Wellens' Syndrome: Incidence, Characteristics, and Long-Term Clinical Outcomes

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Abstract

Background: Sparse study of large sample size are available on patients with Wellens' syndrome. We sought to assess the current incidence, risk factors, clinical presentation and long-term outcomes of this population. **Methods:** Among a total of 3528 patients with ACS underwent angioplasty from 2017 to 2019 in our center, 2127 NSTEMI-ACS patients with culprit vessel of LAD were enrolled in this study. According to electrocardiographic criteria, they were divided into Wellens' group (n = 200) and non-Wellens' group (n =1927). The primary endpoint was cardiac death; the secondary endpoint was MACCE, a composite of all-cause death, cardiac death, recurrent myocardial infarction, target lesion revascularization, heart failure and stroke.

Results: The incidence of Wellens' syndrome was 5.7% (200 of 3528) in all the ACS patients. Wellens' syndrome was more often manifested as NSTEMI (69% vs 17.5%, $P=0.001$). Percent of preexisting coronary heart disease (39.6% vs 23%) and previous PCI (19.5% vs 9%) were significantly higher in the non-Wellens' group than in Wellens' group (all $P<0.001$). More importantly, the proportion of early PCI was higher in Wellens' group (68% vs 59.3%, $P=0.017$). At a median follow-up of 24 months, Wellens' syndrome was not a factor that affects the prognosis of MACCE ($P=0.05$) and cardiac death ($P=0.188$).

Conclusions: In patients with NSTEMI-ACS, Wellens' syndrome does not affect the prognosis. The presence of age $\geq$ 65years, diabetes, NSTEMI, eGFR $<$ 60ml/min and left main disease were associated with an incidence of cardiac death. Early recognition and aggressive intervention are critical as they may help to attenuate adverse outcomes.

1. Introduction

Acute coronary syndrome (ACS) remains a leading cause of mortality and morbidity worldwide, need for emergency care and eventual hospitalization. (1–3). The diagnosis of ACS relies on clinical history, electrocardiographic (ECG) changes, and cardiac biomarkers; but within the spectrum of ACS, there exist subtle presentations that cannot afford to be overlooked. Wellens' syndrome is one such example, in which a patient can present with both ECG changes that are not classic for myocardial ischemia and even negative cardiac biomarkers. As well-known high-risk ACS, Wellens' syndrome first described by de Zwaan and Wellens in 1982 (4), is the characteristic ST-T segment changes in the precordial leads indicating a critical stenosis high in the left anterior descending arterial (LAD). Identifying the syndrome carries significant diagnostic and prognostic value (5). According to the Fourth Universal Definition of myocardial infarction (6), absence of ST-elevation in the precordial leads, the symmetrical, often deep (>2 mm), T wave inversions in the anterior precordial leads is an early sign that may precede the elevation of the ST-segment. Thus, this syndrome was thought to be an acute ST-elevation myocardial infarction (STEMI) equivalent (7).

Patients with Wellens' syndrome have an increased risk for extensive anterior wall myocardial infarction and early coronary revascularization is essential in the management of these cases. They are a special

cohort with their own clinical characteristics, which may affect the outcomes in this population. But limited literature on the syndrome is mostly sporadic case reports and clinical experience. There is still a paucity of recent data on patients with Wellens' syndrome. Updated information on incidence, risk factors, angiographic findings and prognosis of this subset of patients should be taken into consideration when taking care of these patients.

The aims of this retrospective control study were therefore to investigate the incidence and the risk factor profile in Wellens' syndrome patients versus other ACS patients with culprit vessel of LAD admitted to Beijing Friendship hospitals in China between 2017 and 2019, and to study the clinical presentation, treatment and long-term outcomes in these patients.

1.1 Study methods

1.1.1 Study design and participants

This retrospective study was based on data from Cardiovascular Center of Beijing Friendship Hospital Data Bank. The protocol was approved by the ethical committee of Beijing Friendship Hospital (2021-P2-096-01). From January 2017 to December 2019, coronary angioplasty was performed in 3528 consecutively ACS patients at our center, a total of 2621 patients with culprit vessel of LAD were enrolled in this study. To rule out pathological Q waves in the ECG, 460 patients with STEMI were excluded. And 34 patients were lost to follow up. Finally, a total of 2127 patients were included in the final analysis. Among the 2127 patients, 200 cases met the ECG criteria of Wellens' syndrome, including 64 cases of type A, 136 cases of type B, all of whom were shown angiographically to have significant LAD stenosis. Baseline characteristics, percutaneous coronary intervention (PCI) procedures, management, and long-term outcomes were collected from medical records and Data Bank, and then analyzed. Flowchart of patient enrolment is shown in Figure 1.

In all patients 12-lead ECGs were routinely obtained once daily while in hospital. Additional ECGs were checked during and after new attacks of chest pain. The criteria for Wellens' syndrome are (8, 9): a) prior history of chest pain, b) minimal or no elevation of cardiac enzymes, c) insignificant ST-segment elevation usually (<1 mm), d) no loss of precordial R waves, e) absent precordial Q waves and f) biphasic T waves in leads V_2 and V_3 , or asymmetric, often deeply inverted T waves in leads V_2 and V_3 . Wellens' syndrome can be divided into two different types according to the precordial T wave pattern that are seen at the painless period. In type A, there are biphasic T waves typically observed in V_2 and V_3 . In Type B, which is the commonest form, there are deep negative T waves in leads V_2 and V_3 .

1.1.2 Data collection and clinical outcomes

The patients' demographic information and cardiovascular risk factors including hypertension, dyslipidemia, diabetic mellitus, chronic kidney disease (CKD), peripheral arterial disease (PAD), heart failure (HF), smoking history, preexisting coronary heart disease (CHD) and previous PCI were retrospectively collected from medical records. Body mass index (BMI) was calculated by dividing weight

in kilograms by height in meters squared (kg/m^2). Smoking history was defined as regularly smoking one or more cigarette daily or smoking cessation within the past 12 months. Left ventricular ejection fraction (LVEF) and end diastolic dimension (EDD) were measured by transthoracic echocardiology before PCI. The angiogram data including the number of stenosed coronary vessel, left main (LM) disease and PCI strategy was obtained by reading the surgical report.

The primary endpoint for this analysis was cardiac death, defined as death caused by myocardial infarction, heart failure, arrhythmia and unexplained sudden death (10). The secondary endpoint were major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all cause death, cardiac death, recurrent myocardial infarction, target lesion revascularization, heart failure, and stroke. Recurrent myocardial infarction was defined by the Fourth Universal Definition (6).

All MACCE were thoroughly analyzed and confirmed by two separate cardiologists simultaneously. Follow-up information discharged from the hospital was obtained by clinic visits or phone interviews every 1-3 months, that was recorded in Data Bank.

2. Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation or as median with interquartile range, and one-way analysis of variance was used to compare differences between continuous variables. Categorical variables are expressed as percentages and were analyzed using the Pearson's χ^2 test or Fisher's exact test of variance. The cumulative incidence was estimated by the Kaplan-Meier method, and differences between groups were assessed by the log-rank test (11).

Cox regression was used to estimate relative risks among groups of patients. All statistical tests were two-tailed, with statistical significance defined as a p value of < 0.05 . All analyses were performed by using SPSS (version 25.0, Chicago, IL, USA);

Kaplan–Meier survival curves were generated with the use of the GraphPad Prism software (version 5; GraphPad, Inc, San Diego, CA) (11).

3. Results

3.1 Baseline characteristics

Patients stratified by Wellens' syndrome characteristics are summarized in Table 1. The study cohort included 2127 NSTEMI-ACS patients with culprit vessel of LAD. Of these, 200 (9.4%) were Wellens' syndrome. Wellens' syndrome was more often manifested as non-ST-elevation myocardial infarction (NSTEMI) (69% vs 17.5%, $P=0.001$). Percent of preexisting coronary heart disease (39.6% vs 23%) and previous PCI (19.5% vs 9%) were significantly higher in the non-Wellens' group than in Wellens' group (all $P<0.001$). Two groups of patients had a similar prevalence of gender distribution, hypertension, diabetes mellitus and hyperlipemia. There were also no significant differences in the medical history of old

myocardial infarction (OMI), HF, CKD, PAD and stroke. Compared with non-Wellens' patients, more Wellens' patients had lower BMI (25.21 ± 2.97 vs $25.93 \pm 3.45 \text{ kg/m}^2$, $P=0.005$), abdominal circumference (90.79 ± 9.84 vs $92.5 \pm 10.08 \text{ cm}$, $P=0.025$) and LVEF (0.62 ± 0.09 vs 0.65 ± 0.08 , $P=0.002$). However, the LDL-C and EDD was higher in the Wellens' group.

Table 1
Comparison of the baseline characteristics among patients.

Variables	Wellens' (N=200)	non-Wellens' (N=1927)	P value
Age (years)	63.3±10.4	64.2±9.7	0.158
Male	146(73)	1314(68.2)	0.163
Days	6(5,8)	6(4,7)	0.001
BMI (kg/m ²)	25.21±2.97	25.93±3.45	0.005
AC (cm)	90.79±9.84	92.5±10.08	0.025
Smoking	114(57)	1017(55.8)	0.255
HT	133(66.5)	1353(70.2)	0.276
DM	70(35)	810(42)	0.055
Hyperlipemia	100(50)	1030(53.5)	0.352
History of CHD	46(23)	763(39.6)	0.001
OMI	15(7.5)	199(10.3)	0.206
HF	1(0.5)	13(0.7)	0.771
CKD	10(5)	71(3.7)	0.355
PAD	14(7)	202(10.5)	0.121
Stroke	39(19.5)	317(16.5)	0.271
Previous PCI	18(9)	376(19.5)	0.001
NSTEMI	138(69)	338(17.5)	0.001
EDD (cm)	5.19±0.56	5.08±0.52	0.006
LVEF	0.62±0.09	0.65±0.08	0.002
LDL-C(mmol/L)	2.5±0.73	2.25±0.75	0.001
eGFR(ml/min)	86.69±24.76	88.09±22.2	0.408

Bold values indicate that the difference is statistically significant ($P < 0.05$)

Data are presented as absolute numbers and percentages (for categorical variables) or mean value ± SD (for continuous variables) unless otherwise specified.

BMI, body mass index; *AC*, Abdominal circumference; *HT*, hypertension; *DM*, diabetes mellitus; *CHD*, coronary heart disease; *OMI*, old myocardial infarction; *HF*, heart failure; *CKD*, chronic kidney disease; *PAD*, peripheral arterial disease; *PCI*, percutaneous coronary intervention; *NSTEMI*, non-ST-elevation myocardial infarction; *EDD*, left ventricular end diastolic dimension; *LVEF*, left ventricular ejection fraction; *LDL-C*, low-density lipoprotein cholesterol; *eGFR*, estimated glomerular filtration rate (calculated via Modification of Diet in Renal Disease equation); *HbA1c*, glycated hemoglobin.

Variables	Wellens' (N=200)	non-Wellens' (N=1927)	Pvalue
HbA1c (%)	6.54±1.46	6.7±21.45	0.159
Bold values indicate that the difference is statistically significant ($P < 0.05$)			
Data are presented as absolute numbers and percentages (for categorical variables) or mean value ± SD (for continuous variables) unless otherwise specified.			
<i>BMI</i> , body mass index; <i>AC</i> , Abdominal circumference; <i>HT</i> , hypertension; <i>DM</i> , diabetes mellitus; <i>CHD</i> , coronary heart disease; <i>OMI</i> , old myocardial infarction; <i>HF</i> , heart failure; <i>CKD</i> , chronic kidney disease; <i>PAD</i> , peripheral arterial disease; <i>PCI</i> , percutaneous coronary intervention; <i>NSTEMI</i> , non-ST-elevation myocardial infarction; <i>EDD</i> , left ventricular end diastolic dimension; <i>LVEF</i> , left ventricular ejection fraction; <i>LDL-C</i> , low-density lipoprotein cholesterol; <i>eGFR</i> , estimated glomerular filtration rate (calculated via Modification of Diet in Renal Disease equation); <i>HbA1c</i> , glycated hemoglobin.			

Table 2 shows the differences of angiographic characteristics and treatment data with Wellens' and non-Wellens' patients. Between the two groups, they had a similar rate of LM disease and multivessel disease. Compared to non-Wellens' group, Wellens' patients had more drug-eluting stent implanted (96.5% vs 84.8%, $P=0.001$) and stent numbers (1.35 ± 0.63 vs 1.14 ± 0.69 , $P=0.001$), but less plain balloon angioplasty (3.5% vs 14.6%, $P=0.001$). More importantly, the proportion of early PCI (≤ 48 h after first presentation) was higher in Wellens' group (68% vs 59.3%, $P=0.017$).

Table 2
Angiographic characteristics and treatment data.

Variables, n (%)	Wellens' (N=200)	no- Wellens' (N=1927)	Pvalue
Multivessel disease	177(88.5)	1712(88.8)	0.884
LM disease	18(9)	229(11.9)	0.226
Plain balloon angioplasty	7(3.5)	279(14.6)	≤ 0.001
Drug-eluting stent	193(96.5)	1635(84.8)	≤ 0.001
Stent length ≥ 30 mm	58(29)	542(28.1)	0.794
Number of stents	1.35 ± 0.63	1.14 ± 0.69	≤ 0.001
Early PCI (≤ 48 h after first presentation)	136(68)	1143(59.3)	0.017
Values are n (%), mean ± SD or median with interquartile range.			
<i>LM</i> , left main.			

3.2 Clinical outcomes

The median follow-up time was 24 months. The clinical outcomes in Wellens' and non-Wellens' group are shown in Table 3. Compared with Wellens' group, non-Wellens' group had significantly higher rates of re-hospitalization (19.3% vs 10.5%, $P=0.002$). There were no differences in MACCE (Wellens' 4.5% vs non-

Wellens' 6.5%, $P=0.26$), all-cause death, cardiac death, HF, target vessel revascularization, recurrent myocardial infarction and stroke. Kaplan-Meier analysis also revealed no difference in MACCE($P_{\log\text{-rank}}=0.28$) and cardiac death ($P_{\log\text{-rank}}=0.44$) between Wellens' and non-Wellens' group (Figure 2).

Table 3. Comparison of clinical outcome between Wellens' and non-Wellens' group.

Variables, n (%)	Wellens'(N=200)	no-Wellens' (N=1927)	Pvalue
MACCE	9(4.5)	126(6.5)	0.26
All-cause death	4(2)	58(3)	0.419
Cardiac death	2(1)	34(1.8)	0.425
Re-hospitalization	21(10.5)	372(19.3)	0.002
Heart failure	1(0.5)	25(1.3)	0.329
Target vessel revascularization	0	18(0.9)	0.17
Recurrent myocardial infarction	5(2.5)	48(2.5)	0.994
Stroke	2(1)	21(1.1)	0.907
Values are n (%).			
MACCE: major adverse cardiac and cerebrovascular events, a composite of all-cause death, cardiac death, recurrent myocardial infarction, target vessel revascularization, heart failure, and stroke.			

3.3 Predictors of survival

Considering all patients, a multivariable Cox regression analysis (Table 4) was used to identify clinical and angiography independent predictors of cardiac death and MACCE. For MACCE, the final multivariable mode included age $\geq$ 65years, diabetes mellitus, NSTEMI and LM disease. For cardiac death, the final multivariable mode included age $\geq$ 65years, diabetes mellitus, NSTEMI, eGFR $\leq$ 60ml/min and LM disease. Overall, Wellens' syndrome was not a factor that affects the prognosis of MACCE ($P=0.05$) and cardiac death ($P=0.188$). In Figure 3, NSTEMI was the biggest influencing factor of poor MACCE (HR 2.49, 95% CI 1.73–3.58) and cardiac death (HR 3.38, 95% CI 1.71–6.66).

Table 4
Multivariate Cox regression analysis in the overall patients

	Predictor variable	HR (95% CI)	P value
MACCE	Age≥65years	2.33(1.6-3.39)	0.001
	Male	1.15(0.79-1.67)	0.468
	HT	1.11(0.74-1.66)	0.606
	DM	1.83(1.29-2.58)	0.001
	eGFR<60ml/min	1.22(0.77-1.95)	0.396
	NSTEMI	2.49(1.73-3.58)	0.001
	Wellens' syndrome	0.5(0.25-1)	0.05
	Multivessel disease	1.5(0.69-3.26)	0.302
	LM disease	1.56(1.02-2.39)	0.04
Cardiac death	Age≥65years	2.31(1.09-4.88)	0.029
	Male	1.06(0.52-2.15)	0.883
	HT	0.79(0.37-1.68)	0.534
	DM	2.16(1.09-4.29)	0.027
	eGFR<60ml/min	2.61(1.24-5.51)	0.012
	NSTEMI	3.38(1.71-6.66)	0.001
	Wellens' syndrome	0.38(0.09-1.61)	0.187
	Multivessel disease	1.11(0.26-4.8)	0.884
	LM disease	2.22(1.05-4.69)	0.037
HR, Hazard ratio; CI, Confidence interval; MACCE, major adverse cardiac and cerebrovascular events; HT, hypertension; DM, diabetes mellitus; NSTEMI, non-ST-segment elevation myocardial infarction; LM, Left main.			

4. Discussion

Wellens' syndrome is a pattern of precordial T-wave abnormalities, first described by Wellens and his group, representing critical LAD coronary artery stenosis. In Wellens' initial study group of 145 patients admitted for unstable angina, 9% had the typical pattern upon presentation, with a further 9% developing the T-wave changes within 24 h. Seventy-five percent of these patients went on to suffer an anterior wall myocardial infarction despite relief of symptoms with medical therapy. In a second prospective study,

14% of patients with unstable angina met the ECG criteria, all of whom were shown angiographically to have significant LAD stenosis (12).

In our study, patients with Wellens' syndrome represented 5.7% (200 of 3528) of ACS patients hospitalized during three years. More specifically, the incidence of Wellens' syndrome in NSTEMI-ACS patients with culprit vessel of LAD was 9.4% (200 of 2127). Of these patients, 64 cases presented with Type A Wellens', which comprises 32% (64 of 200) of cases and has biphasic T waves in lead V₂ and V₃. The remaining 68% (136 of 200) are Type B Wellens' syndrome, which is deeply inverted, symmetrical T waves in predominantly V₂ and V₃. The percentage is roughly in line with previous findings, which had shown the type A Wellens' constitutes roughly 24% of cases and the type B Wellens' accounts for the remaining 76% of cases (9). We also confirmed that type B Wellens' syndrome is more common.

The mechanism of Wellens' syndrome remains unclear. It is considered a pre-infarction stage of CHD as the T-wave changes in the syndrome usually occur during the pain-free period (13, 14). It is also postulated that the changes in the ECG account for reperfusion of the ischemic myocardium due to alleviation of spasm of proximal LAD artery (15–17). There is also a view that it may be related to myocardial stunning or myocardial hibernation.

Multiple risk factors are common in patients with Wellens' syndrome, and the majority of these patients are reported to have at least one traditional cardiovascular risk factor. Such as hypertension, diabetes mellitus, dyslipidemia, and these are no difference with non-Wellens' group in our study. More than half of the patients with Wellens' syndrome were current smokers (57%). Compared with non-Wellens' patients, they had higher LDL-C levels (2.5 ± 0.73 vs 2.25 ± 0.75 mmol/L, $P=0.001$), but were less likely to be diagnosed with hyperlipemia (50% vs 53.5%, $P=0.352$). Patients with Wellens' syndrome were also less likely than non-Wellens' patients to have history of CHD and previous PCI at admission, which means Wellens' syndrome tends to occur in patients with new-onset cardiovascular disease. In addition, there were no significant differences between the two groups in comorbidities, such as HF, CKD, PAD, and stroke.

NSTEMI was the clinical presentation in 69% of Wellens' patients, that was much higher than the 17.5% in non-Wellens' group. But previous studies have suggested that unstable angina is the main clinical manifestation of Wellens' patients (4, 12). The increased incidence rate of NSTEMI should be due to the adoption of Fourth Universal Definition of Myocardial Infarction defined by raised cardiac troponin, especially with hs-cTn that detect myonecrosis.

The angiographic characteristics of coronary heart disease in patients with Wellens' syndrome may differ from the presentation in other ACS patients. Although there were no differences in LM disease and multivessel disease between the two groups, Wellens' patients had more drug-eluting stent implanted and stent numbers than non-Wellens' patients. This discrepancy may, to a large degree, be explained by a higher percentage of proximal and mid LAD lesions of patients with Wellens' syndrome. And balloon angioplasty, including plain old balloon and drug coated balloon, is not appropriate for these critical sites (18–20).

It is well known that patients with Wellens' syndrome are at high risk of extensive anterior wall infarction, that might lead to serious left ventricular dysfunction, malignant arrhythmias, and sudden death. To our surprise, there was no statistically significant difference in MACCE between the two groups during the follow-up period (mean 24 months), even though the Wellens' group had a higher rate of myocardial infarction at admission. Furthermore, the 2-year incidence of cardiac death was similar in the two groups (Wellens' 1% vs. non-Wellens' 1.8%, $P=0.425$). We believe that this low incidence was obtained by our approach, which was to treat these patients aggressively in urgent angiography and intervention. Data showing that the proportion of early PCI was higher in the Wellens' group (68% vs. 59.3%, $P=0.017$). This highlights the importance of timely identification of Wellens' syndrome and appropriate management in this group of patients. Most patients, when identified early and taken for cardiac catheterization, do well after appropriate intervention. On the strength of improvement of medical procedures, a small number of Wellens' patients (10.5%) are readmitted after PCI during 2 years, that was much lower than non-Wellens' group (19.3%, $P=0.002$). We did not find any relation between Wellens' syndrome and the poor prognosis in patients with NSTEMI. And NSTEMI was the biggest influencing factor of poor MACCE and cardiac death. This suggests the prognosis of CHD depends on its severity.

Early PCI is the preferred treatment for patients with high-risk NSTEMI-ACS at now(21, 22). But few patients can receive it within 24 h recommended by the guideline in the real world, especially for patients with pain-free at admission. In our study, we presume that the aggressive invasive strategy (<48h after first presentation) could attenuate the risk of MACCE and avoid long-term adverse outcomes in patients with Wellens' syndrome.

The main strengths of this study are the large and unselected population comprising nearly all NSTEMI-ACS patients with culprit vessel of LAD in our hospital from 2017 to 2019 and a nearly complete follow-up. However, there are some important limitations associated with the study design. First, this was a single-center, retrospective, observational study. So, decision of therapy strategy reflected the convention and tendency of our single center, which may affect the objectivity of the conclusion.

Second, this study only included NSTEMI-ACS patients with culprit vessel of LAD. Therefore, our findings may not apply to other subtypes of CHD. Further prospective multicenter studies are needed to validate our findings.

5. Conclusions

First, our study has revealed that the incidence of Wellens' syndrome could reach up to 5.7% by coronary arteriography in clinical practice. Second, the Wellens' patients had a lower prevalence of history of CHD and previous PCI at admission, thus Wellens' syndrome is more common in population with new-onset cardiovascular disease. Third, Wellens' syndrome does not affect the prognosis in patients with NSTEMI-ACS. And early recognition and aggressive intervention are critical as they may help to attenuate the adverse outcomes.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Beijing Friendship Hospital (approval number 2021-P2-096-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

All participants gave informed consent.

Competing interests

None declared.

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Authors' contributions

All authors gave the final approval of the version published. LZ wrote the first draft of the manuscript. Xh G did the statistics. TD and Hh C collected data. HC and Hw L made revisions to the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to database principle but are available from the corresponding author on reasonable request.

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Figures

ACS, acute coronary syndromes; *PCI*, percutaneous coronary intervention; *LAD*, left anterior descending arterial; *STEMI*, ST-elevation myocardial infarction; *MACCE*, major adverse cardiac and cerebrovascular events.

Figure 1

Flow chart of patient enrollment

Figure 2

Kaplan–Meier analysis of MACCE (secondary endpoint, panel A) and cardiac death (panel B) for overall patients stratified by Wellens’ syndrome (green line) and non-Wellens’ syndrome (red line).

Figure 3

Factors independently associated with MACCE and cardiac death in overall patients in multivariable Cox regression analysis.