

Temporal trends in diagnosis, treatment, and outcome for non-ST-segment elevation acute coronary syndrome in three regions of China, 2008–2015

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To the Editor: As acute coronary syndromes (ACS) is common causes of morbidity and mortality in China, they serve as an important case example to assess the impact of these health reforms on the quality, safety, and efficiency of healthcare.^[1]

ACS comprises a wide spectrum of disease subgroups, including ST-segment elevation myocardial infarction (STEMI), unstable angina (UA), and non-ST-segment elevation myocardial infarction (NSTEMI). Previous studies have shown increases in the intensity of testing and treatment while stable in-hospital mortality for STEMI in China between 2001 and 2011.^[2] As non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) patients, who account for about two-thirds of ACS patients, have a wide spectrum of disease severity, risk-stratified management is recommended to ensure appropriate allocation of resources, especially in limited-resource settings of China. As limited data exist on the use of medical services and clinical outcomes in relation to health reforms, we aimed to determine temporal trends in diagnosis, treatment, and outcome for hospitalized NSTEMI-ACS patients in three regions of China between 2008 and 2015.

A retrospective review of medical records in 38 hospitals (24 tertiary, 14 secondary) located in three provincial regions (Beijing, Henan, and Jilin) of China between January 1, 2008, and December 31, 2015. Adult (age

≥18 years) in-patients were included with a primary discharge diagnosis of NSTEMI or UA determined by the treating physician. Excluded were patients who died within 10 min of hospital arrival (death was more likely attributable to disease severity rather than in-hospital care); self-discharged; were transferred from another hospital; or were non-permanent residents of the local region. Participating hospitals received ethics approval from their local Institutional Review Board, with a waiver of informed consent due to the chart review study design.

In-hospital patient clinical outcomes included major adverse cardiovascular events (MACE), including all-cause death, recurrent nonfatal myocardial infarction (MI), non-fatal stroke, heart failure (HF), and major bleeding.^[3] MI or stroke was defined by the diagnosis documented by the treating physician. HF included any episodes of acute pulmonary edema or cardiogenic shock during hospitalization, or clinically diagnosed at discharge. Major bleeding included situations when a patient's hemoglobin declined by 2 g/dL or more, if a patient needed a blood transfusion, or medical or surgical intervention, or if bleeding resulted in permanent physical dysfunction from intracranial hemorrhage.^[4]

Temporal trends of diagnostic testing, treatment, and MACE, adjusted for patient-level and hospital-level characteristics, were assessed through a generalized linear

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mixed-effect model (GLMM) with patient admission year, age, sex, insurance status, treating hospital level, history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, history of diabetes mellitus, systolic blood pressure (SBP < 100 mmHg), heart rate (HR, > 100 bpm), estimated glomerular filtration rate (eGFR < 60 mL·min⁻¹·1.73 m⁻²), and a random intercept by participating hospital, as independent variables. These covariates were included in the Global Registry of Acute Coronary Events (GRACE) risk model, which was used to categorize patients into high- (GRACE score > 140) and low- or intermediate- (GRACE score ≤ 140) risk groups.^[5] Differences between the two GRACE risk groups were tested through the coefficient of an interaction term between the admission year and the GRACE group. Data are presented with odds ratios (OR) and 95% confidence intervals (CI). A two-sided significance level of 0.05 was predefined. All statistical analyses were undertaken using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>).

The analytical sample of 13,759 patients with NSTEMI-ACS was drawn from 14,729 patients admitted to all participating hospitals between 2008 and 2015. There were 883 (6.0%) and 78 (0.5%) patients excluded for missing admission and incorrect admission dates, respectively, and 9 (0.1%) were of young age (<18 years). Over the study period, similar percentages of patients were recruited from the three provincial regions (approximately 40% from Beijing, 30% from Henan, and 30% from Jilin; $P_{trend} = 0.460$), but more patients were recruited from tertiary hospitals (63% in 2008 to 70% in 2015; $P_{trend} = 0.001$) and had medical insurance (82.5% in 2008 to 94.9% in 2015; $P_{trend} < 0.001$) over the study period. The median age of the study sample was 64.1 years (56.2–73.3), 54.7% males, and sex distribution was stable [Supplementary Digital Content, Table 1, <http://links.lww.com/CM9/A700>].

From 2008 to 2015, an increasing proportion of NSTEMI-ACS patients were diagnosed with NSTEMI (14% [212/1518] in 2008 to 19% [346/1793] in 2015, $P_{trend} < 0.001$), along with rising socioeconomic status and prevalence of comorbidities [Supplementary Digital Content, Table 1, <http://links.lww.com/CM9/A700>]. More patients had a history of MI (from 12.6% to 13.3%, $P_{trend} = 0.003$), PCI or CABG (9.2% to 16.9%, $P_{trend} < 0.001$), diabetes mellitus (22.3% to 28.2%, $P_{trend} = 0.001$), stroke or transient ischemic attack (13.6% to 15.2%, $P_{trend} < 0.001$), and dyslipidemia (12.0% to 20.1%, $P_{trend} < 0.001$) from 2008 to 2015. Conversely, the proportion of patients with kidney dysfunction (defined as eGFR < 60 mL min⁻¹ 1.73m⁻²) decreased from 7.2% in 2008 to 5.5% in 2015 ($P_{trend} = 0.010$). Similar trends were observed both in patients with NSTEMI and UA.

Supplementary Digital Content, Table 2, <http://links.lww.com/CM9/A700> depicts the temporal trends in diagnostic test utilization. Overall, troponin testing increased (42.8% to 77.6%, adjusted OR 1.290 [95% CI: 1.260, 1.330], $P_{trend} < 0.001$), while creatine kinase-myocardial band (CK-MB) test decreased (66.7% to 75.6%, adjusted OR 0.960 [95% CI: 0.950, 0.970], $P_{trend} < 0.001$) in patients

with NSTEMI-ACS from 2008 to 2015. Utilization of coronary angiography and coronary computed tomographic angiography (CCTA) also increased (34.8% to 52.5%, adjusted OR 1.090 [95% CI: 1.050, 1.130], $P_{trend} < 0.001$ and 5.2% to 8.2%, adjusted OR 1.120 [95% CI: 1.030, 1.230], $P_{trend} = 0.010$, respectively) during the study period. High-risk NSTEMI-ACS patients had lower rate of coronary angiography (39.7% vs. 54.8% in 2015) and lower rate of CCTA (2.9% vs. 9.2% in 2015) compared with patients in the low-to-intermediate group. Stress testing remained very low in low-to-intermediate risk patients (4.5% to 2.4%, adjusted OR 0.990 [95% CI: 0.860, 1.130], $P_{trend} = 0.850$).

Treatment with dual antiplatelet therapy, glycoprotein IIb/IIIa inhibitors, and statins increased over the study period (from 56.4% to 76.9%, from 3.0% to 8.3%, and from 73.4% to 92.7%, respectively, all adjusted $P_{trend} < 0.001$). Although PCI increased from 21.2% to 26.2% before adjustment, the likelihood of a patient receiving PCI did not change clinical-importantly (adjusted OR 0.990 [95% CI: 0.990, 1.000], adjusted $P_{trend} = 0.002$). Moreover, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use decreased from 60.3% in 2008 to 50.8% in 2015 (adjusted OR 0.920 [95% CI: 0.910, 0.930], adjusted $P_{trend} < 0.001$); beta-blocker use remained stable around 68% over the study period (adjusted OR 0.970 [95% CI: 0.930, 1.020], adjusted $P_{trend} = 0.290$) [Supplementary Digital Content, Table 3, <http://links.lww.com/CM9/A700>].

In general, a larger proportion of high-risk patients received dual antiplatelet therapy and glycoprotein IIb/IIIa antagonist (GPIIb/IIIa) inhibitors over the study period, but a smaller proportion underwent PCI compared with low-to-intermediate risk patients. Rates of in-hospital statin, ACEI/ARB, and beta-blocker prescription were similar for both risk groups [Supplementary Digital Content, Table 3, <http://links.lww.com/CM9/A700>]. Use of glycoprotein IIb/IIIa inhibitor (from 2.6% to 7.9% vs. from 5.5% to 7.0%) increased both in high- and low-to-intermediate risk patients. The absolute increase of statin use in low-to-intermediate risk patients was greater (from 75.0% to 92.9% in low-to-intermediate risk vs. from 81.1% to 88.8% in high risk). After accounting for patient-level and hospital-level characteristics, the likelihood of undergoing PCI did not change clinical-importantly in both risk groups over the study period (adjusted OR 1.020 [95% CI: 1.020, 1.020] in a high-risk group and 0.990 [0.990, 0.990] in a low-to-intermediate risk group, $P_{for\ interaction} < 0.001$).

Supplementary Figure 1, <http://links.lww.com/SLA/D390> presents the temporal trends of MACE. Crude MACE rate ranged between 3% in 2008 and 3.7% in 2015 ($P_{trend} = 0.880$) with wide variability based on baseline risk: 1.6% in 2008 and 2.7% in 2015 in low-to-moderate risk patients ($P_{trend} = 0.090$), and 13.4% in 2008 and 9.5% in 2015 in high-risk patients ($P_{trend} = 0.030$). The adjusted overall MACE rate decreased over the study period (adjusted OR 0.930 [95% CI: 0.930, 0.940], $P_{trend} < 0.001$). No interaction was observed between risk groups ($P_{for\ interaction} = 0.390$). The lower incidence of

MACE was driven by a decrease in in-hospital HF among high-risk patients, which declined from 9.1% in 2008 to 5.4% in 2015 ($P_{trend} = 0.010$). Other MACE components remained stable over the study period.

In this large retrospective study of hospitalized ACS patients, an increasing proportion was diagnosed as NSTEMI compared with UA in the three provinces surveyed in China from 2008 to 2015. This finding may be partially explained by increased rates of biomarker testing. Diagnostic imaging, including coronary angiography and CCTA, also increased substantially among patients with NSTEMI-ACS over the study period. In contrast, the rate of stress testing remained very low (<5%) in both risk groups. Adjusted rates of in-hospital MACE decreased significantly over time in patients with NSTEMI-ACS, which was concurrent with marked increases in most diagnostics and treatments.

Our findings highlight increases in medical resource consumption for patients with NSTEMI-ACS over the study period. Although rates of some diagnostic testing and treatments increased in high-risk patients, absolute increases were greater in low-to-intermediate risk patients. With an increase in access to health services, low-to-intermediate risk patients appeared more likely to receive invasive and more aggressive medical therapies. This risk-treatment paradox has also been reported in previous studies from China and other countries.

The considerable room remains to optimize the management of patients with NSTEMI-ACS in these hospitals in China. Antiplatelets, statins, beta-blockers, and ACEIs/ARBs are essential medicines to treat patients after NSTEMI-ACS. Although these treatments are simple, low-cost, and evidence-based, there were still nearly 20% high-risk patients who did not receive dual antiplatelet therapy, >10% high-risk patients who did not receive statin, about one-third of patients did not receive a beta-blocker, and about one-half of patients did not receive an ACEI/ARB during hospitalization.

To our knowledge, this study is one of the largest evaluations of patients with NSTEMI-ACS since the 2009 healthcare reform in China. The findings of this study should be interpreted in the context of several limitations. First, only in-hospital MACE outcome was assessed in this study, and thus it is not known whether the observed trends in practice translated into improvements in longer-term outcomes. Second, this was a retrospective chart review study that relied on documentation of diagnostics, treatments, and outcomes, which could possibly have been

underreported or misclassified. Third, this was not a nationally representative sample and the results might not be generalizable throughout China, though the three provinces included representing areas of high, medium, and low levels of economic development in China.

To conclude, these results show trends in NSTEMI-ACS presentation, diagnostics, treatments, and outcomes in three regions in China. Further implementation of evidence-based practices, monitoring the quality of acute cardiovascular care, and limiting unnecessary or inappropriate treatments are important strategies to improve China's health system efficiency.

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Conflicts of interest

None.

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