Figure 1. Consort diagram of patient enrollment.

demographics included a median Marshall score of 2 (IQR, 2–3) (Table 1). There were 80.7% of patients had an Intraventricular device placed. In these enrolled patients, 12.2% underwent a craniotomy within 6 hours from the time of admission and 22.8% within 12 hours. 80.7% patients were endotracheal intubated, 52.1% in the trauma resuscitation unit, and 47.8% in the field during transport. The mean for days of mechanical ventilation for the study patients was 8.2 days (SD ± 8.8 days).

All subjects enrolled were evaluated for the presence or absence of thoracic injury. Two groups of patients were defined, patients with chest injury (AIS chest score, ≥1) and patients without chest injury (AIS chest score, 0). All included patients underwent chest CT scans during initial assessment and thoracic injuries were defined as PC, pulmonary laceration, pneumothorax, hemothorax, and/or fractured ribs. The AIS chest injury was defined as presence or absence of thoracic injury based on CT imaging. In TBI patients with chest trauma, 24.5% had an AIS chest score of 3. 73% or greater of patients sustained blunt trauma and 27% penetrating trauma as the mechanism of chest injury. Further analysis of the AIS, in Table 2 summarizes a subset of enrolled patients with an AIS score of 3 or greater per injury. In Table 3, an AIS of 3 or greater for maximum severity region is included. This is then further differentiation into head, neck, thorax, abdomen, spine, upper extremity, lower extremity, and unspecified. Described in this subset of enrolled patients is the number of patients who died compared with those who lived and the number of patient with NW compared with those without NW.

The outcomes of interest, NW at 24 hours, and in-hospital mortality were compared between the two groups (Fig. 2). Comparing patients with and without chest injury revealed higher mean serum levels of IL-4, IL-5, IL-8, and IL-10, and lower mean IFN-γ and IL-7 levels in patients with chest injury (Table 3). Neurologic worsening within 24 hours was seen in 40.4% of the entire cohort and 42.1% with concomitant chest trauma. IL-7 levels, adjusted for the presence of chest injury predicted NW with an AUROC of 0.59 (p value = 0.011). In-hospital mortality rate for the 57 enrolled patients was 21.1% and 36.8% in patients with concomitant chest trauma. In the patients with TBI and chest trauma, IL-4 and NSE levels predicted in-hospital mortality within 24 hours of admission, AUROC of 0.67 and 0.63 (p = 0.0001, 0.003), respectfully (Fig. 2).

DISCUSSION

Traumatic brain injury afflicts millions of people each year, including civilian and military populations. Patients with TBI often present with associated thoracic injuries and PC seen in 29% of patients with TBI.[27] Traumatic brain injury contributes to worse mortality and morbidity in patients with thoracic injuries[28,29] and despite advances in pulmonary care and ventilator management, several studies have demonstrated that chest injury is related to a poorer outcome in the patient with TBI.[4] In recent literature, elevated biomarkers in thoracic trauma have been identified and associated with increased mortality and an increased risk of morbidity including Acute Lung Injury (ALI) or acute respiratory distress syndrome.[30] The development of ICH and CH has been demonstrated to be associated with elevations of IL-8 and, to a lesser extent, TNF-α.[31] Biomarker levels may be different in patients with chest injury and TBI compared with TBI patients without chest injury, and this study sought to examine the effect of chest injury on serum biomarkers in patients with TBI.

A number of candidate circulating TBI biomarkers have shown promise for aiding in the diagnosis of TBI and in identifying patients with traumatic abnormalities on head CT scan.[32–36] Representative biomarkers are derived from acute neuronal, axonal, astroglial and endothelial injuries or secondary inflammatory,

TABLE 1. Demographics of 57 Study Subjects

B	TBI (n = 57)	TBI With Chest Injury (n = 19)	TBI Without Chest Injury (n = 38)	p (Chest Injury Compared to no Chest Injury)
Age: mean (STD), y	40.5 (22.0)	33.3 (16.6)	44.1 (23.7)	0.08
Male, n (%)	45 (79.0%)	17 (89.5%)	28 (73.7%)	0.30
ISS, median (IQR)	25 (15–35)	33 (20–43)	20 (9–27)	0.02*
Admission mGCS, median (IQR)	3 (1–5)	3 (1–5)	3 (1–5)	0.71
mGCS at 24-hour, median (IQR)	4 (3–5)	4 (2–5)	4 (3–5)	0.96
Marshall score				0.24
2	39 (68.4%)	17 (89.5%)	22 (57.9%)	
3	9 (15.8%)	2 (10.5%)	7 (18.4%)	
4	3 (5.3%)	0 (0%)	3 (7.9%)	
6	6 (10.5%)	0 (0%)	6 (15.8%)	
Type of injury n (%):				
Blunt	41 (71.9%)	13 (68.4%)	28 (73.7%)	0.92
Penetrating	2 (3.5%)	0 (0.0%)	2 (5.3%)	0.80
Other	14 (24.6%)	6 (31.6%)	8 (21.0%)	0.59
Outcomes:				
NW at 24 h	23 (40.4%)	8 (42.1%)	15 (39.5%)	1.00
Mortality	12 (21.1%)	7 (36.8%)	5 (13.2%)	0.08

Two-sample t-test was used for mean difference comparison. Wilcoxon rank sum test was used for median comparison. χ^2 Test was used for proportional difference test.
ISS, Injury Severity Score.

TABLE 2. AIS score ≥ 3 per Injury

AIS Score ≥ 3	Maxsev	Headsev	Necksev	Thoraxsev	Abdsev	Spinesev	Upperextsev	Lowerextsev	Unspecsev
In-hospital Mortality									
Dead 12	7	1	0	2	0	0	0	1	0
Lived 45	33	4	2	12	5	1	2	5	0
NW									
Worsen[23]	17	2	1	6	1	0	1	4	0
Nonworsen[26]	23	3	1	8	4	1	1	2	0

Subset of enrolled patients, AIS ≥ 3 per injury. AIS ≥ 3 for maximum severity region and further differentiation into head, neck, thorax, abdomen, spine, upper extremity, lower extremity and unspecified. Described in this subset of enrolled patients is the number of patients who died compared to lived and number of patient with radiographic NW compared to those without NW.

and reparative processes, such as inflammation, oxidative stress, excitotoxicity, and other host-derived pathophysiological mechanisms. Inflammation and neuroinflammation appear to be major mediators of outcomes following TBI.[37] These inflammatory systems are being studied using animal models and human translational studies in the effort to understand the mechanism of TBI and develop therapeutic strategies to improve the outcome of these patients.[38]

The mechanism behind the influence on thoracic injuries in patients with TBI could be due to worsening of gas exchanges and acute respiratory failure, resulting in hypoxemia and hypercarbia, which may aggravate secondary injury. Several studies have demonstrated that hypoxemia constitutes a secondary insult that is related to poor outcome.[26,39,40] In patients with TBI and chest trauma, knowledge of the outcome determinants is important because it may provide early accurate information, allow better allocation of resources, and timing of care in this subset of TBI patients.

The science of biomarkers is generally defined as measurable internal indicators of change in organisms at the molecular or cellular level. In recent literature, a clinically relevant large animal multiple injuries model was able to demonstrate a significant systemic inflammatory response in a nonhuman primates multiple injuries model (liver hemorrhage, cecal, and soft tissue injury) using a laparoscopic technique.[39] In this study, accumulating evidence suggests that the upregulation of adhesion molecules, the infiltration of neutrophils and the production of mediators that release CYTs, chemokines, proteolytic enzymes, reactive oxygen species and other inflammatory/cytotoxic mediators within the pulmonary microvasculature, are key to the initiation and perpetuation of lung injury following trauma, shock, and sepsis.[41,42] Similarly, in animal models of multiple injuries-induced lung injury/inflammation, increased transcriptional activation of NF-κB signaling leading to increased transcription of specific proinflammatory CYT and chemokine genes as well as a host of receptors including IL-7. Increased expression of these mediators leads to recruitment and leukocyte-transendothelial migration of neutrophils, monocytes/macrophages, and lymphocytes to the inflammatory site and stimulates proinflammatory activation and cellular apoptosis.[41,42] Although this animal study did not include TBI patients, it did demonstrated evidence based on lung tissue examination of the direct hit effect the lungs incurred after multiple injuries.

TABLE 3. Individual CYT Levels With Mean Values (SD) in Each 6-h Period

	TBI With Chest Injury	TBI Without Chest Injury	*p* value
IFN-G	0.32 (1.2)	3.9 (22.3)	<0.001*
TNF-A	68.7 (185.1)	69.8 (533.5)	0.192
IL-2	16.3 (42.0)	12.6 (29.7)	0.683
IL-4	1.4 (3.8)	0.8 (2.7)	0.042*
IL-10	28.8 (68.3)	18.9 (44.3)	<0.001*
IL-18	0.01 (0.1)	1.5 (18.8)	0.055
IL-6	141.2 (386.0)	177.5 (652.5)	0.08
IL-8	34.4 (49.0)	24.4 (39.5)	<0.001*
GMCSF	0.2 (0.7)	1.0 (5.6)	0.014*
IL-12p70	0.3 (2.5)	0.4 (2.0)	0.004*
IL-13	13.6 (98.2)	4.5 (36.1)	0.93
IL-5	0.6 (1.9)	0.2 (0.9)	0.001*
IL-7	1.3 (2.6)	2.3 (3.2)	<0.001*
NSE	9.9 (7.3)	8.9 (8.0)	0.01*
S100B	994.4 (1379.8)	791.1 (669.7)	0.99

Comparing the two group of patients: TBI with chest injury and TBI without chest injury. *p* Values determine significant group differences using the Wilcoxon rank sum test (*$p < 0.05$.

GMCSF, granulocyte macrophage colony stimulating factor.

The objective of our study is to determine whether there are differential biomarker profiles in patients with TBI and concomitant chest injury as compared to those without chest injury and to determine the impact of thoracic injuries on NW and mortality. Comparing patients with TBI with and without chest injury revealed differential levels of biomarkers, namely, higher levels of IL-4, IL-5, IL-8, and IL-10 and lower levels of IFN-γ and IL-7. Specifically, IL-7 in our patients with TBI and chest trauma was found to be significantly predictive of NW. Inflammatory responses to TBI, both local and systemic, are complex. By comparing each biomarker profile, we were able to describe biologically relevant changes that could reflect underlying pathophysiology in chest trauma and TBI. Suggesting CYT levels are specific to those injuries and inflammatory response in trauma. This systemic inflammatory response and central inflammatory response could be correlated. It is reasonable to conclude that the biomarker levels identified in each group may provide prognostic data for proximate events in patients after TBI and chest trauma, such as mortality and radiographic worsening that are specific to the patient's injury profile. These studied biomarkers provide promise in diagnosing or monitoring patients with these concomitant injuries.

This study is limited in its results. It is a single-center study with a small sample size and should be validated in a

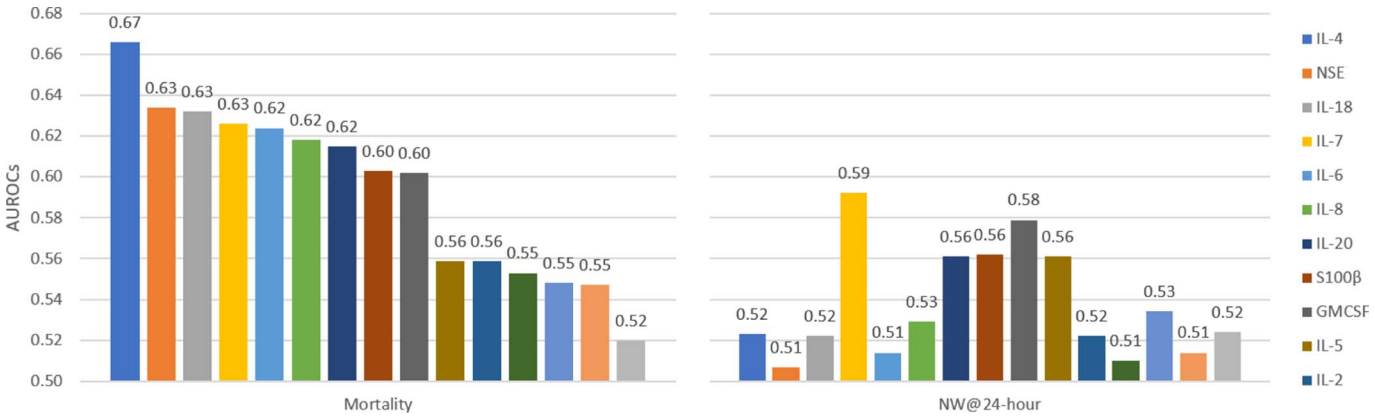

Figure 2. Each biomarker measured at 18 hours to 24 hours. AUROCs of models to predict mortality and NW within 24 hours after admission.

larger population with intercenter variability in clinical care and patient outcomes. Additional study of biomarker patterns in TBI and chest trauma could include enrollment of patients that are not too severe or too mild to detect any benefit, decreasing potential outcome scales insensitive to important consequence of brain injury. This would limit bias that could skew the literature on biomarkers and make a thorough evaluation of treatment effects. Likewise, subset analysis of chest trauma patients alone compared with chest trauma with TBI could potentially further elucidate the question of TBI as a significant contributor to the inflammatory response inflammatory mediator elaboration compared between chest injury alone and chest injury and TBI to see if TBI is a significant contributor to the inflammatory response. The authors recognize this limitation to the study and consider this second phase patient analysis may be warranted.

Future studies may build upon our analysis by using other statistical modeling tools to examine one or more markers and continue to refine incorporating biomarker levels to predict impending events in patients with multiple injuries. Development of a TBI algorithm which better predicts the development of clinical worsening could potentially standardize treatment and designate patient resources in military and civilian populations. Biomarkers may be able to assist in predicting impending events in patients with TBI and the models will need to be adjusted accordingly for multiple injuries such as thoracic injury. Our data suggest there are a variety of biomarkers that are differentially found to be involved in patients with chest injury and TBI that need to be further elucidated in larger case numbers and multicenter studies.

CONCLUSION

The challenge of accurate diagnosis and monitoring of TBI with multiple injuries has created a need for biomarkers that reflect core elements of the injury process. Our study was able to predict development of adverse events such as radiographic NW and mortality, with subsequent biomarker changes. Multiple trauma may lead to systemic inflammatory and biomarker changes that could potentially affect the neuroinflammatory response of TBI. Utilizing biomarkers in severe TBI with chest trauma has a potential role as a diagnostic and prognostic monitoring tool In TBI patients. Incorporating biomarkers with the goal of modifying outcomes, treatment options, therapeutic implications and timing of care in the subset of TBI patients.

AUTHORSHIP

S.Y. contributed to study design, data collection, analysis and interpretation, A.C. contributed to study design, data analysis and interpretation, preparation of the article, and critical revisions of the article. Y.L. contributed to study design, data collection, analysis and interpretation. P.L. contributed to study design, data collection, analysis and interpretation. P.H. contributed to study design, data collection, analysis and interpretation and critical revisions of the article. T.M.S. contributed to critical revisions of the article. D.M.S. contributed to study design, analysis and interpretation and critical revisions of the article.

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DISCLOSURE

The authors declare no conflicts of interest.
The authorship requirements have been met and all authors and the final manuscript approved by all authors. The authors confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. The authors confirm that the source of funding for the study, potential conflicts of interest for all authors, adhering to ethical guidelines, use of informed consent, and ethical approvals (IRB) are described in the article.

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