META-ANALYSIS

Systematic Review and Meta-analysis of Tongxinluo Capsule Therapy for Acute Myocardial Infarction

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ABSTRACT

Context • An acute myocardial infarction (AMI) is a serious, life-threatening disease. Practitioners of traditional Chinese medicine (TCM) commonly use the Tongxinluo (TXL) capsule, a Chinese patent medicine, to treat AMIs. The benefits of TXL capsules for AMIs remain unknown.

Objective • The systematic review and meta-analysis intended to investigate the effects of TXL capsules for AMI patients.

Design • The research team conducted a comprehensive literature search of the PubMed, Embase, Cochrane Library, and Web of Science databases from inception to February 2023. The team used the search terms acute myocardial infarction, myocardial infarction, TXL Capsule Therapy, and TXL Capsule. The team also performed a meta-analysis and evaluated the features of the included studies using the Cochrane Collaboration tool for assessing the risk of bias.

Setting • The study took place at the Second Affiliated Hospital at Heilongjiang University of Chinese Medicine in Harbin City, Heilongjiang Province, China

Outcome Measures • The research team: (1) evaluated the studies' quality using the Cochrane Collaboration tool for assessing the risk of bias; (2) analyzed the curative effect of the TXL capsules for AMI; (3) explored the effects of the TXL capsules on left ventricular end-diastolic dimension (LVEDD), left ventricular end systolic diameter (LVESD), and left ventricular ejection fraction (LVEF); and (4) explored the effects of the TXL capsules on creatine kinase isoenzyme (CK-MB) peak time, CK-MB peak value, and cardiac index.

Results • The literature search found ten studies. Compared with routine treatment alone, a combination of routine treatment and TXL capsules significantly improved the curative effects (odds ratio = 3.48; 95% CI: 2.34, 5.17; $P < .00001$) Compared with the control groups, the TXL capsule groups' LVESD and LVEF were significantly lower, with MD=-0.23; 95% CI: -0.37, -0.10; and $P = .0007$ and MD=-0.43; 95% CI: -0.61, -0.25; and $P < .00001$, respectively, and its LVEDD was significantly higher, with MD=5.27; 95% CI: 4.33, 6.21; and $P < .00001$. For myocardial enzymes, the TXL capsule groups' creatine kinase isoenzyme (CK-MB) peak values and cardiac indexes were significantly lower than those of the control groups, with MD=-53.11; 95% CI: -55.26, -50.97; and $P < .00001$ and MD=-1.87; 95% CI: -2.03, -1.70; and $P < .00001$, respectively.

Conclusions • The meta-analysis showed that the TXL capsule can bring greater therapeutic benefits for AMI patients in combination with routine treatment. The current study was a meta-analysis, and the field needs more well-designed studies. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

An acute myocardial infarction (AMI) is a common, acute, and critical disease, with a rapid onset, and can seriously endanger patients' health, having a high mortality rate that 11.4% died within first 28 days.[1-5]

AMI refers to a sudden decrease or complete blockage of the coronary artery's blood supply and to continuous and serious ischemic symptoms affecting the myocardium, which can lead to sudden cardiac arrest or even sudden death.[6]

The coronary artery's spasm and a sharp increase in myocardial oxygen consumption can induce an AMI.[7] An AMI's occurrence and development also involves reactions,

such as endothelial cell dysfunction, an inflammatory response, and oxidative stress, that can further lead to the apoptosis of cardiomyocytes.[8]

AMI's clinical manifestations include such symptoms as severe sternal pain, arrhythmia, and heart failure. Although a percutaneous coronary intervention (PCI) can significantly reduce the incidence of coronary-artery stent thrombosis, the mortality of patients hasn't effectively improved in short-term (less than 30 days) follow-up and long-term (1 year or longer) follow-up.[4,9,10]

Traditional Chinese Medicine

China has a long history of traditional Chinese medicine (TCM), which can reduce or eliminate the symptoms of some diseases and the whole country has widely recognized it. The medical costs are low, and the therapies are safe.

For AMI, TCM follows the treatment concept of holistic treatment and syndrome differentiation; it can relieve myocardium damage by adjusting systemic functioning, thus achieving the purpose of protecting patients' damaged myocardia and improving prognosis.[11] Clinically, AMI patients receive TCM drug interventions, but the prognostic effect of different TCM prescription interventions is different.[11] TCM practitioners commonly use the Tongxinluo (TXL) capsule, a Chinese patent medicine, to treat AMIs.

TXL's Components and Therapeutic Effects

The TXL capsule mainly includes 12 Chinese herbs: (1) ginseng, (2) red peony root, (3) scorpions, (4) leeches, (5) cicada slough, (6) centipedes, (7) falling scents, (8) ground beetle worms, (9) sandalwood, (10) sour jujube kernels, (11) frankincense, and (12) borneol [11]. Its main pharmacological effects include activating the blood, dredging collaterals, relieving pain, and replenishing qi. It can relieve chest distress, colic and other clinical symptoms of blood stasis and collateral obstruction syndrome, such as angina pectoris and coronary heart disease.

Wei and Jiang found that the TXL capsule's pharmacological action was mainly related to the ginseng, centipedes, leeches, borneol, and other traditional Chinese medicines for clearing collaterals and replenishing qi.[12] Those researchers found that: (1) red peony root, scorpions, and leeches can improve myocardial ischemia and accelerate blood circulation; (2) borneol can relieve pain and provide sedation; and (3) ginseng can regulate qi and blood and promote coronary expansion. In addition, those researchers indicated that the TXL capsule, from the perspective of modern medicine, can relax blood vessels, promote blood circulation, act as an anticoagulant, decrease cardiovascular spasms, and inhibit disease deterioration.

Liu, et al and Yang, et al found that TXL capsules can significantly inhibit atherosclerosis, improve vascular endothelial function, stabilize plaques, inhibit vasospasms, inhibit cardiomyocyte apoptosis, and prevent ventricular remodeling and other symptoms.[13, 14]

Wang, et al found that the TXL capsule could protect human, cardiac, microvascular endothelial cells from damage under hypoxia.[15] In addition, Li, et al found that the TXL capsule can effectively protect the heart from reperfusion injury and reduce myocardial cell damage.[16] Two other studies found that the TXL capsule can also play an important regulatory role, not only in cardiac tissue but also in systemic inflammation and immune imbalance.[17, 18]

Li, et al's meta-analysis focused on the secondary preventive effects of the TXL capsule on adverse cardiac events for AMI patients.[19] Those researchers found that TXL provides good clinical therapeutic effects.

The TXL capsule has a definite effect on AMI and can reduce the number of attacks, improve cardiac function, and improve patients' blood-lipid levels.[19, 20] It's a safe treatment and suitable for patients' long-term use.[21] Clinicians can base AMI's treatment on dredging blood vessels, relaxing muscles, and activating collaterals, and they can select TXL capsule for that purpose.

Current Study

Robust evidence-based results about the effectiveness of the TXL capsule in the treatment of AMI are still lacking. The present systematic review and meta-analysis intended to investigate the effects of TXL capsules for AMI patients.

METHODS

Procedures

The study took place at the Second Affiliated Hospital at Heilongjiang University of Chinese Medicine in Harbin City, Heilongjiang Province, China

Literature search. The research team conducted a comprehensive literature search of the PubMed, Embase, Cochrane Library, and Web of Science databases from inception to February 2023. The MeSH terms and free words adopted as search terms were: acute myocardial infarction, myocardial infarction, Tongxinluo Capsule Therapy, and Tongxinluo Capsule. The team manually checked the reference lists of previous relevant reviews to find additional publications of interest. The team limited the language of the publications to English and Chinese.

Inclusion and exclusion criteria. The systematic review included studies if they: (1) were randomized controlled trials (RCT); (2) included people with clinically diagnosed AMI; (3) treated the intervention group for AMI using TXL capsules, with the control group not receiving that treatment; and (4) reported one of the following results: curative effects, echocardiography, or myocardial enzyme. The systematic review excluded studies if they were: (1) abstracts, reviews, case reports, or comment letters; (2) animal studies; or (3) duplicate publications.

Data extraction. Two independent reviewers using a standardized form extracted the relevant data from eligible studies, including the name of the first author, publication year, patient type, intervention, control, and outcomes.[22] The primary outcome was the curative effects, and the secondary outcomes included echocardiography results and myocardial enzyme levels.

Table 1. Characteristics of the Included Studies. All studies took place in China; the ethnicity of all participants was East Asian; and the intervention groups in all studies received the Tongxinluo capsule.

Study, Year	Sample Size	Group		Treatment: Control Group	Outcomes
		Intervention	Control		
Yang, 2011[23]	76	42	34	Symptomatic treatment combined with metoprolol.	CE
Ma, 2018[24]	260	130	130	Symptomatic treatment combined with aspirin.	CE
Yue, 2018[25]	200	100	100	Symptomatic treatment combined with aspirin, clopidogrel, and atorvastatin.	LVEDD, LVESD, LVEF, CK-MB peak time, CK-MB peak value, CI
Liu, 202[02]6	214	107	107	Symptomatic treatment combined with clopidogrel and atorvastatin.	CE
Chen, 2008[27]	70	35	35	Symptomatic treatment combined with aspirin, urokinase, low molecular weight heparin, isosorbide mononitrate, angiotensin converting enzyme inhibitors.	LVESD, LVEF
Wang, 2021[28]	55	32	23	Symptomatic treatment combined with clopidogrel.	CE, LVEDD
Li, 2017[29]	100	50	50	Symptomatic treatment combined with aspirin, clopidogrel, isosorbide dinitrate tablets, captopril, metoprolol, trimetazidine.	CE, LVEDD, LVESD, LVEF
Tian, 2014[30]	60	30	30	Symptomatic treatment combined with aspirin, clopidogrel, isosorbide dinitrate tablets, atorvastatin.	LVEDD, LVESD, LVEF
Deng, 2014[31]	62	31	31	Symptomatic treatment combined with low molecular weight heparin.	CE
Liu, 2016[32]	86	43	43	Symptomatic treatment combined with aspirin, clopidogrel, low molecular weight heparin.	CE, LVEDD, LVESD, LVEF, CK-MB peak time, CK-MB peak value, CI

Abbreviations: CE, curative effect; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase- isoenzyme; CI, cardiac index

Intervention strategies The intervention groups all received TXL capsules combined with routine treatment and the control groups received routine treatment only.

Outcome Measures. The research team: (1) evaluated the studies' quality using the Cochrane Collaboration tool for assessing the risk of bias; (2) analyzed the curative effect of the TXL capsules for AMI; (3) explored the effects of the TXL capsules on left ventricular end-diastolic dimension (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular ejection fraction (LVEF), and cardiac index; and (4) explored the effects of the TXL capsules on creatine kinase isoenzyme (CK-MB) peak time, CK-MB peak value.

Outcome Measures

Curative effects. A significant effect indicates that chest distress and colic symptoms disappeared. The obvious effect indicates that chest distress and colic symptoms were relieved, the number and duration of attacks were reduced, and the symptoms were alleviated. Curative effects rate = (The number of significant effect patients + the number of obvious effect patients)/the number of total patients ×100%.

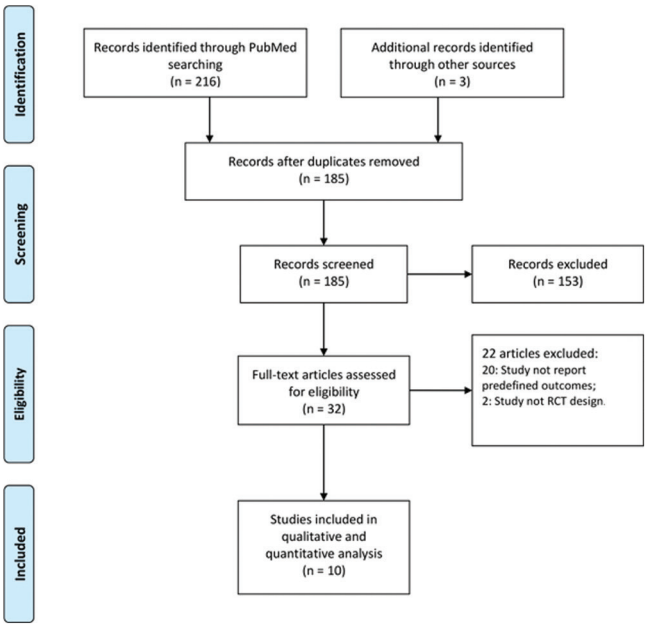
LVEDD, LVESD, and LVEF. Echocardiography detection outcomes, including LVEDD, LVESD, LVEF, and cardiac index results, were assessed after the total course of treatment.

CK-MB peak time and value. After the TXL capsule and routine treatments, if the patients underwent PCI, the post-PCI CK-MB peak time and value were assessed.

Statistical Analysis

The research team analyzed the data using Review Manager 5.3 (The Cochrane Collaboration, Oxford, England), as described in the literature.[22] The team: (1) used odds ratios (ORs) with 95% confidence intervals for pooling discontinuous data; (2) used the mean difference (MD) with 95% confidence interval for pooling continuous data; (3) examined heterogeneity among studies using the Chi-square (χ^2)-based Q test, in which I^2 indicates the level of heterogeneity, with I^2<50% or P of heterogeneity>0.1 representing low heterogeneity, and vice versa; and (4) used a funnel plot to evaluate whether potential publication bias existed in the pooled results. $P < .05$ indicated statistical significance.

Figure 1. Flowchart of Literature Selection Process



RESULTS

Included Studies

Figure 1 shows the literature selection process. The comprehensive literature search identified 216 studies through the search and three through other sources, for a total of 219 studies. 185 items were left after duplicates were removed. 153 records were excluded after screening title and abstract. And then 32 articles were screened and excluded 22 studies due to not reported the predefined outcomes (n = 20) and not RCT design (n = 2) with the meta-analysis then included 10 studies.

Table 1 shows the basic features of the 10 studies dating from 2008 to 2021.[23-32] The sample size ranged from 55 to 260 participants, and the total sample size was 1183 participants.

Figure 2A shows the assessment of the risk of bias to determine the quality of the literature, and the risk of bias was low for al criteria. All studies were randomized and had correct allocation-concealment strategies (Figure 2B).

Figure 2. Risk of Bias for the Included Studies. Figure 2 A shows the risk-of-bias summary, and Figure 2B shows the risk-of-bias graph.

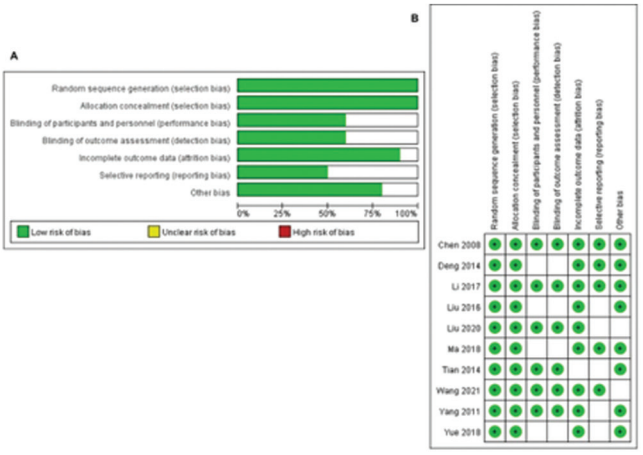
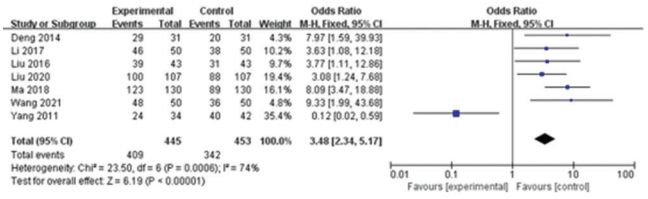
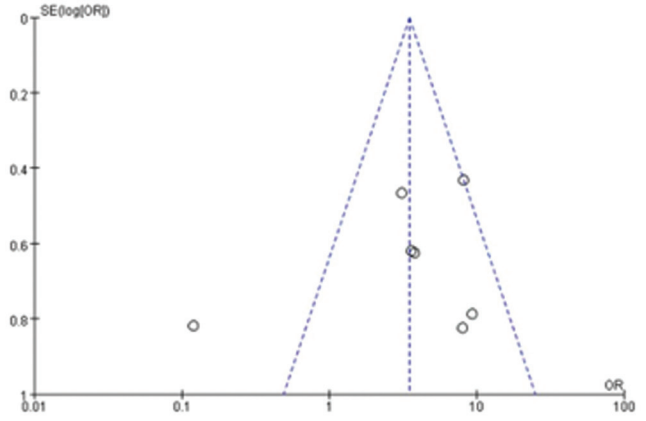


Figure 3. Forest Plot of the Curative Effects of Tongxinluo Capsules for AMI. The TXL capsule groups' curative effects for AMI were significantly better than those of the control groups.



Abbreviations: AMI, acute myocardial infarction

Figure 4. Funnel Plot of the Curative Effects of Tongxinluo Capsules for AMI

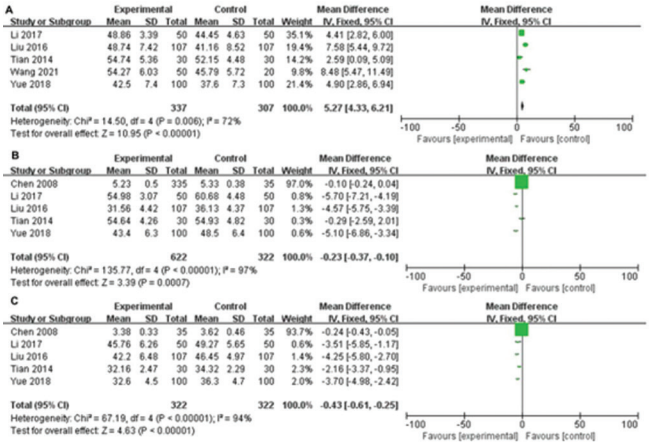


Abbreviations: AMI, acute myocardial infarction

Curative Effects

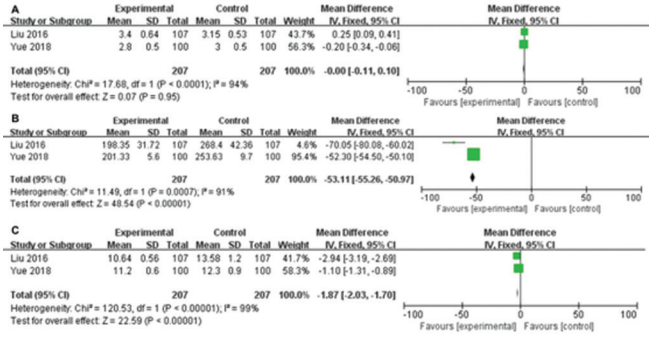
Figure 3 shows that the TXL capsule groups' curative effect for AMI were significantly better than those of the control groups (OR=3.48; 95% CI: 2.34, 5.17; $P < .00001$). Figure 4 shows the funnel plots for the meta-analysis of the curative effects the of TXL capsules. The symmetric funnel plot indicated that no publication bias existed in the pooled results for curative effect.

Figure 5. Forest Plots of Echocardiographic Results for the Tongxinluo Capsules for AMI. Figure 5A shows the LVEDD; Figure 5B shows the LVESD; and Figure 5C shows the LVEF. The TXL capsule groups' LVEDD was significantly higher and the groups' LVESD and LVEF were significantly lower than those of the control groups



Abbreviations: AMI, acute myocardial infarction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction

Figure 6. Forest Plots of Myocardial Enzyme Results of Tongxinluo Capsule for AMI. Figure 6a shows the CK-MB peak time; Figure 6B shows the CK-MB peak value; and Figure 6C shows the CI. The TXL capsule groups' CK-MB peak values and levels of CI were significantly lower than those of the control groups. No significant differences existed between the groups for the CK-MB peak time.



Abbreviations: AMI, acute myocardial infarction; CI, cardiac index; CK-MB, creatine kinase isoenzyme

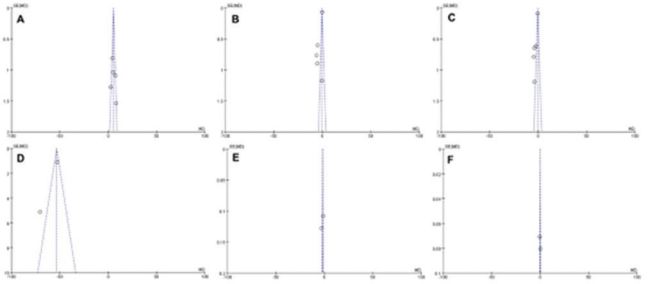
LVEDD, LVESD, and LVEF

Figures 5A-5C show the echocardiographic results. The TXL capsule groups' LVEDD (MD=5.27; 95% CI: 4.33, 6.21; $P < .00001$) was significantly higher and the groups' LVESD (MD=-0.23; 95% CI: -0.37, -0.10; $P = .0007$) and LVEF (MD=-0.43; 95% CI: -0.61, -0.25; $P < .00001$) were significantly lower than those of the control groups.

CK-MB Peak Time and value and cardiac index

Figure 6A shows that no significant differences existed between the groups for the CK-MB peak time (MD=-0.00;

Figure 7. Funnel Plots for Results of Echocardiography and Levels of Myocardial Enzymes. Figure 7A shows the LVEDD; Figure 7B shows the LVESD; Figure 7C shows the LVEF; Figure 7D shows the CK-MB peak time; Figure 7E shows the CK-MB peak value (E); and Figure 7F shows the CI. No significant publication bias existed in the pooling results.



Abbreviations: CI, cardiac index; CK-MB, creatine kinase isoenzyme; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction

95% CI: -0.11, 0.10; $P = .95$). Figure 6B shows that the TXL capsule groups' CK-MB peak values (MD=-53.11; 95% CI: -55.26, -50.97; $P < .00001$) and Figure 6C shows that its levels of CI (MD=-1.87; 95% CI: -2.03, -1.70; $P < .00001$) were significantly lower than those of the control groups.

Publication Bias

Figure 7 shows the funnel plots for the meta-analysis of the TXL capsule for LVEDD, LVESD, LVEF, CK-MB peak time, CK-MB peak value and CI. The symmetric funnel plots indicated that no significant publication bias existed in the above pooling results.

DISCUSSION

Li, et al. analyzed the secondary protective effect of TXL capsules on patients with AMI. The results show that TXL treatment can reduce secondary cardiovascular events, including reducing cardiac death, recurrent myocardial reinfarction, arrhythmia, and recurrent angina. TXL treatment also has the effects of improving heart function, regulating blood pressure, and reducing inflammation.[19] Hui, et al. evaluated the therapeutic benefits of TXL in patients with coronary heart disease after PCI and concluded that TXL can reduce the risk of restenosis, myocardial infarction, heart failure, angina, revascularization, all-cause mortality and mortality due to any cardiovascular event.[20] Lv, et al. also believe that for patients with CHD, TXL could reduce the risk of myocardial infarction, target vessel revascularization or in-stent restenosis and reduce the rates of cerebrovascular accidents, heart failure and unscheduled readmission for cardiovascular diseases.[11] The results of the above studies are consistent with those of this work. It is believed that TXL can bring additional therapeutic benefits to patients with coronary heart disease and AMI.

The current study found that TXL capsules, when combined with routine treatment, can significantly improve the curative effects and effectively improve the patients' LVEDD, LVESD, and LVEF as well as CK-MB peak value and levels of CI. Therefore, in clinical practice, TXL capsule intervention can be considered in the management of AMI, post-PCI and CHD patients to bring more therapeutic benefits.

The current study had some limitations. First, the research team performed a meta-analysis instead of new study, which didn't allow analysis of the impacts of individual characteristics on the outcomes. Second, the number of included studies was small, and all of them were from China. The research team needs to perform more studies on other ethnic populations to confirm the current study's results. Third, significant heterogeneity existed in the pooling results, and the source of heterogeneity may have come from the individual studies' characteristics, which the current study couldn't explore further.

CONCLUSIONS

The meta-analysis showed that the TXL capsule can bring greater therapeutic benefits for AMI patients in combination with routine treatment. The current study was a meta-analysis, and the field needs more well-designed studies.

AUTHORS DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest with respect to the research, authorship, or publication of the article.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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