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Comparisons of potential values of D-dimer and the neutrophil-to-lymphocyte ratio in patients with suspected acute aortic syndrome

Haixia Zhang, M.M. *, Ning Yuan, M.M., Jie Guo, M.M., Min Hou, M.M. *

Department of Laboratory Medicine, Tianjin Chest Hospital, 261 South Taierzhuang Road, Tianjin 300222, China

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ABSTRACT

Objectives: This study aimed to investigate and compare the discriminative performance and clinical utility of D-dimer and the neutrophil-to-lymphocyte ratio (NLR) in the early differential diagnosis of acute aortic syndrome (AAS).

Methods: The consecutive patients presenting to Tianjin Chest Hospital for suspected AAS were retrospectively investigated between June 2018 and December 2021. The baseline values of D-dimer and NLR were analyzed and compared in the study population. The discriminative ability of D-dimer and NLR was illustrated and compared using the area under the receiver operating characteristic (ROC) curve (AUC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Clinical utility was evaluated by means of decision curve analysis (DCA).

Results: In the study period, a total of 697 participants suspected of having AAS were enrolled and 323 had a final diagnosis of AAS. The baseline level of NLR as well as D-dimer was higher in patients with AAS. The use of NLR showed excellent overall diagnostic performance for AAS with a comparable AUC to that of D-dimer (0.845 vs. 0.822, $P > 0.05$). The reclassification analyses further confirmed that NLR had better discriminative properties for AAS with a significant NRI of 66.1% and IDI of 12.4% ($P < 0.001$). Moreover, NLR provided higher net benefit than D-dimer as shown by DCA. Similar results were observed in subgroup analyses according to the different classes of AAS.

Conclusions: NLR outperformed D-dimer with improved discriminative performance and superior clinical utility in identifying AAS. As a more readily available biomarker, NLR may be a reliable alternative to D-dimer for the screening of suspected AAS in clinical practice.

1. Introduction

Acute aortic syndrome (AAS) comprises a complex and potentially deadly group of cardiovascular emergencies with poor outcomes, including classic aortic dissection (AD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU) [1-5]. Given the time-dependent high mortality of AAS after occurrence and its severe complications [1,3,4,6-9], the early and rapid diagnosis of AAS is essential for prompt and appropriate interventions to improve survival and prognosis in specialized cardiovascular centers [5,7].

AAS is relatively rare and often presents with a variety of non-specific signs and symptoms, many of which may overlap with other more prevalent conditions, such as acute coronary syndrome, pulmonary embolism (PE), muscle-skeletal pains, gastrointestinal diseases and so on [3-5,7,10]. Hence, the definitive diagnosis of AAS is often difficult [3,9,11].

When clinical suspicion of AAS is present, advanced imaging modalities with excellent diagnostic accuracy, such as echocardiography, computed tomography angiography (CTA), or magnetic resonance imaging, are usually necessary to confirm or exclude the diagnosis of an AAS [3,7,12]. On the other hand, laboratory tests have a great potential for the early differential diagnosis of AAS because of widespread availability, rapidity, noninvasiveness, low-cost, and no risk of radiation exposure, allergy or kidney injury [1,7,12].

Abbreviations: NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; ROC, receiver operating characteristic; AUC, the area under the ROC curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; DCA, decision curve analysis; AD, aortic dissection; IMH, intramural hematoma; PAU, penetrating aortic ulcer; PE, pulmonary embolism; CTA, computed tomography angiography; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; FIB, fibrinogen; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; ALT, alanine aminotransferase; AST, aspartate transaminase; Glu, glucose; CHO, cholesterol; TG, triglyceride; Cr, creatinine; hs-CRP, high sensitivity C-reactive protein; hs-cTnT, high sensitivity cardiac troponin T; NLR/PLR, negative/positive likelihood ratios; NPV/PPV, negative/positive predictive values; CI, confidence interval; AMI, acute myocardial infarction..

* Corresponding authors.
E-mail addresses: zhanghaixia_2005@163.com (H. Zhang), houmin6997@sina.com (M. Hou).

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Although highly accurate biomarkers are not yet available for AAS, D-dimer, a degradation product of cross-linked fibrin, is a widely accepted laboratory biomarker for AAS with high sensitivity [1,3,5,6,12]. Furthermore, as an easily acquired blood parameter, the neutrophil-to-lymphocyte ratio (NLR) is thought to be an inflammatory biomarker associated with AD [3,13-15] and shows potential to be a clinically useful biomarker for identifying AD [16]. However, there is a dearth of data about discriminatory performance of NLR for AAS. Moreover, there are few studies in the available literature comparing the diagnostic performance and clinical utility of D-dimer and NLR in patients with suspicion of AAS. Thus, we designed and conducted the following study to focus on these issues.

2. Materials and methods

2.1. Study population

The consecutive patients presenting to Tianjin Chest Hospital for suspected AAS were retrospectively investigated between June 2018 and December 2021. The inclusion criteria included: (1) the presence of the suspected symptoms or signs of an AAS: shortness of breath, chest tightness, chest/precordial discomfort or pain, abdominal/back/lumbar/lower extremity pain, vomiting, dizziness, syncope, loss of consciousness and so on, as reported by the clinical guidelines and literature [1,17,18]; and (2) the asymptomatic subjects with a clinician-defined suspicion of AAS, who were initially discovered incidentally by clinicians in local hospitals during health check or examinations for other indications, and required advanced imaging techniques for further definitive diagnosis in our hospital [7,11]. The exclusion criteria were: (1) patients with an already confirmed diagnosis before presenting to our hospital; (2) some diseases, such as malignancies or hematologic disorders [16], or (3) insufficient laboratory or clinical information. The selection process for the study population was shown in Fig. 1.

According to the Stanford classification scheme [1,7], any AD involving the ascending aorta was defined as type A AD, whereas dissection not involving the ascending aorta as type B AD. Based on time course suggested by the latest guidelines [1], AD is divided into acute (<14 days), sub-acute (15–90 days), and chronic (>90 days) AD.

Conclusive diagnosis was made on the basis of typical clinical manifestations, chest X-ray, electrocardiography, echocardiography, coronary angiography, aortic angiography, or CTA by specialized clinicians, who were blinded to the study purpose.

The study complied with the Declaration of Helsinki. This study was approved by the ethics committee of Tianjin Chest Hospital (approval No. 2022LW-002) with a waiver of informed consent due to the retrospective study design.

2.2. Methods and data collection

The peripheral venous blood was collected from each participant before any therapeutic intervention and was immediately sent to the laboratory. Next, the 3.2% sodium citrate- anticoagulated whole-blood specimens were further processed into plasma by centrifugation at 2301*g* for 15 min according to the standard operating procedure. Plasma D-dimer levels were detected by means of immunoturbidimetric assay on a fully automated coagulation analyzer (STA-R Max, Diagnostica Stago, France), with a detection range of 0.22–20 μg/mL. In the meantime, the complete blood cell counts were measured in EDTA-K_2-anticoagulated whole-blood specimens using a fully automated hematology analyzer (XN-9000, Sysmex Corp., Hyogo, Japan). The following hematological parameters were obtained and analyzed: white blood cell (WBC) count, the neutrophil count, the lymphocyte count, hemoglobin (Hb) level, and platelet (PLT) count. The neutrophil-to-lymphocyte ratio (NLR) was computed as follows: the neutrophil count / the lymphocyte count.

Other blood test data were also collected for this study, including fibrinogen (FIB), creatine kinase (CK), creatine kinase MB isoenzyme

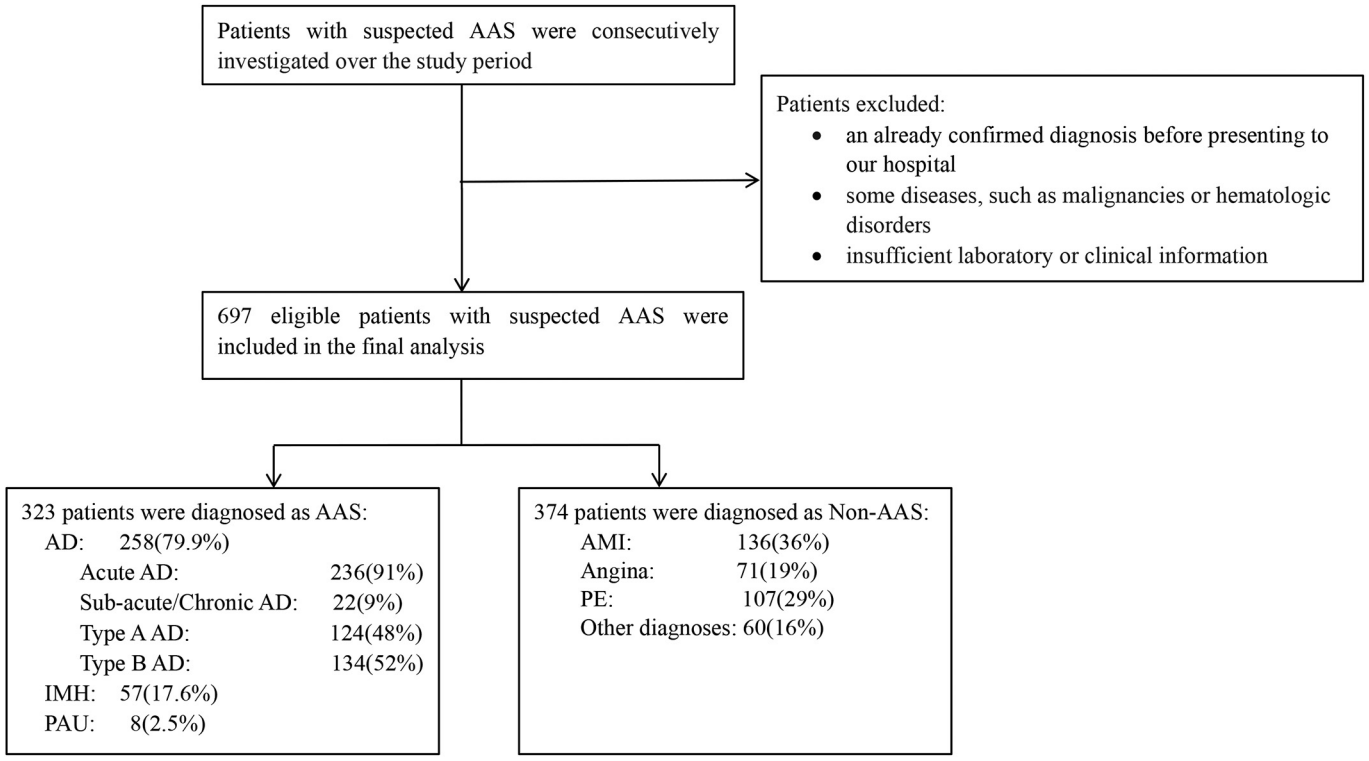

Fig. 1. The flow diagram of the study. AAS, acute aortic syndrome; AD, aortic dissection; IMH, intramural hematoma; PAU, penetrating aortic ulcer; AMI, acute myocardial infarction; PE, pulmonary embolism.

Table 1
Baseline characteristics of study participants in the AAS and Non-AAS groups.

Characteristics	AAS (n = 323)	Non-AAS (n = 374)	χ^2/Z	P-value
Gender [male, n (%)]	253(78)	218(58)	31.765	0.000[a]
Age(years)	59(47–66)	65(56–72)	−6.730	0.000[b]
Duration from symptom onset to visit (days)	0.50(0.29–2.00)	3.0(0.5–10.0)	−7.319	0.000[b]
Presenting symptoms [pains/others/no symptoms, n (%)]	286(88.5)/23(7.1)/14(4.4)	230(61.5)/143(38.2)/1(0.3)	100.900	0.000[a]
Heart rate (bpm)	78(70–84)	73(66–82)	−4.619	0.000[a]
LVEF (%)	60(56–62)	58(51–62)	−2.984	0.003[a]
History of hypertension [yes, n (%)]	226(70)	230(62)	5.499	0.019[a]
The grade of hypertension [normal/grade 1/grade 2/grade 3, n (%)]	81(25)/21(7)/49(15)/172(53)	192(51)/19(5)/45(12)/118(32)	52.004	0.000[c]
History of diabetes [yes, n (%)]	17(5)	83(22)	40.422	0.000[b]
History of smoking [yes, n (%)]	195(60)	159(43)	22.115	0.000[a]
History of drinking [yes, n (%)]	72(22)	79(21)	0.139	0.709
AD, n (%)	258(79.9)	NA	NA	NA
Therapeutic strategy [surgical/interventional/medical, n (%)]	116(36)/151(47)/56(17)	NA	NA	NA
Clinical outcomes [survivor/death/self-discharged, n (%)]	227(70)/29(9)/67(21)	373(99.7)/1(0.3)/0(0)	125.601	0.000

AAS, acute aortic syndrome; bpm, beats per minute; LVEF, left ventricular ejection fraction; AD, aortic dissection; NA, not applicable.
The results of comparisons between groups: [a] AAS > Non-AAS; [b] AAS < Non-AAS; [c] grade 3 hypertension: AAS > Non-AAS.

(CK-MB), alanine amino transferase (ALT), aspartate transaminase (AST), glucose (Glu), cholesterol (CHO), triglyceride(TG), creatinine (Cr), high sensitivity C-reactive protein (hs-CRP), and high sensitivity cardiac troponin T (hs-cTnT).

Two independent researchers (HZ and NY) retrieved and extracted laboratory data and clinical information of participants from our laboratory information system (LIS) and electronic medical records, respectively. The results of the biomarker assays were blinded to final diagnoses and vice versa [19].

2.3. Statistical analysis

All continuous data, which were not normally distributed tested by Kolmogorov-Smirnov test, were reported as median (25th–75th percentile), and compared using the Mann-Whitney U test or Kruskal-Wallis one-way ANOVA test (Bonferroni correction was used for post hoc comparison). Categorical data were reported as frequency (percentage) and compared using the χ^2 test, with Bonferroni correction where appropriate.

Diagnostic performance was estimated by the area under a receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, negative/positive likelihood ratios (NLR/PLR), and negative/positive predictive values (NPV/PPV), along with corresponding 95% confidence interval (CI). Comparisons between AUCs were performed using DeLong's test [20]. Sensitivities and specificities were compared with the McNemar test. Additionally, Youden's index was also reported.

The reclassification metrics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI), were employed to quantify and evaluate improvement in discrimination [21,22].

Clinical utility was assessed with the use of decision curve analysis (DCA), which was graphically expressed as a curve with net benefits on Y-axis and threshold probabilities on X-axis [23,24]. In a decision curve, two default reference strategies should always be present: treating none and treating all.

Data analyses for this paper were completed by SPSS 25.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA, USA), MedCalc 18.2.1 (MedCalc statistical software, Inc., San Diego, CA,USA), and R software package (version 4.1.2, https://www.r-project.org/). All reported P values were two-sided and a P value <0.05 indicated statistical significance.

3. Results

3.1. Baseline characteristics

In all, 697 patients with suspicious AAS were eligible for the current analysis, including 323 cases of confirmed AAS and 374 with an initial suspicion of AAS but a different final diagnosis. The baseline characteristics of the study subjects in the AAS and Non-AAS groups were detailed in Table 1.

Among all AAS patients, 258(79.9%) were diagnosed with AD (124 type A AD and 134 type B AD), 57(17.6%) with IMH, and 8 (2.5%) with PAU. Moreover, 91% (236/258) of AD cases were of acute AD. The median age of the AAS patients was 59 years (range 47–66 years), with 253 (78%) males.

Of the Non-AAS patients, 136 (36%) were diagnosed with acute myocardial infarction (AMI), 71(19%) with angina, 107(29%) with PE, and 60 (16%) with other diseases with AAS-compatible symptoms (e.g., pneumothorax, gastrointestinal disease, pneumonia, pericarditis, myocarditis, or pleurisy, etc.). The median age of the Non-AAS patients was 65 years (range 56–72 years), with 218 (58%) males.

Compared with the Non-AAS patients, the AAS patients tended to be younger (59 years vs. 65 years, $P < 0.001$) and were more likely to be male (78% vs. 58%, $P < 0.001$). Furthermore, the AAS patients presented more often with pain, and had a higher heart rate and left ventricular ejection fraction but a shorter duration from initial onset of symptoms to visit. Also, the AAS patients more frequently had concomitant hypertension and smoking but less commonly had diabetes mellitus ($P < 0.001$). No statistical difference in a history of drinking was found between the two groups ($P > 0.05$).

Interestingly, grade 3 hypertension was more common in the AAS patients compared with the Non-AAS patients (53% vs. 32%, $P < 0.001$), whereas grade 1 and 2 hypertension occurred with similar proportions between the two groups (7% vs. 5% and 15% vs. 12%, respectively; $P > 0.05$).

3.2. Blood test results

Blood test results of the study population were displayed in detail in Table 2. As compared to the Non-AAS patients, the AAS patients had significantly higher levels of WBC, neutrophil, Glu, Cr, and hs-CRP but lower levels of lymphocyte, PLT, FIB, CK, CK-MB, ALT, AST, CHO,TG, and hs-cTnT. However, no significant difference regarding Hb levels was noted between the two groups ($P > 0.05$).

The distributions of NLR and D-dimer levels according to final diagnosis were presented in Table 3 and Fig. 2. As expected, the patients with AAS exhibited significantly higher NLR (8.77 vs. 2.90, $P < 0.001$) as well as D-dimer (3.16 μg/mL vs. 0.47 μg/mL, $P < 0.001$) than those with Non-AAS. In the subgroup analyses, the median levels of NLR and D-dimer were found to be highest in AD patients, followed by other AAS and Non-AAS patients (P after Bonferroni correction <0.001), but the levels of these two markers did not differ significantly between IMH and PAU patients ($P > 0.05$).

Table 2
Blood test results of study subjects in the AAS and Non-AAS groups.

Parameters	AAS (n = 323)	Non-AAS (n = 374)	*Z*	*P*-value
WBC ($\times 10^9$/L)	10.74(8.29–13.68)	7.49(5.94–9.76)	−11.410	0.000[a]
Neutrophil ($\times 10^9$/L)	8.92(6.38–11.96)	5.08(3.74–6.96)	−13.552	0.000[a]
Lymphocyte ($\times 10^9$/L)	1.03(0.70–1.53)	1.73(1.31–2.26)	−12.443	0.000[b]
Hb (g/L)	135(124–148)	137(126–146)	−0.806	0.420
PLT ($\times 10^9$/L)	192(156–231)	227(191–267)	−7.819	0.000[b]
FIB (g/L)	2.89(2.27–3.75)	3.36(2.85–3.96)	−5.863	0.000[b]
CK (U/L)	81(55–139)	95(61–284)	−3.533	0.000[b]
CK-MB (U/L)	17(13−22)	17(13–40)	−2.163	0.031[b]
ALT (U/L)	16.8(11.8–30.7)	21.5(14.3–37.6)	−3.678	0.000[b]
AST (U/L)	18.7(14.8–24.8)	22.5(16.3–51.6)	−5.090	0.000[b]
Glu (mmol/L)	7.02(6.05–8.41)	6.18(5.19–8.31)	−4.653	0.000[a]
CHO (mmol/L)	4.14(3.51–4.78)	4.30(3.73–5.07)	−2.479	0.013[b]
TG (mmol/L)	1.33(0.96–1.90)	1.55(1.07–2.00)	−2.860	0.004[b]
Cr (μmol/L)	83(70–104)	75(64–89)	−5.441	0.000[a]
hs-CRP (mg/L)	11.30(3.70–35.10)	3.90(1.20–11.53)	−8.783	0.000[a]
hs-cTnT (ng/mL)	0.016(0.008–0.060)	0.032(0.010–1.175)	−5.276	0.000[b]

AAS, acute aortic syndrome; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; FIB, fibrinogen; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; ALT, alanine aminotransferase; AST, aspartate transaminase; Glu, glucose; CHO, cholesterol; TG, triglyceride; Cr, creatinine; hs-CRP, high sensitivity C-reactive protein; hs-cTnT, high sensitivity cardiac troponin T.
The results of comparisons between groups: [a] AAS > Non-AAS; [b] AAS < Non- AAS.

3.3. Assessment of discriminative performance

The ROC curve analyses that described the discriminative abilities of D-dimer and NLR were illustrated in Table 4 and Fig. 3. For the detection of AAS, NLR provided good discrimination with an AUC of 0.845(95% CI: 0.816–0.871), which was comparable with that of D-dimer [AUC (95% CI):0.822(0.792–0.850), $P > 0.05$]. The sensitivity and specificity of NLR for AAS did not differ from those of D-dimer ($P = 0.786$). According to the results of the reclassification analyses in Table 5, NLR showed better discriminative properties compared to D-dimer, with a positive NRI of 66.1% (95% CI: 52.2%–80.0%) and IDI of 12.4% (95% CI: 8.7%–16.1%) for AAS ($P < 0.001$). That is to say, compared to D-dimer, the proportion of correct classification and overall predictive ability by NLR significantly increased by 66.1% and 12.4%, respectively.

Further analysis according to the different classes of AAS was done. As shown in Table 4 and Fig. 3, the AUCs for NLR to identify AD and acute AD were 0.850 and 0.873, respectively, without any significant differences compared with 0.827 and 0.844 for D-dimer ($P > 0.05$). Compared to D-dimer, NLR showed similar sensitivities ($P = 0.087$ and 0.471, respectively) but higher specificities ($P = 0.000$ and 0.002, respectively). Likewise, the NRI and IDI values were significantly positive, indicating that NLR had better discriminatory ability than D-dimer (see Table 5).

3.4. Assessment of the clinical utility

The decision curves that graphically depicted net benefits of D-dimer and NLR across an entire range of threshold probabilities were illustrated in Fig. 4.

For identifying AAS, these two biomarkers clearly provided net benefit above two default strategies of treating all or none at threshold probabilities of 15%–80%, as shown in Fig. 4(A). Moreover, NLR achieved greater net benefit in comparison with D-dimer over a wide range of threshold probabilities (10%–95%). For example, the net benefits for D-dimer and NLR at a threshold probability of 20% were 0.122 and 0.144, respectively (see Table 6). This could be interpreted that, compared with the reference strategy of "treating none", a net benefit of 0.144 would be the equivalent of identifying 14.4 true positives per 100 patients, 2.2 more than D-dimer, without increasing the number of false positives. On the other hand, if the reference strategy was "treating all", the net benefits for D-dimer and NLR was 0.060 and 0.082, respectively (see Table 6). That is, at a threshold of 20%, according to the calculation formula [25], the use of NLR would be the equivalent of a strategy that reduced the number of false positives by 33 per 100 patients, 9 more than D-dimer, without increasing the number of false negatives.

In the subgroup analyses, it could be seen from Fig. 4 (B) that NLR achieved greater net benefit than D-dimer or two default strategies, at threshold probabilities above 10%. And in Fig. 4(C), for threshold probabilities of 10%–60%, the use of NLR provided the highest net benefit. For threshold probabilities of 60%–85%, the net benefit of NLR was about the same as that of D-dimer. In comparison, neither diagnostic biomarker had positive net benefit for threshold probabilities over 85%.

4. Discussion

To the best of our knowledge, this study is the first to compare the discriminative capability and clinical utility of D-dimer and NLR for AAS. The major findings of the current study were summarized as follows: (1) the baseline level of NLR was higher in AAS patients than in Non-AAS patients. Also, the levels of NLR differed significantly among the subgroups of AAS; (2) NLR provided good discriminating

Table 3
The results of D-dimer and NLR according to the final diagnosis.

Groups	Case (n)	D-dimer(μg/mL)			NLR		
		Median(25th–75th)	*Z*/H	*P*-value	Median(25th–75th)	*Z*/H	*P*-value
AAS	323	3.16 (1.39–13.18)	−14.689	0.000[a]	8.77(4.53–15.68)	−15.716	0.000[a]
AD	258	4.41(1.71–20.00)	232.746	0.000[b]	11.16(5.25–16.69)	266.045	0.000[b]
Acute AD	236	5.51(2.05–20.00)			11.80(6.03–16.93)		
Sub-acute/chronic AD	22	1.03(0.57–2.12)			3.15(2.19–6.53)		
Type A AD	124	11.43(2.98–20.00)			13.79(6.90–19.14)		
Type BAD	134	2.53(1.03–6.94)			7.35(4.15–14.68)		
Other AAS	65	1.56(0.70–4.00)	29.132	0.000[c]	4.77(3.19–8.68)	32.418	0.000[c]
IMH	57	1.71(0.73–4.00)			5.47(3.37–9.02)		
PAU	8	0.82(0.40–3.79)			3.52(2.17–5.45)		
Non-AAS	374	0.47(0.28–1.42)			2.90(2.03–4.13)		
AMI	136	0.39(0.26–0.80)			3.96(2.66–6.10)		
Angina	71	0.31(0.23–0.42)			2.33(1.78–3.22)		
PE	107	2.40(1.31–4.59)			2.66(2.01–3.30)		
Other diagnoses	60	0.31(0.21–0.54)			2.49(1.63–3.59)		

NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; AD, aortic dissection; IMH, intramural hematoma; PAU, penetrating aortic ulcer; AMI, acute myocardial infarction; PE, pulmonary embolism.
The results of comparisons between groups: [a] AAS > Non-AAS. The results of post hoc analysis: [b] AD > Other AAS > Non-AAS. [c] AD> IMH or PAU.

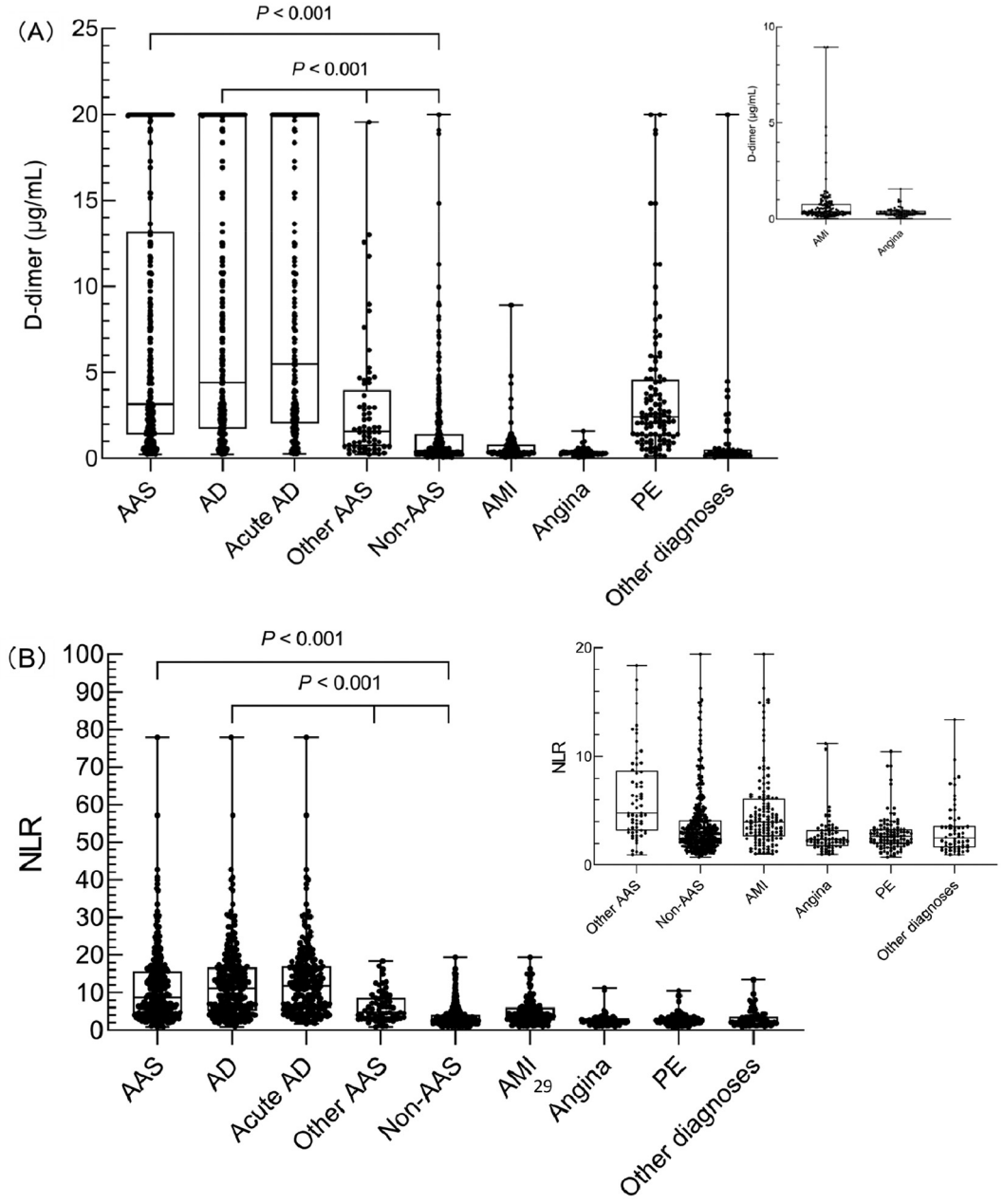

Fig. 2. The distribution of D-dimer (A) and NLR (B) levels in study patients according to final diagnosis. Box & whiskers plots showed medians, percentiles (25th and 75th), and minimum and maximum. AAS, acute aortic syndrome; AD, aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; NLR, the neutrophil-to-lymphocyte ratio.

Table 4
Characteristics of ROC curve analyses for D-dimer and NLR in identifying AAS and its subgroups.

Parameters	AUC(95% CI)	*Z* statistic	*P*-value	Sensitivity (95% CI), %	Specificity (95% CI), %	Youden's index	PLR (95% CI)	NLR[a] (95% CI)	PPV (95% CI), %	NPV (95% CI), %
To identify AAS										
D-dimer	0.822(0.792–0.850)[b]	20.988	<0.001	74(69–79)[e]	76(72–80)[e]	0.51	3.1(2.6–3.8)	0.34(0.3–0.4)	51(46–56)	90(88–92)
NLR	0.845(0.816–0.871)	23.234	<0.001	76(71–81)	79(74–83)	0.55	3.6(2.9–4.4)	0.3(0.2–0.4)	54(49–59)	91(89–92)
To identify AD										
D-dimer	0.827(0.797–0.855)[c]	21.041	<0.001	79(73–84)[e]	71(67–76)[f]	0.50	2.7(2.3–3.2)	0.3(0.2–0.4)	48(44–52)	91(89–93)
NLR	0.850(0.821–0.875)	23.014	<0.001	74(68–79)	82(78–85)	0.55	4.0(3.3–5.0)	0.32(0.3–0.4)	57(52–63)	90(88–92)
To identify acute AD										
D-dimer	0.844(0.815–0.870)[d]	22.793	<0.001	81(75–85)[e]	73(69–77)[f]	0.53	3.0(2.5–3.5)	0.27(0.2–0.3)	50(46–54)	92(90–94)
NLR	0.873(0.846–0.897)	27.260	<0.001	78(72–83)	81(78–85)	0.59	4.2(3.4–5.1)	0.27(0.2–0.3)	58(53–63)	92(90–93)

ROC, receiver operating characteristic; NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; AUC, the area under ROC curve; CI, confidence interval; PLR, positive likelihood ratio; NLR[a], negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; AD, aortic dissection.
The results of pairwise comparisons of AUCs between D-dimer and NLR: [b] z statistic = 1.227, $P = 0.2197$; [c] z statistic = 1.313, $P = 0.1890$; [d] z statistic = 1.762, $P = 0.0780$.
The comparisons of sensitivity/specificity between D-dimer and NLR: [e] all $P > 0.05$; [f] specificity $_{NLR}$ > specificity $_{D\text{-dimer}}$, $P < 0.05$.

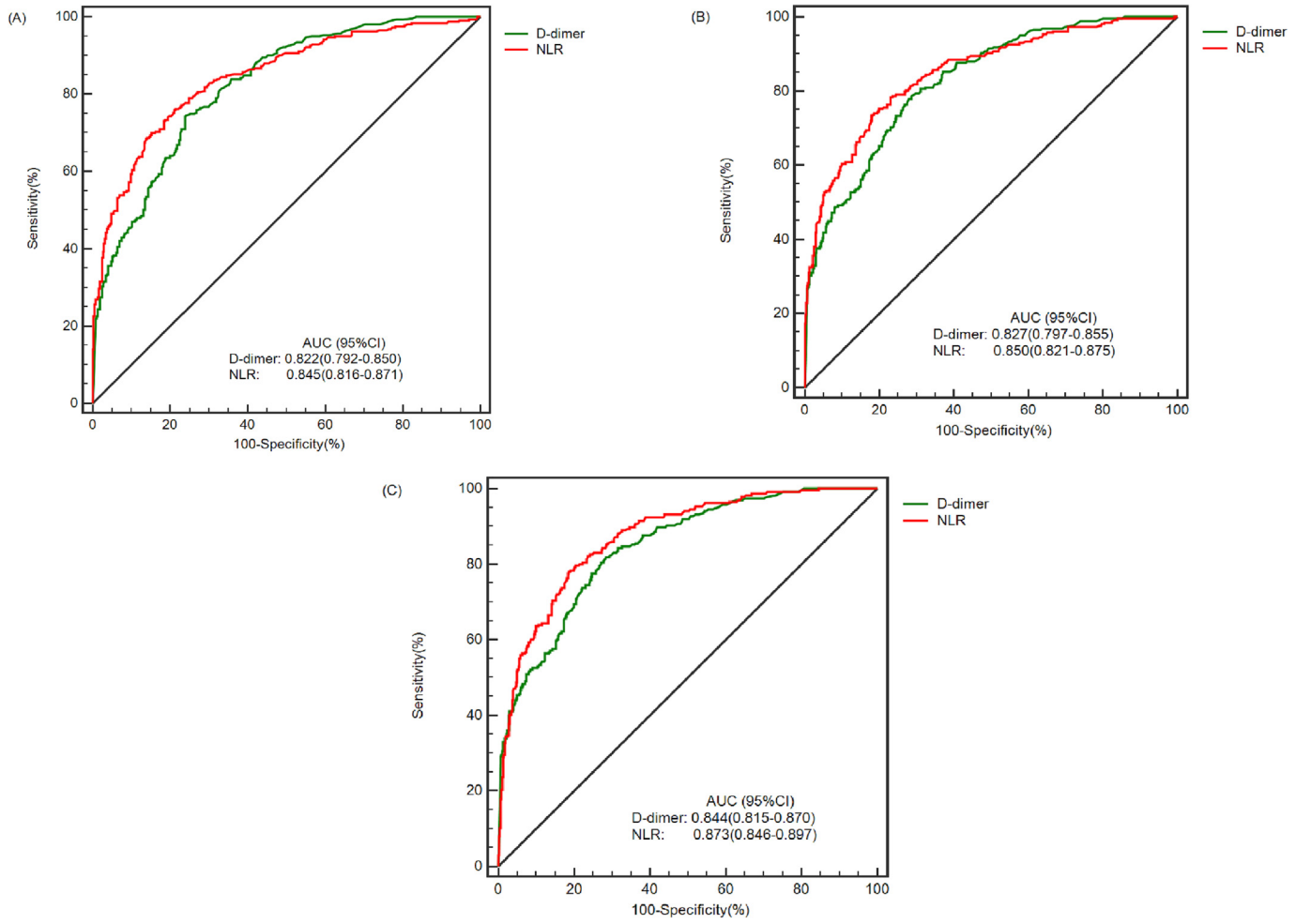

Fig. 3. The ROC curves comparing discrimination properties of D-dimer and NLR for the detection of (A) AAS, (B) AD, and (C) acute AD.
AUC values with 95% CIs in brackets were presented in insets. ROC, receiver operating characteristic; NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; AD, aortic dissection; AUC, the area under ROC curve; CI, confidence interval.

performance for AAS and its subgroups; (3) although NLR yielded a comparable AUC to that of D-dimer, it had better discriminating power than D-dimer for AAS and its subgroups; and (4) NLR provided higher net benefit than D-dimer for AAS. The study results above indicated potential superiority of NLR to D-dimer and supported the use of NLR as a reliable alternative to D-dimer in identifying AAS.

According to our current results, NLR levels were significantly different between patients with and without AAS as well as among the subgroups of AAS, which enriched and expanded our previous work for using NLR as a potential screening tool for AD [16]. Based on these data, we hypothesized that NLR could contribute to the differential diagnosis of AAS and then compared the diagnostic performance and clinical utility of D-dimer and NLR for AAS.

Table 5
NRI and IDI statistics providing incremental value in identifying AAS and its subgroups.

Reclassification statistics	D-dimer	NLR	*P*-value
To identify AAS			
Continuous NRI (95% CI, %)	Ref.	66.1(52.2–80.0)	<0.001
IDI (95% CI, %)	Ref.	12.4(8.7–16.1)	<0.001
To identify AD			
Continuous NRI (95% CI, %)	Ref.	55.7(41.0–70.4)	<0.001
IDI (95% CI, %)	Ref.	10.0(5.8–14.2)	<0.001
To identify acute AD			
Continuous NRI (95% CI, %)	Ref.	49.5(34.4–64.7)	<0.001
IDI (95% CI, %)	Ref.	7.7(3.3–12.2)	<0.001

NRI, net reclassification improvement; IDI, integrated discrimination improvement; AAS, acute aortic syndrome; NLR, the neutrophil-to-lymphocyte ratio; CI, confidence interval; Ref., Reference; AD, aortic dissection.

The area under a receiver operating characteristic (ROC) curve (AUC) is the most commonly used performance measure reflective of discrimination [21,26,27]. However, the change in AUC is often insensitive to the improvement in performance [22,28]. Therefore, two reclassification metrics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI), were introduced to our analysis, which can provide incremental information over AUC and are more sensitive in judging improvement in performance [21,22,29]. A significantly positive NRI or IDI value indicates improvement [19,29].

As indicated in the ROC curve analysis, NLR indeed offered superior overall diagnostic performance for AAS. Compared with D-dimer, the use of NLR yielded an increase in the AUC from 0.822 to 0.845. However, the small improvement in the AUC did not reach a statistically significant level, which seemed to suggest that the two biomarkers had a similar identifying power for AAS. In contrast, the subsequent reclassification analyses demonstrated that NLR offered better discriminating power than D-dimer due to a significantly positive increase in NRI and IDI values even though no significant improvement in the AUC was noted. The use of NLR hence was more informative. The conclusion above could not be drawn with mere reliance on a statistically significant increase in the AUC. Moreover, similar results were obtained in subgroup analyses according to the different classes of AAS.

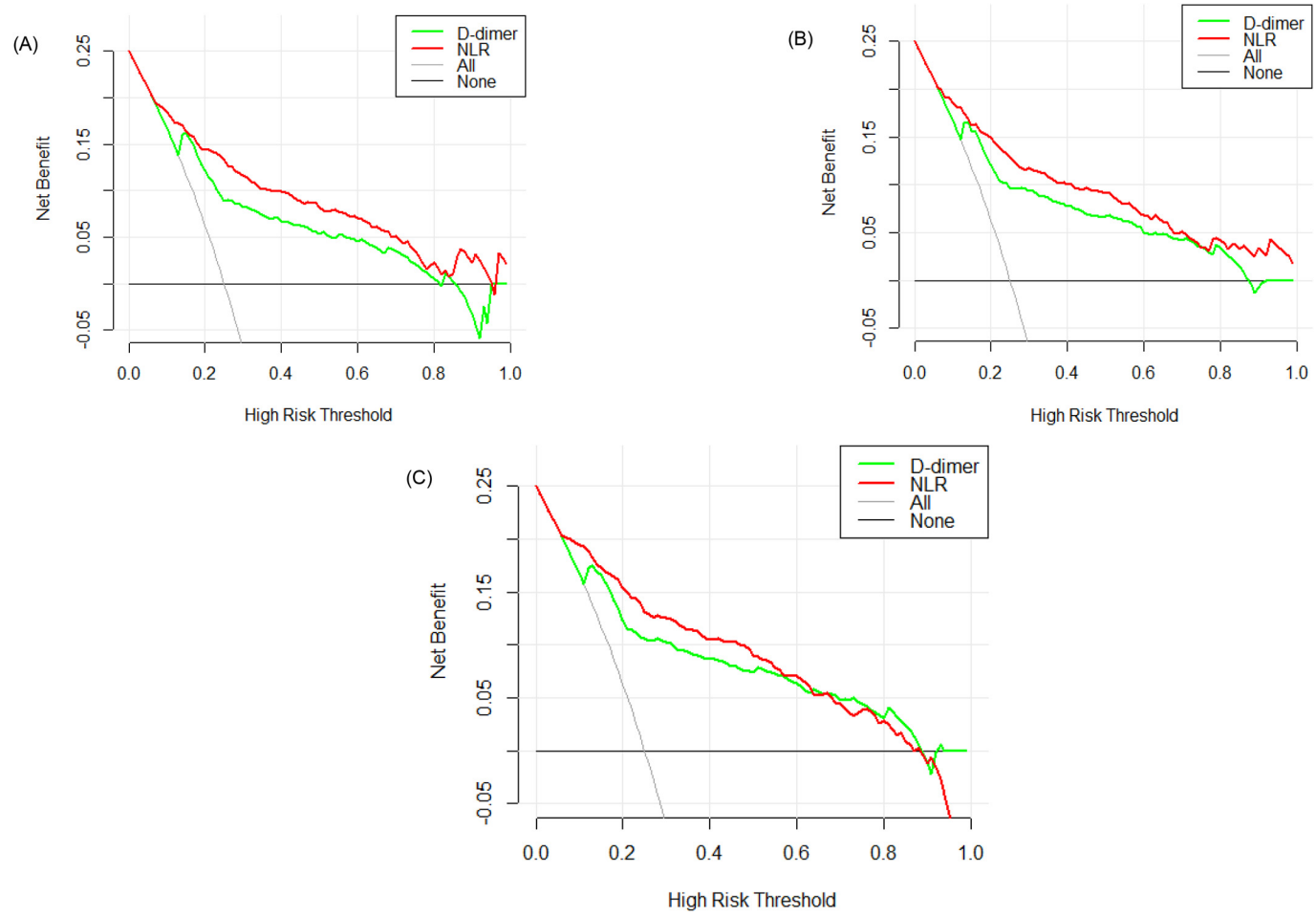

Fig. 4. The decision curves depicting net benefits of D-dimer and NLR at various thresholds for identifying (A) AAS, (B) AD, and (C) acute AD. The black line indicated the "treating none" strategy with a net benefit of 0 (i.e. assume no subject has target diseases). The grey line indicated the "treating all" strategy (i.e. assume all subjects have target diseases). NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; AD, aortic dissection.

Decision curve analysis (DCA) is a biostatistical method to quantify net benefit of a diagnostic biomarker and reflect its usefulness in clinical practice [24,25,30]. A diagnostic biomarker is useful only when it has a higher net benefit than default reference strategies across a range of reasonable thresholds [23,26] and the biomarker with the highest net benefit would be the best choice for clinical use [23-25].

According to the results of DCA in the current study, D-dimer and NLR outperformed two default strategies with positive net benefit at threshold probabilities of 15%–80%, and therefore, they were clinically useful for identifying AAS. Furthermore, NLR was preferable over D-dimer with favorable clinical utility in this range. Similar results were observed for NLR when compared to D-dimer in identifying AD at threshold probabilities above 10%, or in identifying acute AD at threshold probabilities of 10–60%. Additionally, although the use of NLR did not provide any extra net benefit over D-dimer at threshold probabilities of 60%–85% for acute AD, the option to NLR in this case was encouraged for reasons of both convenience and rapidity.

In view of the above, the comparisons of these two biomarkers demonstrated that the main advantage of NLR was represented by improved discriminative ability (also consistently shown in the subgroups of AAS) and superior clinical utility for AAS. As a more easily and rapidly available index, NLR is clearly of clinical value and may be a reliable alternative to D-dimer for the screening of suspected AAS in actual clinical practice, particularly when D-dimer testing is not easily available, for example, in some community hospitals (usually with weak facilities), where the initial diagnosis is made [7,15].

Our study had several strengths. First, to the best knowledge of us , this was the first research to explore and compare the discriminative performance and clinical utility of D-dimer and NLR for AAS. With improved diagnostic performance and clinical utility for AAS, NLR was

Table 6
Net benefit results of D-dimer and NLR for identifying AAS at various threshold probabilities.

Biomarkers	Net benefit (95% CI)	Net benefit of the "treat all" strategy	Net benefit	Reduction in false positives per 100 patients (n)
At a threshold of 20%				
D-dimer	0.122(0.108–0.136)	0.062	0.060	24
NLR	0.144(0.132–0.159)	0.062	0.082	33
At a threshold of 25%				
D-dimer	0.089(0.074–0.108)	0	0.089	27
NLR	0.134(0.116–0.150)	0	0.134	40

NLR, the neutrophil-to-lymphocyte ratio; AAS, acute aortic syndrome; CI, confidence interval.

preferred to D-dimer because of its easy availability, convenience, and rapidity. Second, this study was conducted with a relatively large sample size, which allowed us to evaluate the corresponding results according to the different subgroups of AAS to further reflect possible usage of NLR in clinical setting.

The present study had limitations. First, it was a retrospective analysis in a single institution, which may lead to the potential risk of bias in patient selection. Therefore, more prospective data from other institutions are needed to confirm our results. Second, since the real prevalence of AAS in suspected population is not clearly defined and AD comprises a large majority of all AAS [5,7,9,31], a prevalence of 25% (i.e. 1 in 4 suspected patients) was used in our estimations, consistent with previous studies [31,32]. This may result in potential bias when estimating some performance metrics such as negative and positive predictive values [19]. However, other metrics such as sensitivity, specificity, and likelihood ratios are not affected.

5. Conclusions

In conclusion, NLR proved preferable to D-dimer with improved discriminative performance and superior clinical utility in identifying AAS. As a more routinely available biomarker, NLR has the potential for use as a reliable alternative to D-dimer for the screening of suspected AAS.

Author contributions

HZ and MH contributed to the conception and design of the study. HZ and NY contributed to data collection. HZ, NY and JG contributed to the acquisition, analysis, or interpretation of data. HZ and MH drafted and revised the manuscript. All authors approved the final version to be published. All authors agree to be accountable for all aspects of the work.

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Availability of data and materials

The original data and analytical methods are available by contacting the corresponding author on reasonable request.

Declaration of Competing Interest

The authors report no conflict of interest.

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