Association of Prolonged Emergency Department Length of Stay with Adverse Events in Patients with Non-ST-Elevation Acute Coronary Syndrome

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Objective: To study the association between prolonged emergency department length of stay (EDLOS) and in-hospital adverse events in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods: In this retrospective cohort study, the medical records of 738 patients diagnosed with NSTE-ACS and admitted to the emergency department (ED) from 1 January 2013 to 31 December 2019 were reviewed. The patients were categorized into groups with EDLOS < 4 hours and EDLOS ≥ 4 hours, and baseline characteristics, clinical presentation, Killip classification, Global Registry of Acute Coronary Events score, investigations, use of the European Society of Cardiology (ESC) 0/1-hour and 0/3-hour algorithms, and treatments in the ED were compared between the groups. The associations of in-hospital adverse events with EDLOS were examined using univariate logistic regression.

Results: Four hundred and twenty-three (57.3%) patients had an EDLOS of ≥ 4 hours, and the median (IQR) EDLOS was 4.48 hours (3.03, 6.20 hours). EDLOS ≥ 4 h was associated with a prolonged time to receive P2Y$_{12}$ inhibitors and anticoagulants ($P < 0.001$). However, the two groups showed no significant differences in in-hospital adverse events (congestive heart failure [CHF], shock, stroke or transient ischemic attack [TIA], major bleeding, arrhythmia, recurrent myocardial infarction, death, and one or more adverse events). Nevertheless, a non-significant trend for a higher rate of adverse events (CHF, shock, major bleeding, arrhythmia, recurrent myocardial infarction, death, and one or more adverse events) with longer EDLOS was observed in the subgroup of patients who received diuretic or antiarrhythmic drugs, ventilator or bilevel positive airway pressure support, oxygen support, or inotropic/vasopressor drugs in the ED.

Conclusion: Prolonged EDLOS showed a significant association with longer times to receive P2Y$_{12}$ inhibitors and anticoagulants. However, the EDLOS < 4 hour and EDLOS ≥ 4 hour groups of patients with NSTE-ACS showed no significant differences in the rates of in-hospital adverse events. Patients who receive cardiovascular medications in the ED or are on respiratory support should be hospitalized as soon as practically possible. Proper use of the 0/1-hour algorithm over the 0/3-hour algorithm without unnecessary repeated cardiac troponin tests in the ED could reduce the EDLOS in patients with NSTE-ACS.

Keywords: emergency department, length of stay, acute coronary syndrome, adverse events

Introduction

Non-ST-segment elevation acute coronary syndromes (NSTE-ACS) encompasses unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI).1 Most patients with NSTE-ACS often require prolonged emergency department (ED) stays because of delays in the diagnosis attributable to cardiac troponin testing to distinguish between NSTEMI and UA. However, patients with ST-segment elevation myocardial infarction (STEMI) can be diagnosed from clinical symptoms and electrocardiography (ECG) results without laboratory tests.2 Thus, these patients can be admitted directly to the Coronary Care Unit (CCU) or cardiac catheterization laboratory with a short emergency department length of stay (EDLOS). The 2015 European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommend testing for high-sensitive cardiac troponin (hs-cTnT) to rule out or rule in NSTEMI.3 However, renal dysfunction and the time from onset of chest pain are confounders of cardiac troponin evaluations;4
therefore, repeated troponin testing may be performed following the ESC 0/1-hour and 0/3-hour algorithms for the diagnosis of NSTEMI or for ruling out NSTEMI. Since the ESC 0/1-hour algorithm was the newer algorithm in the ED of Songklanagarind Hospital, the emergency physicians were more familiar with the 0/3-hour algorithm than the 0/1-hour algorithm. Using the 0/3-hour algorithm more often than the 0/1-hour algorithm and performing unnecessary repeated troponin T tests in patients with non-chronic kidney disease (CKD) with an initially high abnormal result can lead to a prolonged EDLOS. In addition, the limitations associated with the hospital admission capacity or the existing number of patients in the ED can affect the admission waiting times and thereby cause ED overcrowding.

EDLOS directly affects ED overcrowding and is a key indicator to monitor ED performance. Overcrowding reduces the effective capacity for the management and treatment of critically ill patients in the ED, and was reported to be associated with the rates of hospital admission and 10-day mortality. Patients who spend over 8 hours in the ED are less satisfied with the hospital environment than those who spend less than 4 hours. The National Health Service of the United Kingdom announced its intention to improve the quality of ED care by instituting a maximum EDLOS of 4 hours. In addition, patients who developed intensive care unit (ICU) complications had a longer EDLOS than those who did not. Thus, the aim of this study was to determine the association of prolonged EDLOS with adverse events in patients with NSTE-ACS.

**Materials and Methods**

**Study Design and Setting**

A retrospective cohort study was conducted in the ED of Songklanagarind Hospital, a teaching hospital and a tertiary care medical center with a capacity of 850 beds and an ED volume of over 45,000 patient visits per year. Data were collected from January 2013 to December 2019. Patients older than 18 years with a final diagnosis of UA or NSTEMI who were admitted to the hospital from the ED were enrolled. The exclusion criteria were pregnancy, referrals from other hospitals, referrals to other hospitals before discharge, incomplete data, normal coronary angiography or non-significant results in coronary angiography, a diagnosis of secondary myocardial infarction, and presentation with cardiac arrest or cardiac arrest in the ED.

**Data Collection**

The data were collected from the electronic medical records by searching for the following ICD-10 codes: I20.0, unstable angina; I20.9, angina pectoris; I21.4, NSTEMI; I21.9, acute myocardial infarction; and I24.9, acute ischemic heart disease. The data included baseline patient characteristics, underlying diseases, final diagnosis, EDLOS, vital signs, ST-segment deviation on ECG, elevation of cardiac enzymes in the ED, initial hs-cTnT level, number of troponin T tests performed, use of ESC algorithms (0/1-hour and 0/3-hour when hs-cTnT testing was performed twice in the ED), creatinine level, estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI equations, the Global Registry of Acute Coronary Events (GRACE) score, Killip class, oxygen use, mechanical ventilation/bilevel positive airway pressure (BiPAP) use, inotropic drug or vasopressor use, antiarrhythmic drug use, diuretic drug use, and initial treatment in the ED with aspirin or P2Y12 inhibitors. The patients were categorized into the EDLOS ≥ 4 hour or EDLOS < 4 hour groups.

A review of the literature revealed no study that had similar outcomes as the present study. One study that closely resembled the present study enrolled 497 patients during the study period but did not show statistically significant outcomes. Another previous study reported that approximately 19% of all patients with NSTE-ACS had one or more adverse events. We hypothesized that in the EDLOS < 4-hour group, 11% of the patients with NSTE-ACS would experience one or more adverse events.

We calculated the sample size from the following formula to test two independent proportions (two-tailed test):

\[
n_1 = \left[ \frac{z_{1-\alpha}^2 \sqrt{\hat{p} \hat{q} (1 + \frac{1}{r})} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2
\]

\[
\Delta = \sqrt{\hat{p} \hat{q} (1 + \frac{1}{r}) + p_1 q_1 + \frac{p_2 q_2}{r}}
\]
\[ r = \frac{n_2}{n_1}, q_1 = 1 - p_1, q_2 = 1 - p_2 \]

\[ \bar{p} = \frac{p_1 + p_2 r}{1 + r}, \bar{q} = 1 - \bar{p} \]

\[ Z_{\alpha/2} = 95\% \text{ confidence level} = 1.959964 \]
\[ Z_{\beta} = \text{Type II error (Beta [\beta] = 0.20, Z [0.800])} = 0.841621 \]

\( P_1 \) was set at 11\%, which was the proportion of patients expected to have in-hospital adverse events in the EDLOS < 4 hour group.

\( P_2 \) was set at 19\%, which was the proportion of patients expected to have in-hospital adverse events in the EDLOS ≥ 4 hour group.

\( n_1 \) was the number of patients in the EDLOS < 4 hour group
\( n_2 \) was the number of patients in the EDLOS ≥ 4 hour group

Ratio (\( r \)) = \( n_2/n_1 = 1 \)

Sample size: Group 1 (\( n_1 \)) = 312; Group 2 (\( n_2 \)) = 312.

**Outcome Measurements**

The primary outcome was the association of prolonged EDLOS with the following in-hospital adverse events in patients with NSTE-ACS: 1) CHF, 2) shock, 3) stroke or TIA, 4) major bleeding, 5) arrhythmia (new-onset atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or cardiac arrest), 6) recurrent myocardial infarction, and 7) death. The secondary outcomes were the associations between EDLOS and hospital length of stay (LOS), total hospitalization cost, and the time to receive P2Y\(_{12}\) inhibitors and anticoagulants.

**Statistical Analysis**

The sample size of the study population was calculated using the n4Studies program to test two independent proportions. A total of 738 patients were enrolled: 423 in the EDLOS ≥ 4 hour group and 315 in the EDLOS < 4 hour group. The confidence level was set at 95\% and the power was 80\%. All data were entered into EpiData Manager (version 4.4.2.1), and statistical analyses were conducted using R software (version 3.5.1). Continuous variables are presented as mean and median values, while discrete variables are presented as percentage values. Comparisons between the continuous variables in the two groups were performed using the Student’s t test or Wilcoxon rank-sum test, while comparisons between discrete variables in the two groups were performed using the Pearson’s chi-square test or Fisher’s exact test. The EDLOS and subgroup adverse event rates were analyzed with a chi-square test. A P-value less than 0.05 was considered statistically significant.

**Compliance with Ethical Requirements**

The ethics committee of Prince of Songkla University approved this study. The institutional review board of Prince of Songkla University is affiliated with the International Conference on Harmonization in Good Clinical Practice. In accordance with the institutional review board protocol for waiver of informed consent, the requirement for consent was waived because the participants had no more than minimal risk and standard treatment procedures were provided. All research information was stored as confidential data in an encrypted file with password and data access was limited to only the authors. The ethics registration number was REC.63–453-20-4. This study was conducted in accordance with the ethical principles of the declaration of Helsinki.

**Results**

**Patient Demographics**

A total of 1654 patients were classified under ICD-10 codes I20.0, I20.9, I21.4, I21.9, and I24.9. The number of patients who met the enrollment criteria with a definite diagnosis of NSTE-ACS was 738, of which 71.3\% were diagnosed as having NSTEMI. The median (IQR) EDLOS was 4.48 hours (3.03, 6.20 hours). The EDLOS < 4 hour group included
315 (42.7%) patients and the EDLOS ≥ 4 hour group included 423 patients (57.3%). The baseline characteristics of the patients are shown in Table 1.

The two groups showed significant differences in five baseline characteristics: oxygen saturation (P = 0.025), elevated cardiac enzyme levels in the ED (P = 0.014), number of hs-cTnT tests and use of ESC algorithms, oxygen use (P < 0.001), and ventilator/BiPAP use (P = 0.032). Patients with low oxygen saturation and oxygen or ventilator/BiPAP use were likely to be in the short EDLOS group, and patients who underwent repeated hs-cTnT tests were likely to have elevated cardiac enzyme levels in the ED. However, the GRACE score was not significantly different between the two groups. The median (IQR) values were 118 (91, 144) and 119 (95, 5143) (P = 0.537).

Table 1 Baseline Characteristics

| Patient Number | EDLOS < 4 h | EDLOS ≥ 4 h | Total | P-value |
|----------------|------------|-------------|-------|---------|
| Diagnosis of NSTEMI (vs UA) | 229 (72.7) | 297 (70.2) | 526 (71.3) | 0.512 |
| Age, median (IQR) | 67 (38.77) | 69 (61.78) | 68 (60.78) | 0.084 |
| Male | 209 (66.3) | 270 (63.8) | 479 (64.9) | 0.528 |
| Previous CAD or MI | 177 (56.2) | 256 (60.5) | 433 (58.7) | 0.269 |
| Hypertension | 213 (67.6) | 297 (70.2) | 510 (69.1) | 0.500 |
| Diabetes mellitus | 121 (38.4) | 172 (40.7) | 293 (39.7) | 0.588 |
| Dyslipidemia | 186 (59) | 261 (61.7) | 447 (60.6) | 0.513 |
| Systolic blood pressure, median (IQR) | 146 (125,166) | 146 (126,168) | 146 (126,168) | 0.534 |
| Pulse rate, median (IQR) | 82 (70.98) | 82 (69.5,94.5) | 82 (70.96) | 0.585 |
| Oxygen saturation, median (IQR) | 98 (95,100) | 98 (96.5,100) | 98 (96,100) | 0.025 |
| Creatinine, median (IQR) | 1.1 (0.9,1.6) | 1.1 (0.9,1.7) | 1.1 (0.9,1.6) | 0.365 |
| eGFR, median (IQR) | 64.9 (36.5,86.5) | 61.4 (33.83,7) | 63.1 (34.5,85) | 0.226 |
| ST-segment deviation on ECG | 170 (54) | 201 (47.5) | 371 (50.3) | 0.097 |
| Elevated cardiac enzymes | 261 (82.9) | 378 (89.4) | 639 (86.6) | 0.014 |
| Number of troponin tests in the ED | <0.001 |
| Non-repeating in ED (0 h) | 274 (87) | 125 (29.6) | | |
| Repeating hs-cTn with 0/1 h algorithm | 2 (0.6) | 5 (1.2) | | |
| Repeating hs-cTn with 0/3 h algorithm | 39 (12.4) | 293 (69.3) | | |
| Initial hs-cTnT in repeating group | | | 1 |
| <5-fold the ULN in the initial test | 23 (56.1) | 164 (55) | 187 (55.2) | 0.063 |
| ≥5-fold the ULN in the initial test | 18 (43.9) | 134 (45) | 152 (44.8) | |
| Killip class | | | | |
| I | 202 (64.1) | 295 (69.7) | 497 (67.3) | |
| II | 31 (9.8) | 52 (12.3) | 83 (11.2) | |
| III | 76 (24.1) | 70 (16.5) | 146 (19.8) | |
| IV | 6 (1.9) | 6 (1.4) | 12 (1.6) | |
| GRACE score, median (IQR) | 118 (91,144) | 119 (95,5143) | 119 (94,144) | 0.699 |
| Initial treatment in ED | | | | |
| Aspirin | 287 (91.1) | 383 (90.5) | 670 (90.8) | 0.893 |
| P2Y12 inhibitor | 194 (61.6) | 280 (66.2) | 474 (64.2) | 0.225 |
| Diuretic drug | 93 (29.5) | 105 (24.8) | 198 (26.8) | 0.180 |
| Antiarrhythmic drug | 5 (1.6) | 7 (1.7) | 12 (1.6) | 1 |
| Ventilator Support/BiPAP | 34 (10.8) | 26 (6.1) | 60 (8.1) | 0.032 |
| Oxygen support | 128 (40.6) | 105 (24.8) | 233 (31.6) | < 0.001 |
| Inotropic/vasopressor drugs | 11 (3.3) | 6 (1.4) | 17 (2.3) | 0.108 |

Note: Data are presented as n (%) unless otherwise indicated.

Abbreviations: ED, emergency department; EDLOS, emergency department length of stay; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; IQR, interquartile range; CAD, coronary artery disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; ED, emergency department; hs-cTn, high-sensitivity cardiac troponin; ULN, upper limit of normal; GRACE, Global Registry of Acute Coronary Events; BiPAP, bilevel positive airway pressure.
We found that in the EDLOS ≥ 4 hour group (n = 423), 298 (70.5%) patients had repeated hs-cTnT tests. Only 1.2% of patients in this group were evaluated with the 0/1-h algorithm for repeated cardiac troponin measurements. Ninety-seven (32.6%) patients who had repeated hs-cTnT tests in the ED showed CHF or cardiogenic shock (Killip class> 1) (Figure 1). Similarly, 134 (45%) patients who underwent repeated hs-cTnT tests in the ED showed an initial hs-cTnT result that was ≥ 5-fold the upper reference limit, and 52% of the 134 patients had an eGFR ≥ 60 mL/min/1.73 m² (Figure 2).

**Patient Outcomes**

No significant differences in the incidence of the following in-hospital adverse events were observed between the EDLOS < 4 hour and EDLOS ≥ 4 hour groups: CHF (7% vs 6.4%, P = 0.861), shock (7.3% vs 6.1%, P = 0.636), stroke or TIA (1.3% vs 0.9%, P = 0.729), major bleeding (0.6% vs 0.5%, P = 1.00), arrhythmia (9.2% vs 8.3%, P = 0.754), recurrent myocardial infarction (1.9% vs 2.4%, P = 0.866), death (4.8% vs 4.3%, P = 0.881), and one or more adverse events (15.6% vs 15.1%, P = 0.956) (Figure 3).

However, the subgroup of patients who received diuretic or antiarrhythmic drugs, ventilator support or BiPAP, oxygen support, or inotropic/vasopressor drugs at the ED showed a non-significant trend for a higher rate of the following adverse events with a longer EDLOS: CHF (6.4% vs 12.2%, P = 0.12), shock (10.8% vs 12.9%, P = 0.71), major bleeding (0.6% vs 1.4%, P = 0.63), arrhythmia (13.5% vs 15%, P = 0.83), recurrent myocardial infarction (3.2% vs 4.8%, P = 0.689), death (7.7% vs 10.2%, P = 0.572), and one or more adverse events (19.8% vs 27.2%, P = 0.17) (Figure 4).

Analyses of the secondary outcomes showed significant intergroup differences in the time to receive P2Y₁₂ inhibitors (median, 150 min vs 305 min; P < 0.001) and the time to receive anticoagulants (median, 178 min vs 333 min; P < 0.001). However, there were no significant differences in hospital LOS (median, 5 days vs 5 days; P = 0.564) and total hospital cost (median, 1546 USD vs 1449 USD; P = 0.903) (Table 2).

**Discussion**

The purpose of this study was to determine the association of prolonged EDLOS with adverse events in patients with NSTE-ACS. Our findings indicated that there is no significant differences in any adverse events between the EDLOS < 4 hour and
EDLOS ≥ 4 hour groups, possibly due to the small sample size or the lower number of adverse events in comparison with the reference study by D Brieger et al.\textsuperscript{14}

However, a non-significant trend toward a longer EDLOS was observed in the subgroup of patients who were treated with specific medications and treatment modalities at the ED. The intergroup differences between the rates of events were the highest for CHF and one or more adverse events.

Our study shared some common findings with the study by C.-C. Chen et al.\textsuperscript{12} which is the only previous study on the effect of EDLOS on clinical outcome in NSTE-ACS patients. Their study also showed no significant difference in the
clinical outcomes between patients with NSTE-ACS without profound shock and CCU waiting times of <12 or >12 h. Their clinical outcomes of interest were hospital mortality, gastrointestinal bleeding and stroke during hospitalization, and hospital length of stay. Our study included more clinical outcomes, which represents a point of difference between the two studies. Although our findings showed no significant difference, they highlighted some important trends worth further investigation, as mentioned above. A larger population study can be expected to yield more statistically significant results in this regard.

Our findings suggested that patients with NSTE-ACS who were treated with cardiovascular medications such as diuretic, antiarrhythmic, or inotropic/vasopressor drugs or were on respiratory support in the ED should be hospitalized as soon as practically possible. These patients should be closely monitored for adverse events in the ward or CCU.

Among the secondary outcomes, prolonged time to receive P2Y$_{12}$ inhibitors and anticoagulants was associated with a prolonged EDLOS because both medications must be administered initially by an internal Medicine physician or cardiologist after diagnosis is confirmed or after admission from the ED. According to the 2020 ESC guideline, initiation of anticoagulants should be started at the time of diagnosis. Moreover, while the timing of P2Y$_{12}$ inhibitor loading in patients undergoing percutaneous coronary intervention is debatable, a meta-analysis by Komosa et al reported that early loading of clopidogrel in patients with NSTE-ACS resulted in a risk reduction of 22% for major adverse cardiac events at 30 days. Similarly, administration of an anticoagulant is effective in reducing ischemic events in patients with NSTE-ACS. Since early CAG as per the recommendations could not be performed on every high-risk NSTE-ACS patient due to our

**Table 2 Secondary Outcomes**

|                  | EDLOS < 4 h (n = 315) | EDLOS ≥ 4 h (n = 423) | P-value   |
|------------------|-----------------------|-----------------------|-----------|
| Hospital length of stay (days), median (IQR) | 5 (4.9)               | 5 (4.8)               | 0.564     |
| Time to receive P2Y$_{12}$, median (IQR)    | 150 (105,195)         | 305 (225,390)         | <0.001    |
| Time to receive anticoagulant, median (IQR) | 178 (130,234)         | 333 (250,430)         | <0.001    |
| Hospital cost (USD), median (IQR)           | 1546 (692,5109)       | 1449 (676,5165)       | 0.903     |

*Abbreviations: EDLOS, emergency department length of stay; IQR, interquartile range.*

Figure 4 Subgroup analysis of the association between the EDLOS and in-hospital adverse events in patients who were treated at the ED with diuretic drugs or antiarrrhythmic drugs, ventilator support or BiPAP, oxygen support, or inotropic/vasopressor drugs. **Abbreviations:** EDLOS, emergency department length of stay; CHF, congestive heart failure; stroke (hemorrhagic or ischemic stroke); TIA, transient ischemic attack; Re-MI, recurrent myocardial infarction.
limited hospital resources, the appropriate implementation of medical strategies may play a larger role in treatment, and the earliest possible time of all necessary medications should be more beneficial to the patients.

Our research also provided some insights that can improve the quality of hospital management. A high rate of repeated hs-cTnT tests was observed in patients who had normal to mild CKD (eGFR ≥ 60) and showed highly abnormal hs-cTnT results (>5-fold the upper limit of normal) at the initial test. Patients in this group should already have a diagnosis of NSTEMI and treatment should be initiated, or the patients should be admitted to the CCU without repeated troponin T testing in the ED. Our study also found that the 0/1-hour algorithm was used less in our ED. Badertscher et al reported that the 0/1-hour algorithm provided safety similar to that of the 0/3-hour algorithm. Therefore, a repeated troponin T test at 3 hours in patients without CKD or patients who had already presented with chest pain >1 hour from the onset will lead to ED crowding. More practical use of the 0/1-hour algorithm could decrease EDLOS by about 2 hours.

Unnecessary repeated troponin T testing leads to ED crowding, which is associated with unfavorable consequences for patients with ACS, including psychosocial problems and lower management quality. Increased crowding at the time of ED admission was associated with poorer perceptions of interpersonal care among patients with suspected ACS, which may eventually affect their satisfaction with emergency care. Similarly, crowding was also significantly associated with prolonged absolute (p < 0.001) and, particularly, relative non-laboratory time (63.3%–71.3%, p < 0.001). Crowding also caused lower utilization of rapid algorithms (p = 0.009) and increased the number of additional hsTnT measurements after diagnosis (p = 0.001). Thus, we suggest using local clinical practice guidelines (CPGs) in hospitals to reduce EDLOS in patients with NSTE-ACS. Even though our hospital was a teaching hospital and a tertiary care medical center, operating without a CPG resulted in inappropriate management. Therefore, CPGs should be developed according to each hospital’s resources and capabilities.

Limitations
This study has several limitations. First, this study had a small sample size. Second, this is a retrospective study conducted at a single center. Third, we focused only on the clinical outcome. The relationship of confounding factors for EDLOS, such as the time of chest pain presentation and ED crowding, were not included in the statistical analysis.

Conclusions
Prolonged time to receive P2Y12 inhibitors and anticoagulants showed a significant association with prolonged EDLOS ≥ 4 hours (P < 0.001). However, the EDLOS < 4 hour and EDLOS ≥ 4 hour groups showed no significant differences in the rates of in-hospital adverse events for patients with NSTE-ACS. Patients who receive cardiovascular medications or are on respiratory support in the ED should be hospitalized as soon as practically possible. Proper use of the 0/1-hour algorithm over the 0/3-hour algorithm without unnecessary repeated cardiac troponin tests in the ED could reduce the EDLOS in patients with NSTE-ACS.

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

Disclosure
The authors have no conflicts of interest to report for this work.
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