Fulminant *Clostridium difficile* colitis: Prospective development of a risk scoring system

Gwendolyn M. van der Wilden, PhD, MSc, Yuchiao Chang, PhD, Catrina Cropano, BS, Melanie Subramanian, BS, Inger B. Schipper, MD, PhD, D. Dante Yeh, MD, David R. King, MD, Marc A. de Moya, MD, Peter J. Fagenholz, MD, *and* **George C. Velmahos, MD, PhD,** *Boston, Massachusetts*

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From the Division of Trauma, Emergency Surgery and Critical Care (G.M.V.D.W., C.C., M.S., D.D.Y., D.R.K., M.A.D.M., P.J.F., G.C.V.), Department of Surgery, and Division of Biostatistics (Y.C.), Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; Department of Trauma Surgery (G.M.V.D.W., I.B.S.), Leiden University Medical Center and Leiden University, Leiden, the Netherlands.
Address for reprints: George C. Velmahos, MD, PhD, Massachusetts General Hospital, 165 Cambridge St, Suite 810, Boston, MA 02114; email: gvelmahos@partners.org.

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BACKGROUND: Of the patients with a *Clostridium difficile* infection, 2% to 8% will progress to fulminant *C. difficile* colitis (fCDC), which carries high morbidity and mortality. No system exists to rapidly identify patients at risk for developing fCDC and possibly in need of surgical intervention. Our aim was to design a simple and accurate risk scoring system (RSS) for daily clinical practice.

METHODS: We prospectively enrolled all patients diagnosed with a *C. difficile* infection and compared patients with and without fCDC. An expert panel, combined with data derived from previous studies, identified four risk factors, and a multivariable logistic regression model was performed to determine their effect in predicting fCDC. The RSS was created based on the predictive power of each factor, and calibration, discrimination, and test characteristics were subsequently determined. In addition, the RSS was compared with a previously proposed severity scoring system.

RESULTS: A total of 746 patients diagnosed with *C. difficile* infection were enrolled between November 2010 and October 2012. Based on the log (odds ratio) of each risk factor, age greater than 70 years was assigned 2 points, white blood cell count equal to or greater than 20,000/μL or equal to or less than 2,000/μL was assigned 1 point, cardiorespiratory failure was assigned 7 points, and diffuse abdominal tenderness on physical examination was assigned 6 points. With the use of this system, the discriminatory value of the RSS (*c* statistic) was 0.98 (95% confidence interval, 0.96–1).The Hosmer-Lemeshow goodness-of-fit test showed a *p* value of 0.78, and the Brier score was 0.019. A value of 6 points was determined to be the threshold for reliably dividing low-risk (<6) from high-risk (≥6) patients.

CONCLUSION: The RSS is a valid and reliable tool to identify at the bedside patients who are at risk for developing fCDC. External validation is needed before widespread implementation. (*J Trauma Acute Care Surg*. 2014;76: 424–430. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Prognostic study, level II.

KEY WORDS: Fulminant *Clostridium difficile* colitis; clinical prediction rule; risk scoring system.

Clostridium difficile is the most common cause of hospital-acquired diarrhea, affecting 10% of all hospital admissions, resulting in 3 million new cases in the United States annually.[1–4] Of those cases, 2% to 8% develop fulminant *C. difficile* colitis (fCDC).[3,5–8] fCDC carries a mortality rate ranging between 13% and 80%.[3,5–23] Many studies on fCDC, including two of our own, have suggested that early surgical involvement in these cases may improve outcomes.[7,9,13,16,22,23] However, it is difficult to expediently identify those patients at risk for developing fCDC and therefore more likely to require surgical intervention. In 2011, a study by Neal et al.[24] from the University of Pittsburgh proposed a scoring system (based on 12 clinical, laboratory, and imaging criteria), to evaluate the severity of *C. difficile* colitis and identify patients at risk for fCDC (Table 1). The complexity of a 12-factor system limits its use in daily clinical practice. The use by health care personnel is typically improved when clinical pathways are simple without sacrificing accuracy.[25,26] The aim of this study was to design a simple and accurate risk scoring system (RSS) for patients who are at risk for developing fCDC. We hypothesized that such patients can be reliably identified based on the RSS.

PATIENTS AND METHODS

Patients

All patients with *C. difficile* colitis admitted to the Massachusetts General Hospital (MGH) between November 1, 2010, and October 31, 2012, were prospectively enrolled in a specific database aiming to collect data on *C. difficile* infections (CDIs). Until September 1, 2012, the diagnosis was based on the toxin A/B enzyme immunoassay. For the final 2 months, this was changed to a membrane enzyme immunoassay that detects *C. difficile* glutamate dehydrogenase antigen (an essential enzyme produced by all *C. difficile* isolates) and toxins A/B. In specimens with discordant tests, an additional polymerase chain reaction test for toxigenic *C. difficile* was performed, and the diagnosis was confirmed if the polymerase chain reaction result was positive. As per our previous reports,[7,13] patients with fCDC were identified by the presence of significant systemic toxic effects and shock, resulting in admission to the intensive care unit (ICU), need for urgent colectomy, or death.

Data

Data were collected through the prospective database and supplemented by the infection control registry and the electronic medical records. We recorded age, sex, race, ethnicity, admitting service, previous hospitalization (within last 2 months before current admission), previous antibiotic use (within the past 2 months), use of proton pump inhibitors, recurrent infection, ICU admission, presence of immunosuppression and/or a chronic medical condition, laboratory values, such as white blood cell (WBC) count, bands, serum creatinine levels, serum albumin levels, fever (defined as temperature > 101.3°F), abdominal computed tomographic (CT) scan results (focusing on findings such as pancolitis, ascites, bowel wall thickening, and dilation), the need for mechanical ventilation or vasopressor support, antibiotic use, and mental status change (disorientation, confusion, or decreased consciousness). Physiologic and laboratory parameters, where necessary, were dichotomized at clinically relevant values. Outcome measures such as mortality, surgical intervention (total abdominal colectomy), hospital length of stay (LOS), ICU LOS, and discharge disposition were also collected.

Statistical Analyses and Development of the Severity Scoring System

Univariate analysis was performed to compare patients with and without fCDC. Continuous variables were summarized using mean (SD) and compared by Student's *t* tests for variables with normal distributions or summarized using median with interquartile range (IQR) and compared by Wilcoxon rank-sum tests for variables that were not normally distributed. Categorical variables were compared by Fisher's exact test.

The following four variables were included in our RSS: age greater than 70 years, WBC count equal to or greater 20,000/μL or equal to or less than 2,000/μL, cardiorespiratory failure (defined as *C. difficile* colitis–related vasopressor and/or mechanical

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TABLE 1. Proposed CDAD Severity Scoring System, Neal et al.[24]*

1–3 Points, Mild to Moderate Disease; 4–6 Points, Severe Disease; ≥7 Points, Severe Complicated Disease	
Criteria	**Points**
Immunosuppression and/or chronic medical condition	1
Abdominal pain and/or distention	1
Hypoalbuminemia (<3 g/dL)	1
Fever (>38.5°C)	1
ICU admission	1
CT scan with nonspecific findings of pancolitis, ascites, and/or bowel wall thickening	2
WBC count > 15,000 or <1.500 and/or band count > 10%	2
Creatinine 1.5-fold > baseline	2
Abdominal peritoneal signs	3
Vasopressors required	5
Mechanical ventilation required attributed to CDAD	5
Disorientation, confusion, or decreased consciousness	5

*This scoring system is for patients with a diagnosis of CDAD and is not yet validated.
CDAD: Clostridium difficile associated disease.

ventilation requirement), and diffuse abdominal tenderness on physical examination. These variables were based on consensus among experts and identified as risk factors for a complicated course (development of fCDC or mortality) by various studies.[7,9,11,13,16,18,22,27] The experts consisted of experienced general and acute care surgeons, gastroenterologists, and intensivists, all practicing at the MGH. They used a modified Delphi technique a priori and before any of the analysis was performed, to select the most pertinent risk factors among those described in the literature. To determine the effects of these four predictors, we performed a multivariable logistic regression model. Calibration of our system was investigated by the Hosmer-Lemeshow goodness-of-fit test. Discrimination was summarized by the area under the receiver operating curve (AUC) and the Brier score. Each variable in the system was assigned a point, proportional to its parameter estimate from the multivariable logistic regression model.[28] Subsequently, a risk score was calculated by adding up all the points. To compare the RSS to the only previously published scoring system,[24] we compared the *c* statistic from each scoring system. We also compared test characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) based on dichotomized scores. We then divided the risk scores into three risk categories and calculated how many patients were reclassified, as well as how many were correctly reclassified when using the new (MGH) scoring system. Statistical significance was considered at a two-sided $p < 0.05$. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). This study was approved by our institutional review board.

RESULTS

Cohort Characteristics

Of 821 patients with confirmed *C. difficile* colitis enrolled in our prospectively collected registry, 75 had incomplete records, were younger than 18 years, or were eventually not admitted to the hospital. The remaining 746 patients were included in this study. Forty-eight (6.4%) progressed to fCDC; Table 2 describes those with and without fCDC. Demographics were similar in the two groups. *C. difficile* colitis was more frequently recorded as the primary diagnosis in fCDC patients. As expected, all clinical parameters were worse in the fCDC group. In addition, fCDC patients were treated more frequently with intravenous metronidazole and vancomycin, while non-fCDC patients more frequently received oral metronidazole. The mortality was significantly higher in the fCDC group, and the ICU LOS was longer; however, the hospital stay was similar between the two groups.

Development of RSS

The four risk factors that were included in the multivariable logistic regression model are shown in Table 3. Each risk factor was assigned a number of points, proportional to its parameter estimate obtained from the logistic regression model. Based on the log (odds ratio) of each risk factor, age greater than 70 years was assigned 2 points, WBC count equal to or greater than 20,000/μL or equal to or less than 2,000/μL was assigned 1 point, cardiorespiratory failure was assigned 7 points, and diffuse abdominal tenderness on physical examination was assigned 6 points. With the use of this system, the discriminatory value of the MGH RSS was high, with an AUC (Fig. 1) of 0.98 (95% confidence interval [CI], 0.96–1). In addition, for the RSS, the Hosmer-Lemeshow goodness-of-fit test showed a *p* value of 0.78, while the Brier score showed a *p* value of 0.019. Table 4 describes the incidence of fCDC in our population according to the RSS. Based on the incidence rate, we used a value of 6 points as the threshold to distinguish low-risk (<6) from high-risk (≥6) patients.

Comparison of the RSS and Previously Published Severity Scoring System

We applied the previously published severity scoring system in our population. The AUC was 0.96 (95% CI, 0.93–0.99). Comparing the *c* statistics of the two systems showed a *p* value of 0.22. The previously published system used a value of 4 points as the cutoff for low risk (<4) versus high risk (≥4). The performance of both scoring systems was tested. This analysis shows a similar sensitivity (97.9%) but a higher specificity (88.4% vs. 46.4%), positive predictive value (36.7% vs. 11.2%), and negative predictive value (99.8% vs. 99.7%) for the RSS.

DISCUSSION

In this study, we present a severity scoring system for the purpose of detecting patients at risk for developing fCDC. With the goal of using a simplified system that can be easily remembered by clinicians and used at the bedside, we included four risk factors selected by an expert panel and based on previous studies.[7,12,29] The RSS successfully discriminates patients with CDI from those who have fCDC (AUC, 0.98). Calibration was low (Brier score, 0.019), indicating that the possibility of developing fCDC could be estimated accurately. A cutoff of 6 points was used to divide patients at high risk for developing fCDC; this classified 97.9% of the patients correctly. In combination with a high specificity (88.4%) and excellent negative

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TABLE 2. CDI Versus fCDC

Variable	CDI (n = 698)	fCDC (n = 48)	*p*
Demographics			
Age, mean (SD), y	66 (17.9)	70.6 (16.2)	0.064
Age ≥ 70 y, n (%)	323 (46.3)	27 (56.3)	0.18
Male, n (%)	334 (47.9)	28 (58.3)	0.16
Race, n (%)			0.84
Caucasian	601 (86.1)	42 (87.5)	
African American	32 (4.6)	1 (2.1)	
Asian	8 (1.1)	1 (2.1)	
Other	38 (5.4)	2 (4.2)	
Unknown	19 (2.7)	2 (4.2)	
Ethnicity, Hispanic, n (%)	27 (3.9)	1 (2.1)	0.80
CDI as primary diagnosis, n (%)	86 (12.3)	23 (47.9)	<0.0001
Admission source, n (%)			0.60
Home	434 (62.2)	25 (52.1)	
Nursing home	44 (6.3)	5 (10.4)	
OSH	125 (17.9)	11 (22.9)	
Rehabilitation	83 (11.9)	6 (12.5)	
Other	6 (0.9)	1 (2.1)	
Unknown	6 (0.9)	0	
Admitting service, n (%)			0.006
Surgery	144 (20.6)	20 (41.7)	
Medicine	536 (76.79)	28 (58.33)	
Obstetrics/gynecology	7 (1)	0	
Other/unknown	11 (1.6)	0	
Premedical history			
Recurrent C. difficile colitis (within last 6 mo), n (%)	143 (20.5)	12 (25)	0.47
Recent hospitalization (within last 2 mo), n (%)	347 (49.7)	27 (56.3)	0.38
Recent antibiotic use (within last 2 mo), n (%)	533 (76.4)	39 (81.3)	0.44
PPI use, n (%)	336 (48.1)	27 (56.3)	0.28
Immunosuppression and/or chronic medical condition, n (%)	586 (84)	36 (75)	0.25
ICU admission, n (%)	192 (27.5)	45 (93.8)	<0.0001
Clinical features			
WBC count, median (IQR), per μL	13.2 (9–19.3)	21.4 (15.6–33.8)	<0.0001
WBC count > 20,000 or <2,000/μL, n (%)	162 (23.2)	29 (60.4)	<0.0001
Neutrophil bands, median (IQR), %	8 (3–17)	18 (10.5–26)	<0.0001
Neutrophil bands > 10%, n (%)	125 (17.9)	30 (62.5)	<0.0001
Albumin, mean (SD), mg/dL	2.8 (0.7)	2.3 (0.6)	<0.0001
Albumin < 3g/dL, n (%)	310 (44.4)	40 (83.3)	<0.0001
Creatinine, median (IQR), mg/dL	1 (0.7–1.7)	1.4 (1.2–2.2)	0.0006
Creatinine 1.5-fold > baseline, n (%)	202 (28.9)	22 (45.8)	0.032
Fever, n (%)	62 (8.9)	9 (18.8)	0.003
Abdominal pain or distention on physical examination, n (%)	97 (13.9)	47 (97.9)	<0.0001
Peritoneal signs on physical examination, n (%)	1 (0.1)	31 (64.6)	<0.0001
Diffuse abdominal tenderness on physical examination, n (%)	80 (11.5)	47 (97.9)	<0.0001
Abnormal abdominal CT scan, n (%)*	161 (23.1)	38 (79.2)	<0.0001
Vasopressors required (*C. difficile* colitis related), n (%)	1 (0.1)	27 (56.3)	<0.0001
Mechanical ventilation required (*C. difficile* colitis related), n (%)	0	19 (39.6)	<0.0001
Cardiorespiratory failure, n (%)**	1 (0.1)	29 (60.4)	<0.0001
Mental status change, n (%)†	107 (15.3)	18 (37.5)	0.0003
Medical treatment			
Metronidazole PO, n (%)	374 (53.6)	18 (37.5)	0.041
Metronidazole IV, n (%)	399 (57.2)	46 (95.8)	<0.0001
Vancomycin PO, n (%)	493 (70.6)	45 (93.8)	0.002
Vancomycin IV, n (%)	255 (36.5)	28 (58.3)	0.009
Vancomycin PR, n (%)	29 (4.2)	19 (39.6)	<0.0001
Outcomes			
Mortality, n (%)	51 (7.3)	13 (27.1)	<0.0001
Total abdominal colectomy, n (%)	0	19 (39.6)	<0.0001
HLOS, median (IQR), d	11 (6–23)	11.5 (6–20.5)	0.61
ICU admission related to *C. difficile* colitis, n (%)	11 (1.6)	45 (93.8)	<0.0001
ICU LOS, median (IQR), d	0 (0–0)	4 (2–8.5)	<0.0001
Discharge disposition, n (%)			<0.0001
Home	302 (43.3)	11 (22.9)	
Deceased	51 (7.3)	13 (27.1)	
Nursing home	89 (12.8)	8 (16.7)	
Rehabilitation	226 (32.4)	16 (33.3)	
Other	13 (1.9)	0	
Unknown	17 (2.4)	0	

*Abnormal abdominal CT scan finding: positive for nonspecific findings such as pancolitis, ascites, bowel wall thickening, dilation.

**Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support.

†Mental status change: disorientation, confusion, or decreased consciousness.

HLOS, hospital LOS; IV, intravenous; PO, per oral; PPI, proton pump inhibitors; PR, per rectum.

predictive value (99.8%), this scoring system proves that it has the potential to be used at the bedside to safely rule out the possibility of fCDC. The positive predictive value of 36.7% is low and should be considered against the background of its estimation in a low-prevalence setting (6.4% of total cohort was diagnosed with fCDC).[30]

TABLE 3. Predictors of fCDC in the RSS Development Cohort

Variable	Odds Ratio	95% Confidence Interval	Points
Age > 70 y	3.80	1.14–13.68	2
WBC count ≥ 20,000/μL or ≤2,000/μL	1.81	0.54–6.05	1
Cardiorespiratory failure*	285	24–21,491	7
Diffuse abdominal tenderness	189	27–8,429	6

*Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support.

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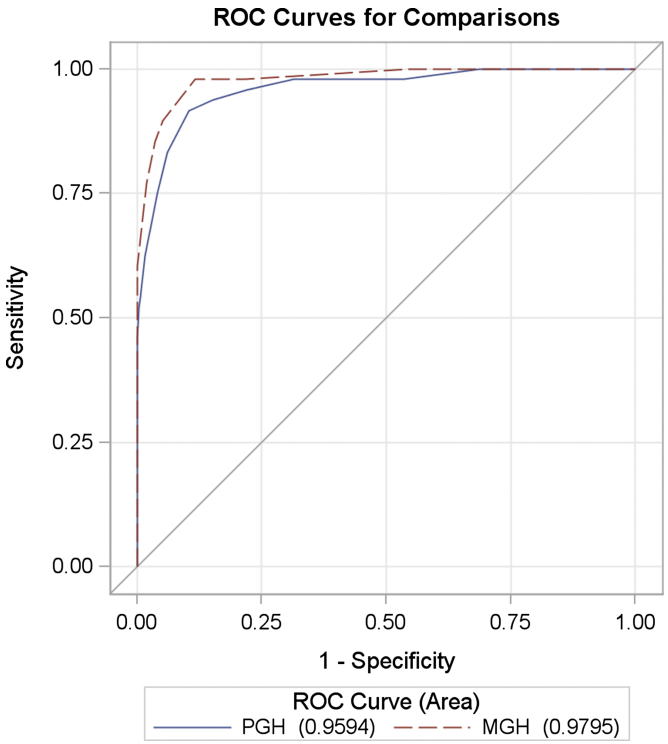

Figure 1. Receiver operating characteristic curves for the RSSs of fCDC (both RSS and previously published severity scoring system included).

Since the beginning of the 21st century, there have been many *C. difficile* outbreaks; the majority are caused by a newly discovered, hypervirulent strain, NAP1/BI/027.[31,32] This strain is associated with an increased severity of the CDI, resulting in a higher likelihood of fCDC (which carries significant morbidity and mortality).[33,34] Prediction rules to detect patients who are at risk for developing CDI and also to predict recurrent CDI are available.[35–40] Commonly used risk factors, such as age greater than 65 years, antibiotic use, and multiple comorbidities populate these prediction rules. Although many studies in the fCDC population have been published, describing risk factors of mortality[6,7,10,15,16,18,20,21] and recommending early intervention to prevent unfavorable outcomes,[7,9,13,16,22,23] systems to score the severity of fCDC are not common. Only one group has proposed such a system for severe, complicated *C. difficile* colitis.[24] Partially based on recommendations of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America,[1] they designed a system that weighs variables such as cardiorespiratory failure and mental status changes heavily, as well as an additional 10 variables. That system had never been tested or validated until now. The risk factors used in our RSS were based on the literature and derived by expert consensus. In a case-control study by Greenstein et al.,[12] risk factors for the development of fCDC were determined to be WBC count greater than 16,000/μL at therapy start, presence of inflammatory bowel disease, operative therapy in the last 30 days, and history of intravenous immunoglobulin therapy. In a similar but more recent study by Girotra et al.,[29] "red flags" for developing fCDC were age greater than 70 years, abdominal pain, and profound leukocytosis (>18,000/μL).

Upon comparison of our four-factor RSS with the 12-factor severity score system,[24] we found a nonsignificant difference in AUC and an equal sensitivity of 97.9%. The two systems are, therefore, similarly effective. However, the RSS has a higher specificity and positive predictive value despite its greater level of simplicity and is more likely to be adhered to. In addition, our analysis showed that when the two systems disagreed, 88.1% of the patients were correctly reclassified by our risk categories (data not shown).

A limitation of our study relates to the low number of patients with fCDC (48 patients, 6.4% of the cohort). It is because of this number that we were unable to divide our cohort into a development and validation cohort; external validation is necessary. Furthermore, the RSS was based on four predictors, which were chosen by an expert panel and derived from previous data, instead of a statistical model. Again, the low number of cases prevented an exhaustive risk factor analysis by stepwise logistic regression. Even with the use of only four risk factors, the 95% CIs are particularly wide, attesting to the limited sample size. Although fCDC is becoming more frequent than in the past, its frequency is still low and multicenter studies will be needed to accrue large sample sizes. An additional limitation pertains to the timing of RSS, which was only calculated at one time point. If the WBC or abdominal examination result changes, the RSS predictability may change as well. Therefore, a low probability score should not put the probability of future deterioration completely at rest. It is notable that our score does not include CT images. For most patients with suspected fCDC, a CT scan will be ordered. However, in our analysis, it was found that such images contributed only a very small margin to the accuracy of the RSS (data not shown here), and therefore, it was elected to exclude CT findings as a risk factor. This buttresses the usual teaching that the physiology rather than the radiology is important for clinical decision making, while it has the added benefits that imaging is not required

TABLE 4. Risks of fCDC by the RSS

	Observed fCDC (Development Cohort, Total n = 746)	
Score	**Number**	**Percentage**
0	0/249	0
1	0/70	0
2	1/229	0.4
3	0/70	0
6	4/49	8.2
7	2/13	15.4
8	4/16	25
9	8/21	38.1
13	5/5	100
14	10/10	100
15	5/5	100
16	9/9	100

Patients with scores 6 points or greater were classified as high risk.

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when calculating the risk, thus lowering the threshold of using the RSS, whereas it also saves costs.

In conclusion, we designed a valid and reliable severity scoring system for fCDC that can be used at the bedside to score the severity of disease and identify patients at risk for developing fCDC. A score greater than 6 points identifies patients at high risk for fCDC. These patients should be monitored aggressively and considered for surgical intervention. Because the score can be calculated easily at the bedside, based on commonly used variables, we expect that clinicians can triage patients to appropriate levels of care and, if needed, the operating room. The next step will be to externally validate our RSS to allow widespread implementation.

AUTHORSHIP

G.M.v.d.W., P.J.F., Y.C., M.A.D.M., and G.C.V. contributed to the conception and design of this study. G.M.v.d.W., C.C., and M.S. acquired the data. G.M.v.d.W. Y.C., I.B.S., D.D.Y., D.R.K., and G.C.V. conducted the analysis and interpretation of data. G.M.v.d.W., G.C.V., and P.J.F. drafted the article. Y.C., C.C., M.S., I.B.S., D.D.Y., D.R.K., M.A.D.M., P.J.F., and G.C.V. revised the article. All authors provided the final approval.

DISCLOSURE

The authors declare no conflicts of interest.

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