BMJ Open Protocol for the Acute Myocardial Infarction Study in Northeastern China (AMINoC): a real-world prospective cohort study

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ABSTRACT

Introduction Acute myocardial infarction (AMI) has become one of the major causes of mortality and morbidity in China. However, little is known about the characteristics, medical care and outcomes of patients with AMI in Northeastern China. The Acute Myocardial Infarction Study in Northeastern China (AMINoC) is aimed at obtaining timely real-world knowledge in terms of characteristics, clinical care and outcomes of patients with AMI and at providing care-quality improvement efforts in Northeastern China.

Methods and analysis The AMINoC is a real-world, prospective, multicentre cohort study. The study selected 20 hospitals using stratified cluster sampling from different levels of hospitals among nine districts throughout Jilin Province. Hospitalised patients with a primary diagnosis of AMI in each site are consecutively enrolled for 1 year. Demographic characteristics, clinical data, treatments, outcomes and cost are collected by local investigators. Patient follow-up after discharge is planned for up to 2 years.

Ethics and dissemination The protocol has been approved by the ethics committee at the Second Hospital of Jilin University. The findings of this study will be published in peer-reviewed journals and medical conferences.

Trial registration NCT04451967.

INTRODUCTION

Acute myocardial infarction (AMI) is among the leading causes of morbidity and mortality worldwide, with more than 7 million cases annually,1 thus causing a great economic burden. Although AMI mortality has been reduced in western countries during the past decades due to evidence-based therapies,1–3 the incidence of AMI is increasing sharply in China.4 Several factors are responsible for this increase: first, improving medical care decreased the mortality of infectious diseases, leading to a shift of the main disease burden in China from infectious diseases to non-infectious diseases, including AMI; second, with the increase in lifespan and economic development, the prevalence of non-infectious diseases such as hypertension, diabetes and hyperlipidaemia, many of which are risk factors of AMI, steadily increased during the past decades4; finally, as the increasing urbanisation and lifestyle of Chinese residents tend to have less physical activity and more cigarette and alcohol consumption,7–8 all of which are risk factors for cardiovascular disease.

Despite the increasing incidence of AMI in China, medical care has not improved accordingly. Moreover, as economic development differs in urban and rural areas, hospital levels vary, and the medical care received by patients with AMI may also differ.9 Hospitals in China are classified as primary (community hospitals with only the most basic facilities and with very limited inpatient capacity), secondary (hospitals with at least 100 inpatient beds providing acute medical care and preventative care services to populations of at least 100 000) or tertiary (major tertiary referral centres in provincial capitals and major cities) according to the Chinese National Health Commission.10 Urban areas have tertiary hospitals where patients with AMI can directly undergo primary percutaneous
coronary intervention (PCI) treatment after hospitalisation, whereas in rural areas with a less developed economy, secondary hospitals are the largest available hospitals, some of which are not capable of performing primary PCI. Under this circumstance, patients with AMI have to be transferred to a tertiary hospital to obtain PCI treatment. Moreover, some patients may be misdiagnosed or inappropriate treatments in clinical practice may be delayed. The increasing prevalence of AMI and inappropriate medical care indicate a severe AMI situation in China.

The government has been increasingly focusing on the AMI situation in China. During the past several years, some large-scale epidemiology studies, for example, China Patient-centered Evaluative Assessment of Cardiac Events (PEACE) and China Acute Myocardial Infarction Registry (CAMI), have been conducted to better understand the AMI situation in China. However, as the economic and geographic situations vary largely across the country, a deep understanding of different regional AMI situations is urgently needed in order to develop targeted policies. Jilin province is located at the centre of Northeastern China, with unique features in comparison with the rest of China. Like other provinces of Northeastern China, Jilin province has a relatively cold climate, less developed economy and greatly unbalanced economic development between urban and rural areas. The residents tend to have a higher in-salt diet and less physical activities than those in southern parts of China. These facts indicate that AMI is a growing problem in Northeastern China. However, to the best of our knowledge, provincial AMI epidemiological data are lacking. Therefore, we designed the Acute Myocardial Infarction Study in Northeastern China (AMINoC), a real-world prospective cohort study, as an integrated research in order to address the current knowledge gap of AMI situations in Northeastern China, and generate knowledge about the characteristics, clinical care and outcomes of hospitalised patients with AMI and provide a deep understanding of education, prevention and treatment of the patients with AMI in the province of Jilin. We herein present the protocol for the AMINoC study.

METHODS AND ANALYSIS

Objectives of the AMINoC study

The specific aims of our study are to describe the characteristics of hospitalised patients with AMI in Jilin province, including their demographic and clinical attributes; characterise patterns of in-hospital treatment; describe in-hospital mortality and morbidity rates (ie, outcomes); determine trends in patient characteristics, clinical care and outcomes over time; develop and test prognostic models for risk stratification; compare treatment across districts in Jilin province and determine whether different therapy patterns by setting may be associated with different outcomes; compare diagnostic testing done to the testing guidelines and compare treatments prescribed to the treatment guidelines; describe and compare characteristics, treatment and outcomes of patients with AMI between different sexes; describe and compare characteristics, treatments and outcomes of patients with AMI between urban and rural areas; compare characteristics, treatments and outcomes of patients with AMI following different hospital transfer methods to a tertiary hospital such as direct transfer to a tertiary hospital versus transfer after thrombolysis or antplatelet therapy and transfer to a tertiary hospital after thrombolysis versus transfer after antplatelet therapy.

Design overview

This real-world prospective cohort study is both descriptive and inferential and includes information on hospitalisations with AMI diagnosis, including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). We did not include hospitalisations with a principal discharge diagnosis of unstable angina.

Sampling design

We intend to include study hospitals that reflect both urban and rural sites of care in Jilin province. As hospital volumes and clinical capacities differ between urban and rural areas, we separately identified hospitals in those areas. An urban area was defined as a downtown or suburban area within a directly controlled autonomous prefecture (Yanbian Korean Autonomous Prefecture). A rural area was defined as the surrounding county-level regions, including counties and county-level cities. Under this framework, Jilin province is composed of nine districts, and each district comprises an urban area and a few rural areas. There are more than 30 hospitals in rural areas and more than 20 hospitals in urban areas within one district in the Jilin province. In total, there are approximately 500 hospitals in the Jilin province. Thus, we decided to perform a random sampling.

We identified patients for study inclusion using a stratified cluster sampling design. With nine districts, wherein each district has an urban stratum and rural strata, we yielded 18 strata. We identified hospitals within each stratum as follows. In the rural area within a district, we used a random number table to order the legible central secondary hospitals to determine the order in which the hospitals would be approached for enrolment in the study; once a hospital agreed, the remaining hospitals would not be approached. In an urban area within a district, we enrolled the largest tertiary hospital as defined by the number of cardiovascular beds. If there were two hospitals of the same bed size, we ordered the hospitals using a random number table and they would be approached for enrolment in the study following this order; with the first hospital to agree being enrolled in the study. Considering that the population in Changchun city and Jilin city, both of which are urban areas within two different districts, is much larger than that of other urban areas, two tertiary hospitals from each area were randomly selected. Prison
hospitals, traditional Chinese medicine hospitals, specialised hospitals without a cardiovascular disease division and military hospitals were excluded.

**Patient population and inclusion criteria**
All eligible and consenting patients with AMI admitted to each of the selected hospitals will be enrolled in a consecutive fashion for 1 year. The sample size of each hospital was determined based on the experience of the Second Hospital of Jilin University (78% of beds for patients with AMI in a month) and the number cardiovascular inpatient beds. The estimated sample size was 3336 patients, with 2124 from territory hospitals in urban areas and 1212 from secondary hospitals in rural areas (table 1).

Eligible patients must be admitted within 7 days of acute myocardial ischaemic symptoms with a primary clinical diagnosis of AMI, including STEMI or NSTEMI. The final inclusion criterion is the ‘Fourth universal definition for myocardial infarction’ (2018). Types 1, 2, 3, 4b and 4c are included in the present study according to the classification of myocardial infarction. Types 4a and type 5 are not eligible for the AMINoC study. There are no other exclusion criteria.

**Data collection**
The input feasibility and data collection burden were discussed among the principal investigators, statisticians, data managers, clinical and research experts of the Scientific Committee and Executive and Steering Committee, and AMINoC study investigators to develop and determine the data elements collected in the study. Standardised data collected encompassed demographic characteristics, medical history, clinical presentation, risk factors, physical examination, laboratory values, imaging results, reperfusion strategies, medications, transfer strategies, clinical events and cost (table 2). The detailed variables collected in this study are listed in online supplemental table.

Data are collected, validated and submitted by trained staff from each site using a unified secure, password-protected, web-based electronic data capture (EDC) system to guarantee the homogeneity. For each patient meeting the inclusion criteria, the demographic characteristics must be filled in using an electronic case report form (eCRF) and submitted online within 24 hours from admission. To avoid duplication and protect the patients’ personal information from being tracked by their own specific social ID number, a unique ID will be assigned to each patient through the patient’s social ID number. Site investigators are required to collect all the data during the hospitalisation and complete and submit the eCRF within 24 hours after the patient’s discharge or death. Data input tracking, regular alerts, rigorous data monitoring and queries are used to support timely and accurate completion of the eCRF. All investigators signed a confidentiality contract regarding all collected data before the study was conducted.

**Patient follow-up**
When a patient is discharged, he or she receives specific guidance on healthy lifestyle and medication. Follow-up visits are planned at 30 days and at 3, 6, 12, 18 and 24 months via either clinic visit or telephone call. The symptoms, medication, reasons for medication discontinuation and clinical events (including cardiovascular events, death, bleeding events etc), will be reviewed and collected. For clinical events, source documents are

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**Table 1 Estimated sample size of each site**

<table>
<thead>
<tr>
<th>Site</th>
<th>Estimated sample amount (patients/month)</th>
<th>Estimated sample amount (patients/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanbian University Hospital</td>
<td>15</td>
<td>180</td>
</tr>
<tr>
<td>Dunhua City Hospital in Jilin Province</td>
<td>11</td>
<td>132</td>
</tr>
<tr>
<td>Liaoyuan City Central Hospital</td>
<td>11</td>
<td>132</td>
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<tr>
<td>Dongliao People’s Hospital</td>
<td>7</td>
<td>84</td>
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<tr>
<td>Songyuan Central Hospital</td>
<td>14</td>
<td>168</td>
</tr>
<tr>
<td>Changling People’s Hospital</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>Siping Central Hospital</td>
<td>16</td>
<td>192</td>
</tr>
<tr>
<td>The First People’s Hospital of Manchu Autonomous County</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>The Second Hospital of Jilin University</td>
<td>34</td>
<td>408</td>
</tr>
<tr>
<td>Changchun Center Hospital</td>
<td>12</td>
<td>144</td>
</tr>
<tr>
<td>Nongan People’s Hospital</td>
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<td>192</td>
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<tr>
<td>Affiliated Hospital of Beihua University</td>
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<td>348</td>
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<tr>
<td>Jilin Hospital of Integrated Traditional Chinese and Western Medicine</td>
<td>10</td>
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<td>Panshi City Hospital</td>
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<tr>
<td>Tonghua Central Hospital</td>
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<td>Baishan Central Hospital</td>
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<td>108</td>
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<tr>
<td>Jingyu People’s Hospital</td>
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<td>96</td>
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<tr>
<td>Meihekou Central Hospital</td>
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<td>96</td>
</tr>
<tr>
<td>Baicheng Central Hospital</td>
<td>12</td>
<td>144</td>
</tr>
<tr>
<td>Tongyu First Hospital</td>
<td>13</td>
<td>156</td>
</tr>
<tr>
<td>Total</td>
<td>278</td>
<td>3336</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Category</th>
<th>Contents/example elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographics</td>
<td>Age, sex, social ID, race, occupation, education, marriage, insurance</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Symptoms, time of presentation, triggering factors</td>
</tr>
<tr>
<td>Initial medical contact</td>
<td>First medical contact, transfer information, cardiac status</td>
</tr>
<tr>
<td>Medical history and risk factors</td>
<td>Hypertension, diabetes, prior cardiovascular disease, prior revascularisation, history of stroke/TIA, history of bleeding, history of surgery, chronic kidney disease, lung disease, smoking, alcohol</td>
</tr>
<tr>
<td>Reperfusion strategy for STEMI</td>
<td>Thrombolysis and timing of thrombolysis, primary and rescue PCI, selected PCI, timing of primary PCI and coronary angiography, complications, CABG</td>
</tr>
<tr>
<td>Revascularisation for NSTEMI</td>
<td>PCI, timing of PCI and coronary angiography, risk stratification, complications</td>
</tr>
<tr>
<td>Medications</td>
<td>Antiplatelet, heparin, statin, β-blocker, CCB, ACEI/ARB, anticoagulant, platelet GP IIb/IIIa receptor inhibitor, nitrates, inotropic medications</td>
</tr>
<tr>
<td>Mechanical circulatory support</td>
<td>IABP, ECMO, LVAD, pacemaker</td>
</tr>
<tr>
<td>Lab results</td>
<td>Cardiac biomarkers, NT-proBNP, BNP, Creatinine, LVEF</td>
</tr>
<tr>
<td>In-hospital outcomes</td>
<td>Death, heart failure, re-infarction, cardiac shock, atrial fibrillation, malignant arrhythmia, AV block, cardiac arrest, stroke, major bleeding events, papillary muscle dysfunction or rupture, ventricular septal perforation, ventricular wall rupture</td>
</tr>
<tr>
<td>Discharge</td>
<td>Discharge status, cost, medications</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Vital status, medications, clinical events including death, MI, heart failure, arrhythmia, revascularisation, cause and mode of death</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CCB, calcium channel blocker; ECMO, extracorporeal membrane oxygenation; GP, glycoprotein; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

required for validation. The data capture ends at the end of the follow-up.

Data management
The whole eCRF must be filled out for each eligible/included patient by investigators at the corresponding site. Web-based data entry access is password-restricted to trained personnel at each site. Data are continuously cleaned systematically. A Chinese digital company is employed to provide a cloud-based server and keep the data safe. To control the data quality continuously, real-time automated range and logical check at the data entry for the validity and completeness are integrated in the EDC system. For any queries about the data validity or logic, data managers can query and validate according to the answers provided by corresponding investigator via the EDC system. Queries can be reissued if necessary.

Progress to date
The AMINoC was launched on 9 September 2019 among a total of 20 hospitals in Jilin province, including 11 in urban areas and 9 in rural areas (figure 1).

As of 9 June 2020, 1,485 patients have been enrolled in the AMINoC study.

Statistical analysis
We will report the summary statistics for patient characteristics, use of diagnostic tests, treatments received, and in-hospital and out-hospital outcomes including complications of care across study sites. All data will be weighted to be representative of Jilin province.

For observational data, standard parametric and non-parametric techniques, including Student’s t-tests, χ² tests, generalised linear models and Wilcoxon rank-sum tests, will be used for each aim. Considering the correlation of patient characteristics, clinical care, and outcomes within study sites, the effect of clustering will be accounted for in the analyses. To examine and adjust for differences between the comparison groups, linear, logistic, Cox proportional hazard and Poisson models with a generalised estimating equation approach and hierarchical models, will be used where appropriate. Models will be developed to stratify the risk of adverse outcomes of patients with AMI. To assess the relationship between candidate variables and clinical outcomes, appropriate statistical techniques will be performed for the dependent variable. The list of candidate variables will be further refined according to their clinical relevance.

Patient and public involvement
The patients and public were not involved in the design, recruitment, and conduction of the study.
ETHICS AND DISSEMINATION

The AMINoC Study is approved by the ethics committee of the Second Hospital of Jilin University. Any amendments to the research protocol will be submitted for ethical approval. The study is conducted in accordance with the principles of the Declaration of Helsinki. There are no safety concerns for enrolled patients. There is a waiver of informed consent for this observational, non-interventional study in all centres.

The findings of this study will be published in peer-reviewed journals and medical conferences.

DISCUSSION

The AMINoC study is a large-scale, comprehensive, multicentre, real-world study on AMI epidemiology in Northeastern China that will provide a platform for understanding and assessing AMI medical practice, medical care improvement, translational medicine, and prevention.

Some myocardial infarction registries such as the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART), the German Multinational MONitoring of trends and determinants in Cardiovascular Diseases (MONICA)/German Cooperative Health Research in the Region of Augsburg (KORA) study, and the Korea Acute Myocardial Infarction Registry, have been carried out in different countries worldwide. Some elements we collect in our study are the same as those in other registries. Through the AMINoC study, it will be possible to obtain a comprehensive and continuous understanding of epidemiology, real-world clinical treatment, outcomes and cost of hospitalised patients with AMI in Northeastern China in real time, and compare those with other parts of China and other countries. We will obtain demographic characteristics, medical histories, lifestyle characteristics and clinical presentations. All this information will help in understanding the distributions and features of hospitalised patients with AMI.

The AMINoC provides a platform to evaluate the clinical therapy of patients with AMI at different hospital levels. Clinicians might make different diagnosis and treatment decisions in clinical practice; some may even misdiagnose or administer inappropriate treatment. This study will collect and evaluate data on all the clinical testing, diagnosis and treatment decisions made by clinicians in different levels of hospitals and compare the clinical practice to prescribed AMI guidelines. This will provide a better understanding of the current clinical practice in different level hospitals and districts.

This study is also an inferential study on the outcomes of different therapeutic strategies and transfer strategies. We will obtain short-term and long-term outcomes of patients with AMI undergoing different therapeutic strategies, including primary PCI, delayed PCI, thrombolysis, non-reperfusion therapy and so on. Analysis of these data will help to assess different therapeutic strategies.
for different AMI patient subgroups. We will also determine the short-term and long-term outcomes of patients with AMI undergoing different transfer strategies from a secondary hospital to a territory hospital. These data will help provide advice for optimum safety and more effective transfer strategies in clinical practice. This comprehensive analysis will help in constructing a regional collaborative rapid-treatment system among different levels of hospitals in different districts in Jilin province, thus promoting medical care and improving the outcomes of patients with AMI.

The AMINoC also provides data to help promote the understanding of AMI patient management among administrative personnel. Chest pain centre is considered to be an effective mode for early diagnosis and treatment of AMI. The Chinese Society of Cardiology has been processing and constructing chest pain centers throughout country during the past few years. However, the effects and benefits of chest pain centres in China are not clear. Among the 20 hospitals enrolled in the study, some are chest pain centres, whereas others are not. This study will provide data to compare the real-world clinical practice between chest pain centres and non- chest pain centres. These results will help in evaluating the effect of chest pain centre in the real world and in understanding the factors associated with delay in AMI management. This will promote management of patients with AMI at the hospital level.

The AMINoC also helps in making specific guidance to educate patients and clinicians. Through this study, we will acquire data about the public understanding of AMI and response to AMI and the medical adherence of patients with AMI. We hope to establish a platform to help make specific guidance to educate the public about AMI knowledge, promote prevention and early recognition of AMI, and increase the adherence of patients with AMI. Meanwhile, this study will acquire data about the clinical practice of AMI in different levels of hospitals, which will provide quality feedback and scientific support to educate clinicians, including cardiologists and emergency departments, to reduce misdiagnosis and delayed diagnosis, and to promote standard AMI management.

The AMINoC study has some potential limitations. Heterogeneity of patients and practices among the 20 sites is expected. This was minimised by standardised tools and training for research staff and data collection. Furthermore, although prospective cohort studies allow for identification of risk factors, there is the potential to identify spurious associations.

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**REFERENCES**


