PROGNOSTIC VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN ACUTE CORONARY SYNDROME PATIENTS: A META-ANALYSIS OF HAZARD RATIOS

Xiao-Qing Quan[1, #], Zhong-Hui Jiang[2, #], Zhong-Bin Yang[2], Hong-Tao Liu[3, *]
[1]Department of Geriatrics, Department of General Pratice, Shenzhen Longhua District Central Hospital, The Affiliated Central Hospital of Shenzhen Longhua District, Guangdong Medical University, Shenzhen 518110, China - [2]Department of Stomatology, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, China - [3]Department of Cardiology, Shenzhen Longhua District Central Hospital, The Affiliated Central Hospital of Shenzhen Longhua District, Guangdong Medical University, Shenzhen 518110, China
[#]These authors contributed equally to this work as co-first author

ABSTRACT

Background*: Previous meta-analyses have revealed the prognostic significance of neutrophil-lymphocyte ratio (NLR) in acute coronary syndrome (ACS) by combining the odds ratios (ORs) or risk ratio (RRs). This study aims to supplement the previous meta-analysis by including only adjusted hazard ratios (HRs). We have investigated the value of NLR in predicting mortality and major adverse cardiovascular events (MACEs) in ACS patients.*

Methods*: Relevant articles published were systematically searched from PubMed, the Cochrane Library, EMBASE and Web of before May 18, 2019. HRs with associated 95% confidence intervals (CIs) were calculated to estimate the effects.*

Results*: A total of 8 articles of 4877 patients were included in the meta-analysis. Our analysis for patients with recent ACS indicated that higher NLR was a prognostic marker in predicting long-term mortality (HR=1.19, 95% CI=1.03–1.39 P=0.022), long-term MACEs (HR=1.41, 95% CI=0.81–2.46, P=0.222), in-hospital mortality (HR=1.27, 95% CI=1.15–1.40, P<0.001). Pretreatment NLR predicted long-term mortality/MACEs in ACS patients (HR=1.17, 95% CI=1.07–1.28, P<0.001).*

Conclusion*: In conclusion, the updated meta-analysis of pooled adjusted HRs provided evidence that ACS patients with higher preconditioning NLR value have a higher risk of mortality.*

Keywords: *acute coronary syndrome, neutrophil-to-lymphocyte ratio, mortality, major adverse cardiovascular events, meta-analysis.*

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Introduction

Acute coronary syndrome (ACS) is one of the leading causes of death worldwide with a serious increase in the social medical burden[(1)]. ACS is a spectrum ranging from unstable angina (UA) to non-ST Segment Elevation Myocardial Infarction (NSTEMI) to ST-Segment Elevation Myocardial Infarction (STEMI). Patients with ACS are at a high risk of major adverse cardiovascular events (MACEs) [(2, 3)] and mortality[(4, 5)]. Although fractional flow reserve (FFR)[(6)], low-density lipoprotein cholesterol level[(7)] and soluble TREM-like transcript-1 (STLT-1)[(8)] were reported associated with the prognosis of ACS, their role as a prognostic factor remains controversial.

Neutrophil-to-lymphocyte ratio (NLR) served as a marker with strong prognostic significance has been in the limelight. Increased NLR as a biomarker as well as a predictor of various cardiac and non-cardiac disorders. It is a good assessment tool of glycemic control for type 2 diabetic patients[(9)], postoperative survival in patients with gastric cancer[(10)], cardiovascular and cerebrovascular diseases[(11, 12)]. Some studies have revealed the prognostic significance of NLR in ACS[(13, 14)].

Previous meta-analyses were studied on prognostic value of NLR in ACS by combined the odds ratios (ORs) or risk ratio (RRs)[15, 16]. Hazard ratios (HRs) are preferable when they are reported because they take into account the timing of the event, not just the number of patient events. Several new studies have been published on the prognostic value of NLR in ACS[17-19].The results of elevated NLR as a prognostic biomarker of mortality and MACEs in patients with ACS have been different. Thus we evaluated the role of elevated NLR as a prognostic biomarker in ACS by a new meta-analysis with HRs. We aimed to identify rational and effective way of predicting the prognosis of ACS patients worldwide.

Materials and methods

Data sources and searches

Systematic literature in PubMed, Embase and Cochrane Library and Web of Science was searched for relevant published prior to May 18, 2019. We used the following keywords to search literature: "neutrophil-to-lymphocyte ratio", "neutrophil to lymphocyte ratio", "NLR", "mortality", "MACE" "major adverse cardiac events", "acute coronary syndrome", "STEMI", "UA", and "NSTEMI". Abstracts and titles of the retrieved articles were assessed to exclude the ineligible ones from the meta-analysis. We excluded case reports, editorials or letters to the editor, review articles, and non-English studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Cohort studies with follow-up time≥6 months for long-term endpoints. (2) Provide multiple adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for pretreatment NLR. (3) NLR cut-off value is clear. (4) Describe the association between NLR and mortality, NLR and MACEs in ACS patients. (5) Adult patients≥18 years old with ACS. Studies that did not meet all of the above criteria were excluded.

Studies were excluded if any of the following characteristics are met: (1) Designed as a review, a case-controlled study or an animal study. (2) Sample size<200. (3) Absence HRs with 95% CIs. (5) Absence of cut-off value. (4) Overlapping or duplicate reports.

Data extraction

We assessed the quality of the studies obtained from the literature search by the Newcastle -Ottawa scale (NOS) (20). A total score≥6 was considered high quality. The basic information includes domains of authors, year of publication, cut-off value, patient characteristics, study regions, duration of follow up, sample size, type of ACS, adjusted HRs with 95% CIs, quality scores, and endpoints. The endpoints of the studies included mortality (in-hospital, or long-term) and MACEs (in-hospital, or long-term). MACEs include nonfatal MI, acute left ventricular failure, unstable angina, cardiogenic shock, nonfatal ischemic stroke, ventricular arrhythmia and cardiovascular death.

Statistical analysis

We performed data analyses by STATA statistical software (version 13.1). The HRs with their 95% CIs from each study were used to calculate the pooled HRs. Heterogeneity among studies was assessed using Cochrane's Q and I2 statistics. If no significant heterogeneity (I2 < 50%) was found, the fixed-effect model was used, or the random effect model was used. We used sensitivity analysis to investigate the influence of a single study for long-term mortality. The value $P<0.05$ was considered to be statistically significant.

Ethics

In this study, ethical approval was not necessary because the included data was based on previous published articles, and no original clinical data was collected or utilized.

Results

Search results and Study characteristics

A total of 461 potential relevant studies were selected from electronic databases. After application of selection criteria, 8 articles were recognized for inclusion in the present meta-analysis. The studies selection process is shown in Figure 1.

Table 1 demonstrates the basic features of the studies. There are 3 endpoints in these studies, in-hospital mortality[21], long-term mortality[17, 18, 21-24], long-term MACEs[3, 19]. There was only one study having clear data on two endpoints[21]. These studies were all observation researches and were conducted in the USA[21], China[3, 17, 19, 24], and Korea[18, 23]. Three studies were STEMI patients[18, 23, 24] while two studies were NTSE-ACS patients[19, 21], and three studies were mixed[3, 17, 22]. For all the studies, the average age of the patients was 50 years to 70 years,

and the follow-up ranged from 24 months to 113 months. Availability of HRs with their 95% CIs was all obtained by multivariate analysis.

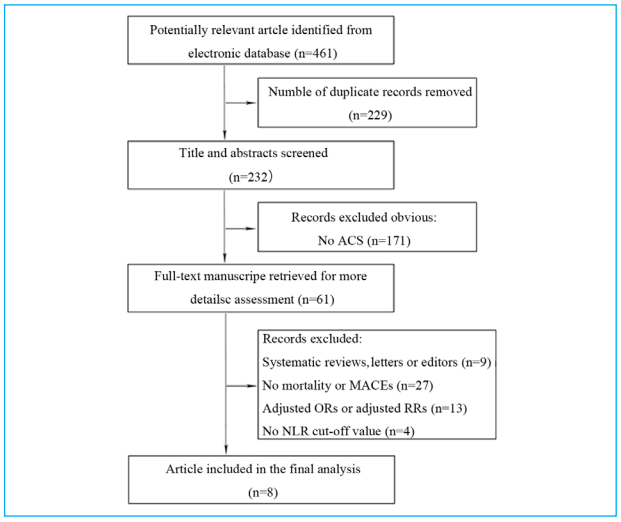

Figure 1: Flow diagram of literature search and study selection. ACS: acute coronary syndrome; NLR: neutrophil to neutrophil to lymphocyte ratio; MACEs: major adverse cardiac events.

Author& year	Country	Sample	Mean Age (years)	STEMI	Cut-off Value	End-point	Follow up (months)	Quality (NOS)
Xu N *et al*, 2018[26]	China	806	58.27	582 (72.21%)	3.39	long-term mortality	24	7
Park JS *et al*, 2018[21]	Korea	326	58	326 (100%)	4.3	long-term mortality	68	6
Fan Z *et al*, 2018[25]	China	678	62.81	0 (0%)	2.15	long-term MACEs	60	7
Shin HC *et al*, 2017[22]	Korea	381	61.64	180 (47.24%)	6.30	long-term mortality	27.5	7
Zhou D *et al*, 2015[3]	China	1050	52.8	NR	3.8	long-term MACEs	60	7
Park JJ *et al*, 2013[23]	Korea	325	60.9	325 (100%)	5.44	long-term mortality	6.4	7
He J *et al*, 2013[24]	China	692	61.7	692 (100%)	4.22	long-term mortality	113	7
Azab B *et al*, 2010[19]	USA	619	64.8	0 (0%)	4.7	long-term mortality in hospital mortality	48	7

NLR = neutrophil to neutrophil to lymphocyte ratio, NR = none reported, STEMI = ST-segment elevation acute coronary syndrome, MACEs = major adverse cardiac events, NOS = Newcastle Ottawa scale.

Table 1: : Characteristics of included studies in the meta-analysis.

Quality Score

We assessed the quality of the studies by Newcastle Ottawa scale (NOS) and the included studies marks are shown in table 2. There are 7 studies scoring 7 and only one 6. According to the NOS, all studies were of great quality and had scores of six or more.

NLR to long-term mortality

Six studies covering 3149 patients documented the relationship between NLR and long-term mortality[17, 18, 21-24]. We performed three subgroup analyses according to the ACS subtype (STEMI, NSTEMI and Mixed; Figure 2), sample size (size≥600 and size<600; Figure 3) and follow-up (follow-up≥48 months and follow-up<48 months; Figure 4). The prognostic role of pretreatment NLR was almost the same as that of large sample size (size≥600) (HR=1.92, 95% CI=0.84-4.40, P=0.123, random effects) and small sample size (size<600) (HR=1.85, 95% CI=0.84-4.09, P=0.129, random effects). Pretreatment NLR predicted long-term mortality in follow-up<48 months (HR=2.95, 95% CI=1.65–5.25, P<0.001, fixed effects) and in follow-up≥48 (HR=1.10, 95% CI=1.00-1.20, P=0.040, random effects). In comparison with subtype of ACS patients, results were identified in the STEMI group (HR=1.94, 95% CI=0.84-4.48, P=0.120, random effects). Analysis showed significant differences in Mixed group (HR=2.86, 95% CI=1.41-5.80, P=0.004, random effects) and NSTMI group (HR=1.09, 95% CI=1.04-1.14, P<0.001, random effects). Differences between disease subgroups were statistically significant (I2 = 65.9%, P=0.006).

A sensitivity analysis aiming to evaluate the impact of a single study on the overall pooled HR was performed. There were significant differences between the outcomes in both arms, and we observed significant interactions with a range from 1.00 to 4.24 (Figure 5).

Association between NLR and in-hospital/ long-term mortality

Only one study comprising 619 patients reported in-hospital mortality[21]. The combined results showed that the higher preconditioning NLR value of ACS patients was associated with higher in-hospital/long-term mortality (HR=1.21, 95% CI=1.07-1.38, P=0.003, random effects; Figure 6). Pretreatment NLR predicted in-hospital mortality (HR=1.27, 95% CI=1.15-1.40, P<0.001, random effects).

Newcastle Ottawa scale for quality of cohort studies									
		Authors							
	Item	Xu N *et al*, 2018	Park JS *et al*, 2018	Fan Z *et al*, 2018	Shin HC *et al*, 2017	Zhou D *et al*, 2015	Park JJ *et al*, 2013	He J *et al*, 2013	Azab B *et al*, 2010
A	**Selection**								
	Representativeness of exposed cohort	√	√	√	√	√	√	√	√
	Selection of non exposed cohort	√	×	√	√	√	√	√	√
	Ascertainment of Exposure	√	√	√	√	√	√	√	√
	Outcome of interest not present at start	×	×	×	×	×	×	×	×
B	**Comparability**								
	On the basis of the design or analysis	√	√	√	√	√	√	√	√
C	**Outcome**								
	Assessment of Outcome	√	√	√	√	√	√	√	√
	Follow up long enough (12months)	√	√	√	√	√	√	√	√
	Adequacy of follow up	√	√	√	√	√	√	√	√
	Score	7	6	7	7	7	7	7	7

Table 2: Newcastle Ottawa scale for quality of the included studies.

Incidence of long-term mortality/MACEs with higher NLR

Here were two trials including 1728 patients reported long-term MACEs[3, 19]. NLR greater than the cut-off was associated with an HR for long-

term mortality/MACEs in ACS patients (HR=1.17, 95% CI=1.07-1.28, P<0.001, random effect; Figure 7). The frequency of long-term MACEs had no significance (HR=1.41, 95% CI=0.81–2.46, P=0.222, random effects) with the higher NLR.

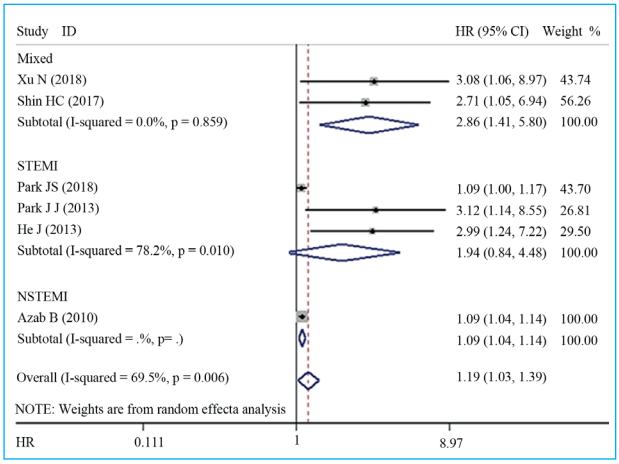

Figure 2: Forest plot of meta-analysis on HR values for long-term mortality. The subgroup analysis is according ACS subtype (STEMI, NSTEMI and Mixed).

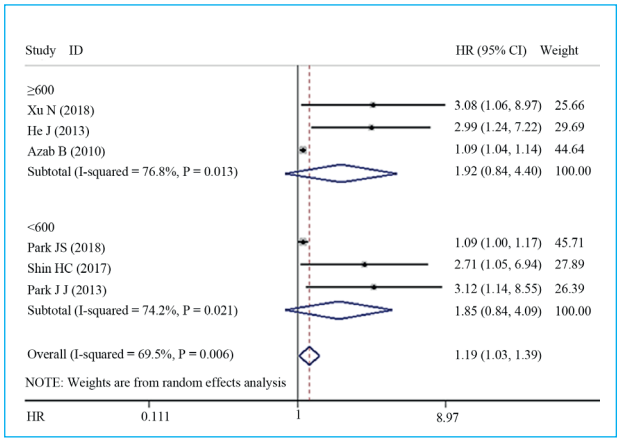

Figure 3: Forest plot of meta-analysis on HR values for long-term mortality. The subgroup analysis is according to sample size (size≥600 and size<600).

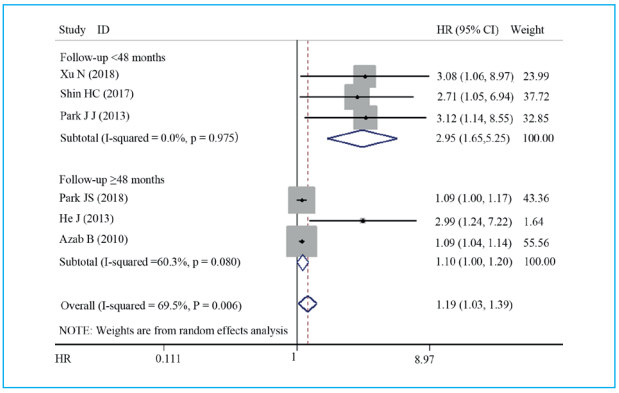

Figure 4: Forest plot of meta-analysis on HR values for long-term mortality. The subgroup analysis is according to follow-up (follow-up≥48 months and (follow-up<48).

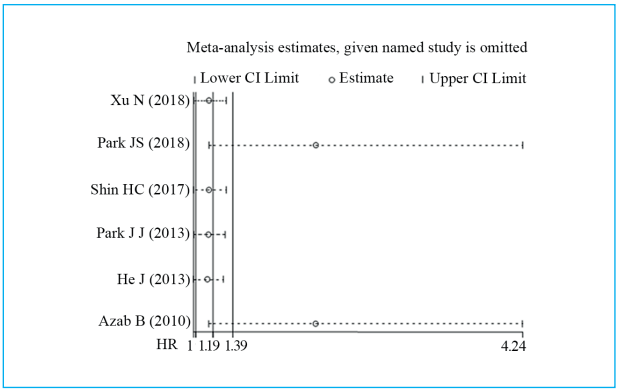

Figure 5: Result of sensitivity analysis for long-term mortality.

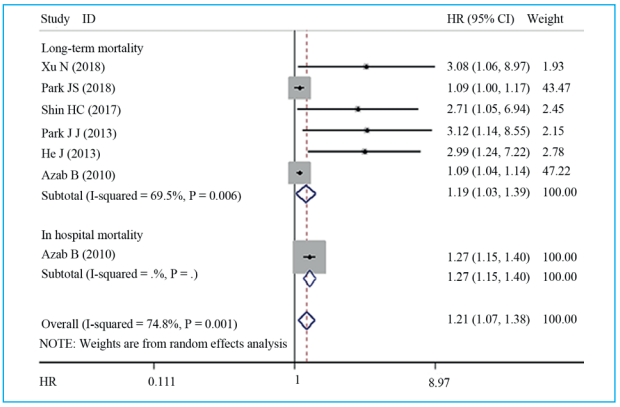

Figure 6: Forest plot of meta-analysis on HR values for in-hospital/long-term mortality.

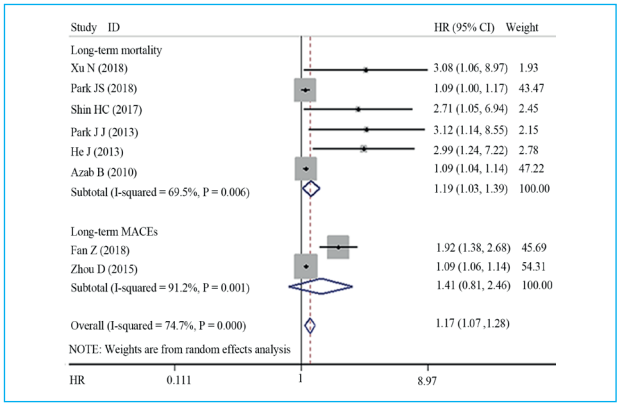

Figure 7: Forest plot of meta-analysis on HR values for long-term mortality/MACEs.

Discussion

The present study showed that high NLR value was associated with a higher long-term mortality and in-hospital mortality in patients with a recent ACS. The long-term mortality estimates for heterogeneity are extreme. Subgroup analyses based on follow-up, subtype of ACS and sample size were employed to account for heterogeneity. The subgroup analysis by sample size suggested that higher-NLR enhanced

the risk of long-term mortality in ACS patients from sample size≥600 and sample size<600 combined, while there was no significant difference between sample size≥600 and sample size<600. No association was identified for either size separately.

Higher-NLR increased long-term mortality in ACS patients from ACS subtype combined, while there was no association identified for STEMI. The sensitivity analysis shows that the results for long-term mortality are dominated by individual studies. These two studies might be the source of heterogeneity through the subgroup analyses and sensitivity analyses. Using this strategy, the studies by Azab B et al[21] and Park JS et al[18] were identified as the major source of heterogeneity. This might be due to both studies enrolled STEMI patient completely. The heterogeneity of the HR was significantly reduced in the stratified analysis by follow-up. Therefore, it may be postulated that subtype of ACS, months of follow-up and sample size might have contributed to the heterogeneity in the present meta-analysis

The study indicated that the prognostic role of pretreatment NLR in predicting long-term mortality has difference in follow-up, sample size and ACS subtype. However, compared with STEMI patients, there was a significant difference in the subgroup analysis of NSTMI or Mixed group, which was different from previous studies[17,25,26]. The calculated HRs were lower in long-term mortality/MACEs compared with long-term mortality, suggesting that high preconditioning NLR could be an indicator for long-term endpoints in ACS patients.

There are several possible explanations for why a higher NLR may increase mortality and MACEs. Reduced lymphocytes reflect physiological stress and poor general health[21]. Neutrophils represent a subclinical inflammatory stage in which the release of pro-oxidants and prothrombotic substances leads to endothelial damage and platelet aggregation[27]. Therefore, NLR is the balance between two important and opposite immune pathways (stress response and inflammation)[27]. These mechanisms also include the release of reactive oxygen species, myeloperoxidase and proteolytic enzymes which facilitate the plaque disruption[27-30]. Standard grayscale intravascular ultrasound (IVUS) can provide more ultrasound information on plaque characterization[31,32].

However, NLR will not be a reliable tool in several situations, such as blood diseases, sepsis, systemic inflammatory disease, cancer, autoimmune diseases, acute/chronic infection and steroid therapy[15]. Although higher NLR increased the incidence of major heart events by 55%, the actual difference in NLR between patients with and without ACS patients was very small (P<0.001)[33]. NLR combines changes in neutrophils and lymphocytes during inflammation to predict cardiovascular disease better than any other leukocyte subtype[34]. In our study, NLR could serve as a tool for predicting the prognosis of ACS patients.

This is the first meta-analysis only included adjusted HRs to address on the association between NLR and mortality, NLR and MACEs in ACS patients. The present results differ from those of the previous meta-analyses in several aspects. In the meta-analysis study by Dong CH et al[15] reported that the higher NLR in STEMI group (OR=2.76, 95% CI=1.77-4.31, P<0.001, random effects) was totally different from our result in STEMI group (HR=1.94, 95% CI=0.84–4.48, P=0.120, random effects). The meta-analysis by Zhang S et al(16) indicated that Pretreatment NLR predicted long-term MACEs (RR=2.49, 95% CI=1.47–4.23, P<0.001, random effects); whereas in the present meta-analysis, the frequency of long-term MACEs had no significance (HR=1.41, 95% CI=0.81–2.46, P=0.222, random effects) with the higher NLR. Therefore, the results obtained by the hazard ratios are valuable for reference.

The current systematic reviews and meta-analyses have several limitations. One potential limitation of the present meta-analysis is the use of different levels of NLR in the included studies. In the study we included, the cut-off value ranges from 2.15 to 6.30. Second, the follow-up duration and the difference in the study population may lead to heterogeneity to some extent. The study region was another possible limitation of the present results, with only one study was conducted in No-Asian(21). Therefore, further meta-analysis is required and should include more studies from No-Asian. Finally, substantial heterogeneity was present in the total pooled analysis of mortality and MACEs. Our meta-analysis results should be interpreted cautiously.

In conclusion, compared with the lower category of NLR, the higher category experiences an increased risk of long-term mortality in ACS patients.

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Abbreviations: NLR = neutrophil-lymphocyte ratio; ACS = acute coronary syndrome; ORs = odds ratios; RRs = risk ratio; HRs = hazard ratios; MSCEs = major adverse cardiovascular events; CIs = confidence intervals; UA = unstable angina; NSTEMI = non-ST Segment Elevation Myocardial Infarction; STEMI = ST-Segment Elevation Myocardial Infarction; FFR = fractional flow reserve; STLT-1 = soluble TREM-like transcript-1; NOS = Newcastle-Ottawa scale

Authors' contributions

Xiao-Qing Quan, Zhong-Hui Jiang: Design of the study; acquisition and interpretation of data; manuscript preparation and the initial draft; accountable for all aspects of the work. Zhong-Hui Jiang, Zhong-Bin Yang: statistical analysis, analysis and interpretation of data; accountable for all aspects of the work. Hong-Tao Liu, Xiao-Qing Quan: design of the study; critical review of the draft and contribution to the writing of the manuscript; final approval of the version to be published and accountable to the accuracy or integrity of the work.

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Corresponding Author:
Hong-Tao Liu
Department of Cardiology, Shenzhen Longhua District Central Hospital, The Affiliated Central Hospital of Shenzhen Longhua District, Guangdong Medical University, Shenzhen, China
Email: lht1376@163.com
(China)