**Invasive management and in-hospital outcomes of myocardial infarction patients in rural versus urban hospitals in the United States.**

**Running Title:** Rural versus urban myocardial infarction outcomes

**Authors:** Hussein Bashar1,2,3, Andrija Matetić3,4, Nick Curzen1,2, Mamas A. Mamas3, \*

1 Faculty of Medicine, University of Southampton, United Kingdom.

2 Coronary Research Group, University Hospital Southampton NHS Foundation Trust, United Kingdom.

3 Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, United Kingdom.

4 Department of Cardiology, University Hospital of Split, Split, Croatia.

**\*Correspondence to:**

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group,

Centre for Prognosis Research,

Institute for Primary Care and Health Sciences, Keele University, Stoke-on-Trent, UK

E-mail: mamasmamas1@yahoo.co.uk; Tel: +44 1782 671654; Fax: +44 1782 734719

**Declarations of interest**: none.

**Word count:** 2,901.

**Indexing words:** MI; Disparity; Rural; country.

# Abstract

**Objectives:** The variation in the management and outcome of acute myocardial infarction (AMI) between rural and urban settings has been previously recognized, but there has previously been no nationwide data reported that is inclusive of the whole adult population.

**Methods**: All discharge records between 2004 to 2018 with AMI diagnosis were extracted from the National Inpatient Sample (NIS) database and stratified by hospital location. The primary outcome was in-hospital mortality, and secondary outcomes included (a) major adverse cardiovascular and cerebrovascular events (MACCE), (b) major bleeding, (c) acute ischemic stroke, the utilization of invasive management in the form of (d) coronary angiography (CA), and (e) percutaneous coronary intervention (PCI). The adjusted odds ratios (aOR) and 95% confidence interval (95% CI) were determined using multivariable logistic regression.

**Results:** 9,728,878 records with AMI were identified, of which 1,011,637 (10.4%) discharges were from rural hospitals. Rural patients were older (median of 71 years vs. 67 years, p<0.001) and had lower prevalence of the highest risk presentations of AMI than their urban counterparts. After multivariable adjustment, patients from rural hospitals had increased aOR of all-cause mortality (aOR 1.15 95% CI 1.13-1.16) and MACCE (aOR 1.04 95% CI 1.04-1.05), as well as the decreased aOR of coronary angiography (aOR 0.29, 95% CI 0.29-0.29, p<0.001) and PCI (aOR 0.40, 95% CI 0.39-0.40, p<0.001), compared to their urban counterparts.

**Conclusion**: Between 2004-2018, the risk of in-hospital mortality and MACCE in AMI patients was significantly higher in rural hospitals, with considerably lower utilization of invasive angiography and revascularization.

# Introduction

Rural communities include 19.3% of the U.S. population(1). Inhabitants of rural areas may be at disadvantage when it comes to cardiovascular health as highlighted recently in the American Heart Association (AHA) presidential advisory(2). Specifically, rural-urban disparities in relation to myocardial infarction patient care and outcome have been reported in the last three decades. For example, rural patients with acute myocardial infarction (AMI) had at least 14% higher mortality in comparison to their urban counterparts(3). Even in the early years of this millennia, there was documented under provision of even basic guideline-directed medical therapies (GDMT), such as aspirin, for these patients(4).

Fortunately, these inequalities between rural and urban application of medical treatment have narrowed over the last decade(5), allowing more focus on the interventional aspect of AMI care. A recent large study, based on elderly Medicare beneficiaries (65 years or older only), demonstrated a significantly lower utilization of coronary angiography (CA) and revascularization, and a higher adjusted short-term mortality (hazard ratio of 1.10, 95% confidence interval [CI] 1.08-1.12) following AMI in in the rural settings compared to urban(6). However, this study did not include an overall rural population and is not representative of payers other than Medicare nor patients below 65 years of age, containing an inherent limitation to its design.

Large, more inclusive, studies based on the National Inpatient Sample (NIS) database have reported the rural-urban variation in mortality and the use of invasive procedures in the management of two specific subsets of AMI patients in the form of cardiac arrest and cardiogenic shock(7, 8). However, to our knowledge, there has been no national, all payer, comprehensive and contemporary study that inspected the rural versus urban association with clinical outcomes in all adult AMI patients, which is the objective of this paper.

# Methods

**National Inpatient Sample database**

This study used the discharge information from the National Inpatient Sample (NIS) database which is one of several databases developed by the Healthcare Cost and Utilization Project (HCUP) via sponsorship from Agency for Healthcare Research and Quality (AHRQ)(9). The NIS is the largest publicly available inpatient database, and covers more than 97% of the U.S. population and approximates a 20% stratified sample of discharges from community hospitals excluding long-term acute care and rehabilitation hospitals. The database uses the Core Based Statistical Area (CBSA) to categorize hospitals located in micropolitan CBSA and non-core areas as rural while those situated metropolitan CBSA as urban. An urban hospital was classified as teaching hospital if it had at least one residency program accepted by the Accreditation Council for Graduate Medical Education (ACGME), had residents and interns to beds ratio of at least 0.25, or held membership of the Council of Teaching Hospitals (COTH).

 **Study sample**

All discharge records with the diagnosis of acute myocardial infarction (AMI) from NIS database in the period between 2004 to 2018 were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and their Tenth Revision (ICD-10-CM), as appropriate. The sample was then stratified based on the location into rural and urban hospitals. Urban hospitals were further stratified into teaching and non-teaching centres for sensitivity analysis. A total of 37,456 records (0.4%) were excluded from the study due to missing data and/or patient age being less than 18 years (**Supplementary** **Figure S1**, study flow diagram).

Similarly, all procedures and diagnosis were identified using ICD-9-CM or ICD-10-CM, as appropriate. A complete list of the codes used, including those used to detect morbidities and outcomes, can be found in **Supplementary Table S1.** The *Strengthening The Reporting of Observational Studies in Epidemiology* (STROBE) checklist was included in **Appendix A** to improve the quality of this observational study.

**Outcomes**

 In-hospital mortality is the primary clinical outcome of this study. Secondary clinical outcomes included (a) major adverse cardiovascular and cerebrovascular events (MACCE; comprising of all-cause mortality, acute ischemic stroke and reinfarction), (b) major bleeding (defined as haematemesis, melaena, gastrointestinal haemorrhage, nontraumatic intracranial haemorrhage, and unspecified haemorrhage), and (c) acute ischemic stroke. In addition, the utilization of invasive management in the form of (d) invasive coronary angiography (CA), (e) percutaneous coronary intervention (PCI) were also included as secondary endpoint. Finally, the length of stay and the total charges in USD were evaluated as outcomes of interest. Sensitivity analyses were conducted to investigate aforementioned outcomes based on the teaching status of urban hospitals, and AMI type.

 **Statistical analysis**

All statistical analysis was done using IBM SPSS statistics software version 26. As advised by HCUP, estimation of the total number of discharges was completed using sample weighting. Numerical variables are presented as median with interquartile range (IQR), whereas categorical variables are presented as percentages. Mann–Whitney U, Kruskal Wallis, or Pearson’s chi square tests were used for variables comparison, as suitable. Multivariable binomial logistic regression models were employed to study the association of hospital location status and outcomes, and were presented as adjusted odds ratios (aOR) with their corresponding 95% CI. The models were adjusted for: age, sex, weekend admission, bed size of hospital, ST-elevation myocardial infarction (STEMI), cardiogenic shock, cardiac arrest, atrial fibrillation, dyslipidaemia, thrombocytopaenia, smoking, previous PCI, previous coronary artery bypass grafting (CABG), previous cerebrovascular accident (CVA), anaemia, heart failure, valvular heart disease, hypertension, peripheral artery disease, diabetes, chronic lung disease, coagulopathy, dementia, liver disease, chronic kidney disease, and metastatic disease.

# Results

 A total of 9,728,878 records with AMI were included in the study. Discharges from urban hospitals were responsible for the majority (89.6%) of the cases (**Table 1**). Teaching urban hospitals represented 52% of all the sample, while non-teaching urban centers accounted for 37.6%(**Supplementary Table 2**).

***Baseline characteristics***

 Compared to urban hospitals, rural AMI patients were older (median of 71 years vs. 67 years, p<0.001) and more likely to be female (44.9% vs 39.0%, p<0.001) and of white ethnicity (87.6% vs 74.4%, p<0.001). In addition, rural patients had a higher prevalence of atrial fibrillation (16.4% vs. 16.3%, p<0.001), heart failure (32.4% vs. 31.0%, p<0.001), peripheral arterial disease (8.9% vs. 8.7%, p<0.001), chronic pulmonary disease (24.5% vs. 20.1%, p<0.001), previous CABG (10.4% vs. 9.9%, p<0.001), dementia (7.5% vs. 5.4%, p<0.001), and metastatic cancer (0.9% vs. 0.8%, p<0.001) compared to those from urban centres (**Table 1**).

 Urban hospital patients had a greater proportion of documented STEMI (26.9% vs. 19.6%, p<0.001), cardiogenic shock (5.3% vs. 2.9%, p<0.001), cardiac arrest (3.0% vs. 2.2%, p<0.001), ventricular tachycardia (VT) (6.1% vs. 3.8%, p<0.001), and ventricular fibrillation (VF) (2.8% vs. 1.5%, p<0.001). Furthermore, they had more prevalent comorbidities such as dyslipidaemia (58.2% vs. 49.1%, p<0.001), thrombocytopenia (3.7% vs. 2.3%, p<0.001), smoking (29.4% vs. 25.9%, p<0.001), previous PCI (13.1% vs. 10.5%, p<0.001), anaemias (16.2% vs. 14.0%, p<0.001), valvular disease (1.8% vs. 1.3%, p<0.001), hypertension (65.4% vs. 62.7%, p<0.001), coagulopathy (4.9% vs. 2.9%, p<0.001), chronic liver disease (1.6% vs. 1.1%, p<0.001), and chronic renal failure (17.9% vs. 16.6%, p<0.001) compared to those from rural hospitals. In addition, non-Medicare/Medicaid patients accounted for 37.2% of the records in urban hospitals compared to 28% in rural centres (**Table 1**).

***Clinical outcomes***

Analysis of crude, unadjusted data demonstrates higher all-cause mortality (5.9% vs. 5.2%, p<0.001) and MACCE (8.8% vs. 8.2%, p<0.001) in rural hospitals compared to urban centres. In contrast, urban hospitals had higher rates of utilization of both coronary angiography and PCI (66.4% vs. 38.8%, p<0.001; 44.7% vs. 24.5%, p<0.001; for CA and PCI respectively). Similarly, there were higher rates of major bleeding (2.4% vs. 2.2%, p<0.001) and ischemic stroke (3.0% vs. 2.8%, p<0.001) in urban hospital versus rural centres (**Table 2 and Supplementary Figure 2.A**). In comparison to rural hospitals, urban centres had longer length of stay (median of 3 days vs. 2 days, p<0.001) and higher total charges (median of $49,435 vs $19,389, p<0.001) (**Table 2**).

After multivariable adjustments for confounding patient characteristics, patients from rural hospitals had a higher all-cause mortality (aOR 1.15, 95% CI 1.13-1.16, p<0.001) and MACCE (aOR 1.04, 95% CI 1.04-1.05, p<0.001) (**Table 3 and Figure 1**). In addition, utilization of invasive management remains significantly lower in the rural settings (aOR 0.29, 95% CI 0.29-0.29, p<0.001; aOR 0.40, 95% CI 0.39-0.40, p<0.001; for CA and PCI respectively). Similarly, the odds of major bleeding (aOR 0.91, 95% CI 0.90-0.92, p<0.001) and ischemic stroke (aOR 0.86, 95% CI 0.85-0.87, p<0.001) were lower in rural hospitals (**Table 3**).

***Sensitivity analysis by urban hospitals teaching status***

 The unadjusted rates of all-cause mortality and MACCE were higher in non-teaching urban hospitals (5.3% and 8.5%, respectively) compared to teaching urban centres (5.1% and 8.0%, respectively) but remained significantly lower than that of rural hospitals (5.9% and 8.8%, respectively, p<0.001 for both) (**Supplementary Table 3** and **Supplementary Figure 2.B)**. On the other hand, urban teaching hospitals had the highest utilization of invasive management in the form of CA (60.6% vs. 70.7% vs. 38.8%, p<0.001; for non-teaching vs. teaching vs. rural, respectively) and PCI (39.6% vs. 48.4% vs. 24.5%, p<0.001; for non-teaching vs. teaching vs. rural, respectively) compared to urban non-teaching and rural centres. Similarly, the incidence of major bleeding was highest in teaching hospitals (2.4%) followed by non-teaching (2.3%) and rural hospitals (2.2%) (p<0.001). Urban non-teaching centres had the highest rates of ischemic stroke (3.1% vs. 2.9% vs. 2.8%, p<0.001; for non-teaching vs. teaching vs. rural, respectively) (**Supplementary Table 3** and **Supplementary Figure 2.B)**.

***Sensitivity analysis by AMI type***

In comparison to urban centres, the adjusted mortality remained higher in rural hospitals regardless of AMI type, with both non-ST-elevation myocardial infarction (NSTEMI) and STEMI patients showing a higher mortality in rural centres (aOR 1.17, 95% CI 1.15-1.18, and aOR 1.11, 95% CI 1.09-1.13, respectively, p<0.001 for both) than those in urban centres (**Supplementary Table 4**). Likewise, the higher risk of MACCE in rural hospitals persisted irrespective of AMI type (aOR 1.06, 95% CI 1.04-1.08, p<0.001; aOR 1.04, 95% CI 1.03-1.05, p<0.001; for STEMI and NSTEMI respectively). On the other hand, the chances of having CA and PCI in rural centres continued to be lower across the AMI types (NSTEMI: aOR 0.29, 95% CI 0.29-0.29, p<0.001; aOR 0.38, 95% CI 0.38-0.39, p<0.001; for CA and PCI respectively), (STEMI: aOR 0.32, 95% CI 0.31-0.32, p<0.001; aOR 0.44, 95% CI 0.43-0.44, p<0.001; for CA and PCI respectively). Similarly, the risk of major bleeding and ischemic stroke continued to be significantly lower in rural setting in comparison to urban hospitals, irrespective of AMI category (**Supplementary Table 4**).

***Trend analysis***

From 2004 to 2018, the utilisation of invasive management for AMI patients has steadily increased, particularly in rural hospitals, where the rate of coronary angiography in AMI patients had at least doubled, but lagged behind urban centres (**Figure 2.A**). A similar increase in PCI is seen, but again remained lower than in urban centres (**Figure 2.B**). There is a progressive reduction in-hospital all-cause crude mortality rates in rural centres (**Figure 3**), so that the adjusted odds ratio for all-cause mortality in rural hospital (in comparison to urban centres) lose its statistical significance in the last 2 years of the sample (**Supplementary Figure 3**).

# Discussion

 This national analysis details the management of AMI patients from a national perspective, comparing rural and urban healthcare settings, and highlights several important disparities in the process of care and clinical outcomes across the two settings. First, rural centres had overall a 15% relatively higher in-hospital mortality for AMI patients. Second, the utilization of invasive management in rural hospital patients remains significantly lower than for their urban counterparts. Third, these differences were present irrespectively of the AMI type. Finally, the trend of rural-urban disparity in invasive management and in-hospital mortality has gradually attenuated over the study years.

 In this study, we observed that the reported rate of high-risk AMI presentations (STEMI, cardiogenic shock, cardiac arrest, VT, VF) was significantly higher in urban centres. This could theoretically reflect a pre-hospital survival advantage in these areas, especially when taking into consideration factors that are known to be associated with increased mortality in AMI, such as (a) the lower availability of paramedics and advanced life support in rural regions, together with (b) the distance to interventional centre (10, 11). It is possible that it also reflects a lower detection and reporting rate in rural centres. Regardless, it is interesting that despite a higher proportion of high-risk presentations at urban centres, the risk of mortality was persistently higher in rural hospitals until 2017-2018, after which is has steadily declined. This may reflect more effective and coordinated transfers to facilitate the access of rural patients to interventional facilities(12).

 The overall risk of MACCE in the current study was 4% relatively higher in rural hospitals, despite the fact that the stroke risk was 14% lower in this setting compared to urban centres. This lower risk of ischemic stroke and the 9% relatively lower risk of major bleeding may be a reflection of the 71% lower chance of having invasive coronary angiography and 60% lower chance of having PCI in rural hospitals, given the previously well documented association of acute ischemic stroke and major bleed with invasive management (13-15).

While this analysis demonstrated a declining in-hospital mortality for AMI patients presenting to rural hospitals after 2016, *Loccoh et al.* based on Medicare hospitalisation between 2016 to 2018, showed persisting higher 30 days mortality (hazard ratio of 1.10, 95% CI 1.08-1.12) with comparable results at 90 days (6). When taking these reports in the context of this analysis findings, this could imply that rural hospitals did improve in stabilising patients to the point of hospital discharge, however the vast significantly lower implementation of invasive treatment is taking its toll later down the line.

Previous nationwide studies on the rural-urban differences in outcome of specific subgroups of AMI patient are variable. Patients with cardiogenic shock and AMI were found to have a lower mortality in urban teaching hospitals (aOR 0.87, 95% CI 0.84-0.91, p <0.001) compared to rural centres between 2000-2014(8), which is in line with the general findings of this paper. On the other hand, those with cardiac arrest complicating AMI appeared to be fare better in rural centres than in urban teaching hospitals (In-hospital mortality aOR 1.36, 95% CI 1.32-1.39, p <0.001) in another NIS study (7), however this is likely due to more severe cases surviving to hospital presentation in the urban compared to the rural settings as discussed above. A recently published analysis from the 2016 NIS database found no difference in adjusted in-hospital mortality between rural and urban centres following PCI (16). However, there are three caveats in comparison to this paper. First, the 2016 analysis included all-comers for PCI which may indicate distinct rural-urban outcomes across chronic coronary syndrome and AMI patients in the context of this study. Second, unlike the 2016 study in which all its population had PCI, this analysis focused on the rural-urban disparity in the utilization of invasive AMI management in the first place which is an established modifier of clinical outcomes. Finally, this analysis included much broader time period and substantially larger sample size. The findings of this paper add to the growing evidence of rural-urban disparities in cardiovascular health. A great increase in the utilisation of invasive management in rural hospitals was realised in the last 15 years but the discrepancy between rural and urban levels of care remains important according to this work. This study supports the AHA intention to expand its quality improvement resources, such as Mission: lifeline, among others, to the rural communities(17). In addition, it draws the attention to one of the major goals of the Centres of Disease Control and prevention (CDC) healthy people initiative for the decade to “*Eliminate health disparities, achieve health equity, and attain health literacy to improve the health and well-being of all”* (18). The concept that provision of healthcare for the same condition varies depending upon the geographical location of the patient remains deeply uncomfortable. This paper should help raise the awareness of clinicians practicing in both rural and urban centres with regards to AMI management expectations in each setting and help them empathise and facilitate the coordination of these patient access to interventional institutes. It also raises the need to establish more inclusive research that includes pre-hospital outcome of AMI to unmask a possible rise in rural demises prior to hospital presentation that could partially account for the apparent in-hospital decline in mortality.

There are some important limitations in this study. First, by relying on discharge records and ICD-9/10 coding, the NIS database is susceptible to miscoding and incomplete information entry which are unmeasurable in this paper. Furthermore, there would be no way of detecting a degree of reporting bias, for example, if cardiogenic shock diagnosis was made and reported more readily at an urban centre compared with a rural one. Second, patients’ regular medications, medical therapies given prior to hospitalization (such as thrombolysis), comorbidities severity, and tests results are not captured by the NIS database and could not be accounted for their effect on outcomes. Third, this analysis is based on inpatient database only and does not take into consideration that some AMI patients might have not survived to presentation, especially in the rural setting where driving to the nearest PCI capable centre can take more than 2.5 times (median) that in the urban setting(19). Fourth, and by the same token, we do not have the ability to report longer term outcomes.

In conclusion, between 2004-2018, AMI patients managed in the rural hospitals had higher in-hospital mortality, with significantly lower utilization of invasive management. These finding support the need for change in health policies to address the rural-urban disparities in cardiovascular health.

# Acknowledgements

None.

# Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

# Tables

**Table 1.** Baseline patient characteristics.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Urban hospitals (N=8,717,241; 89.6%) | Rural hospitals (N=1,011,637; 10.4%) | *P*-value |
|
| Age (years), median (IQR) | 67 (57-78) | 71 (59-82) | <0.001 |
| Female sex, % | 39.0 | 44.9 | <0.001 |
| Ethnicity, % |  |  | <0.001 |
| White | 74.4 | 87.6 |  |
| Black | 10.8 | 6.4 |  |
| Hispanic | 8.5 | 2.7 |  |
| Asian/Pacific Islander | 2.6 | 0.7 |  |
| Native American | 0.5 | 1.2 |  |
| Other | 3.3 | 1.5 |  |
| Weekend admission, % | 25.9 | 26.1 | <0.001 |
| Primary expected payer, % |  |  | <0.001 |
| Medicare | 55.6 | 66.2 |  |
| Medicaid | 7.2 | 5.8 |  |
| Private Insurance | 28.3 | 19.8 |  |
| Self-pay | 5.6 | 5.1 |  |
| No charge | 0.6 | 0.2 |  |
| Other | 2.7 | 2.9 |  |
| Median Household Income (percentile), % |  |  | <0.001 |
| 0-25th | 26.9 | 53.5 |  |
| 26th-50th | 26.5 | 34.5 |  |
| 51st-75th | 25.1 | 10.1 |  |
| 76th-100th | 21.4 | 1.9 |  |
| Bed size of hospital, % |  |  | <0.001 |
| Small | 12.6 | 10.5 |  |
| Medium | 27.7 | 13.7 |  |
| Large | 59.7 | 75.8 |  |
| Hospital Region, % |  |  | <0.001 |
| Northeast | 19.7 | 13.9 |  |
| Midwest | 22.0 | 29.6 |  |
| South | 39.2 | 48.0 |  |
| West | 19.1 | 8.5 |  |
| Record Characteristics, % |  |  |  |
| STEMI | 26.9 | 19.6 | <0.001 |
| Cardiogenic shock | 5.3 | 2.9 | <0.001 |
| Cardiac arrest | 3.0 | 2.2 | <0.001 |
| Ventricular tachycardia | 6.1 | 3.8 | <0.001 |
| Ventricular fibrillation | 2.8 | 1.5 | <0.001 |
| Comorbidities, % |  |  |  |
| Atrial fibrillation | 16.3 | 16.4 | <0.001 |
| Dyslipidaemia | 58.2 | 49.1 | <0.001 |
| Thrombocytopenia | 3.7 | 2.3 | <0.001 |
| Smoking | 29.4 | 25.9 | <0.001 |
| Previous PCI | 13.1 | 10.5 | <0.001 |
| Previous CABG | 9.9 | 10.4 | <0.001 |
| Previous CVA | 4.9 | 4.5 | <0.001 |
| Anaemias | 16.2 | 14.0 | <0.001 |
| Heart failure | 31.0 | 32.4 | <0.001 |
| Valvular disease | 1.8 | 1.3 | <0.001 |
| Hypertension | 65.4 | 62.7 | <0.001 |
| Peripheral artery disease | 8.7 | 8.9 | <0.001 |
| Diabetes mellitus | 34.0 | 33.4 | <0.001 |
| Chronic pulmonary disease | 20.1 | 24.5 | <0.001 |
| Coagulopathy | 4.9 | 2.9 | <0.001 |
| Dementia | 5.4 | 7.5 | <0.001 |
| Chronic liver disease | 1.6 | 1.1 | <0.001 |
| Chronic renal failure | 17.9 | 16.6 | <0.001 |
| Metastatic cancer | 0.8 | 0.9 | <0.001 |

**Abbreviations:** CABG – Coronary Artery Bypass Graft; CVA – Cerebrovascular Accidents; IHD – Ischemic Heart Disease; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction.

**Table 2.** Unadjusted utilization of invasive management and in-hospital clinical outcomes.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Urban hospitals (N=8,717,241; 89.6%) | Rural hospitals (N=1,011,637; 10.4%) | *P*-value |
|
| Invasive management, % |  |  |  |
| CA | 66.4 | 38.8 | <0.001 |
| PCI | 44.7 | 24.5 | <0.001 |
| Clinical outcomes, % |  |  |  |
| All-cause mortality | 5.2 | 5.9 | <0.001 |
| MACCE | 8.2 | 8.8 | <0.001 |
| Major bleeding | 2.4 | 2.2 | <0.001 |
| Ischemic stroke | 3.0 | 2.8 | <0.001 |
| Length of stay (days), median (IQR) | 3 (2-6) | 2 (1-4) | <0.001 |
| Total charges (USD), median (IQR) | 49,435 (26,234-86,760) | 19,389 (8,864-43,154) | <0.001 |

**Abbreviations:** CA – Coronary angiography; IQR – Interquartile Range; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute ischemic stroke and reinfarction); PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

**Table 3.** Adjusted odds ratios (aOR) of rural invasive management and in-hospital clinical outcomes.

|  |  |  |
| --- | --- | --- |
| Characteristics | Rural hospitals aOR [95% CI] | *P*-value |
|
| Invasive management |  |  |
| CA | 0.29 [0.29-0.29] | <0.001 |
| PCI | 0.40 [0.39-0.40] | <0.001 |
| Clinical outcomes |  |  |
| All-cause mortality | 1.15 [1.13-1.16] | <0.001 |
| MACCE | 1.04 [1.04-1.05] | <0.001 |
| Major bleeding | 0.91 [0.90-0.92] | <0.001 |
| Ischemic stroke | 0.86 [0.85-0.87] | <0.001 |

**\*Reference group:** Urban hospitals.

**Abbreviations:** aOR – Adjusted Odds Ratios; CA – Coronary angiography; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute ischemic stroke and reinfarction); PCI – Percutaneous Coronary Intervention.

**Multivariable analysis –** the following variables were adjusted for: age, sex, weekend admission, bed size of hospital, STEMI, cardiogenic shock, cardiac arrest, atrial fibrillation, dyslipidaemia, thrombocytopaenia, smoking, previous PCI, previous coronary artery bypass grafting, previous CVA, anaemia, heart failure, valvular heart disease, hypertension, peripheral artery disease, diabetes, chronic lung disease, coagulopathy, dementia, liver disease, chronic kidney disease, metastatic disease.

**Supplementary Material**

**Supplementary Table 1.** Search codes.

|  |  |  |
| --- | --- | --- |
| **Diagnoses** | **ICD-9 Codes (NIS 2004-2015Q3)** | **ICD-10 Codes (NIS Q42015-2018)** |
| **AMI** | 410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x, 410.70, 410.71, 410.72 | I21.01-I21.09, I21.11-I21.19, I21.21-I21.29, I21.3, I21.4, I21.9 |
| **STEMI** | 410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x | I21.01-I21.09, I21.11-I21.19, I21.21-I21.29, I21.3 |
| **Diabetes Mellitus** | 648.0.x, 249.x, 250.x | E08\* E09\* E10\* E11\* E13\* |
| **Dyslipidaemia** | 272.0, 272.1, 272.2, 272.3, 272.4 | E78\* |
| **Smoking** | V15.82, 305.1  | Z72.0, Z53.01, O9933.x |
| **Previous MI** | 412 | I25.2, I25.6 |
| **Previous PCI** | V45.82  | Z98.61, Z95.5 |
| **Previous CABG** | V45.81 | Z95.1 |
| **Previous CVA (TIA and Stroke)** | V12.54 | Z86.73  |
| **Atrial Fibrillation** | 427.31 | I48.91, I48.20-21, I48.11, I48.19, I48.0 |
| **Heart failure** | 428.x | I50\* Cardiomyopathy: I42\* |
| **Ventricular tachycardia** | 427.1 | I47.0, I47.2 |
| **Ventricular fibrillation** | 427.41 | I49.01, I49.02 |
| **Cardiac arrest** | 427.5 | I46.2 (due to cardiac condition); I46.8 and I46.9 (due to non-cardiac condition) |
| **Thrombocytopenia** | 287.5, 287.49 | D69.4\*, D69.5\*, D69.6\* |
| **Dementia** | 290.x, 294.x | F01\*, F02\*, F03\* |
| **Valvular disease** | 093.2, 394.x-397.1, 397.9, 424.x, 746.3-746.6, V42.2, V43.3 (Elixhauser comorbidity codes) | I34\*, I35\*, I36\*, I37\* |
| **Peripheral Arterial disease** | 440.x, 441.x, 442.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4 (Elixhauser comorbidity codes) | I70.2x-I70.7x; I70.92; Z98.62; E13.51; E13.52; E08.51; E08.52; E10.51; E10.52; E11.51; E11.52 |
| **Arterial hypertension** | 401.1, 401.9, 642.0, 401.0, 402.x-405.x, 642.1,642.2, 642.7, 642.9 (Elixhauser comorbidity codes) | I10\* |
| **Chronic pulmonary disease** | 490x-492.x, 493.x, 494x-505.x, 506.4 (Elixhauser comorbidity codes) | J41\*, J42\*, J43\*, J44\*, J45\*, J47\* |
| **Renal failure** | 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, V42.0, V45.1, V56.x (Elixhauser comorbidity codes) | N18\* |
| **Liver disease** | 070.22, 070.23, 070.32, 070.33, 070.44, 070.54,456.0, 456.1, 456.20, 571.0, 571.2-571.9, 572.3, 572.8, V42.7 (Elixhauser comorbidity codes) | K70\*, K72.1\*, K72.9\*, K73\*, K74\*, K75\*, K76\*, K77\* |
| **Metastatic cancer** | 196.x-199.x (Elixhauser comorbidity codes) | C77\*, C78\*, C79\*, R18.0\*, C7B\* |
| **Coagulopathy** | 286.x, 287.1, 287.3-287.5 (Elixhauser comorbidity codes) | D65, D66, D67, D68\*, D69\* |
| **Anemias** | 280.0, 648.2, 280.1-281.9, 285.2, 285.9 (Elixhauser comorbidity codes) | D62\*, D63\*, D64\*  |
| **In-hospital procedures and outcomes** |  |
| **Acute ischemic stroke** | 433.x, 434.x, 436, 435.x, 362.3 | I63\* |
| **Haemorrhagic stroke** | 430, 431, 432.0, 432.1, 432.9 | I60.x, I61.x, I62.x |
| **Procedure-related haemorrhage** | 998.11  | Complicating CA or PCI: I97.410 and I97.610; Complicating CABG: I97.411 and I97.611 |
| **Major bleeding** | 430, 431, 432x, 578x, 786.3, 786.30, 786.39 | I60\*, I61\*, I62\*, R58, K92.0, K92.1, K92.2 |
| **Hemopericardium** | 423.0 | I31.2 |
| **Pericardiocentesis** | 37.0 | 0W9D40Z |
| **Coronary dissection** | 414.12 | I25.42 |
| **Cardiac complications** | 423.3, 423.0, 414.12, 37.0 | I31.4, I31.2, I25.42, 0W9D40Z |
| **Subsequent infarction (reinfarction)** | 410.02, 410.12, 410.22, 410.32, 410.42, 410.52, 410.62, 410.82, 410.92 | I22\* |
| **Diagnostic Left Cardiac catheterisation/coronary arteriography** | 47 (Clinical Classification Software Procedure code); 37.22 (ICD-9 procedure codes) | B210010, B2100ZZ, B210110, B2101ZZ, B210Y10, B210YZZ, B211010, B2110ZZ, B211110, B2111ZZB211Y10, B211YZZ, B212010, B2120ZZ, B212110, B2121ZZ, B212Y10, B212YZZ, B213010, B2130ZZ, B213110, B2131ZZ, B213Y10, B213YZZ, B2170ZZ, B2171ZZ, B217YZZ, B2180ZZ, B2181ZZ, B218YZZ, B21F0ZZ, B21F1ZZ, B21FYZZ |
| **PCI** | 45 (Clinical Classification Software Procedure code); 36.0, 36.03, 36.04, 36.06, 36.07, 36.09 (ICD-9 procedure codes) | 0270346, 027034Z, 02703D6, 02703DZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 027044Z, 0270446, 02704D6, 02704DZ, 02704Z6, 02704ZZ, 0270356, 027035Z, 02703E6, 02703EZ, 0270456, 027045Z, 02704E6, 02704EZ, 0270366, 027036Z, 02703F6, 02703FZ, 0270466, 027046Z, 02704F6, 02704FZ, 0270376, 027037Z, 02703D6, 02703DZ, 027047Z, 0270476, 02704G6, 02704GZ, 0271346, 027134Z, 02713D6, 02713DZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 027144Z, 0271446, 02714D6, 02714DZ, 02714Z6, 02714ZZ, 0271356, 027135Z, 02713E6, 02713EZ, 0271456, 027145Z, 02714E6, 02714EZ, 0271366, 027136Z, 02713F6, 02713FZ, 0271466, 027146Z, 02714F6, 02714FZ, 0271376, 027137Z, 02713G6, 02713GZ, 027147Z, 0271476, 02714G6, 02714GZ, 0272346, 027234Z, 02723D6, 02723DZ, 02723T6, 02723TZ, 02723Z6, 02723ZZ, 027244Z, 0272446, 02724D6, 02724DZ, 02724Z6, 02724ZZ, 0272356, 027235Z, 02723E6, 02723EZ, 0272456, 027245Z, 02724E6, 02724EZ, 0272366, 027236Z, 02723F6, 02723FZ, 0272466, 027246Z, , 02724F6, 02724FZ, 0272376, 027237Z, 02723G6, 02723GZ, 027247Z, 0272476, 02724G6, 02724GZ, 0273346, 027334Z, 02733D6, 02733DZ, 02733T6, 02733TZ, 02733Z6, 02733ZZ, 027344Z, 0273446, 02734D6, 02734DZ, 02734Z6, 02734ZZ, 0273356, 027335Z, 02733E6, 02733EZ, 0273456, 027345Z, 02734E6, 02734EZ, 0273366, 027336Z, 02733F6, 02733FZ, 0273466, 027346Z, 02734F6, 02734FZ, 0273376, 027337Z, 02733G6, 02733GZ, 027347Z, 0273476, 02734G6, 02734GZ |

**Legend:** AMI – Acute Myocardial Infarction; CABG – coronary artery bypass grafting; CVA – cerebrovascular accident; IABP – Intraaortic Balloon Pump; IHD – Ischemic Heart Disease; MI – myocardial infarction; NSTEMI – non-ST-elevation Myocardial Infarction; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction; PCI – Percutaneous Coronary Intervention; TIA – Transient Ischemic Attack.

**Supplementary Table 2.** Baseline patient characteristics – sensitivity analysis by teaching status in urban hospitals.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Urban hospitals (N=8,717,241; 89.6%) | Rural hospitals (N=1,011,637; 10.4%) | *P*-value |
| **Non-Teaching (N=3,654,320; 37.6%)** | **Teaching (N=5,062,921; 52.0%)** |
| Age (years), median (IQR) | 68 (57-79) | 66 (56-77) | 71 (59-82) | <0.001 |
| Female sex, % | 40.3 | 38.1 | 44.9 | <0.001 |
| Ethnicity, % |  |  |  | <0.001 |
| White | 77.9 | 71.8 | 87.6 |  |
| Black | 7.9 | 12.9 | 6.4 |  |
| Hispanic | 8.5 | 8.4 | 2.7 |  |
| Asian/Pacific Islander | 2.3 | 2.7 | 0.7 |  |
| Native American | 0.4 | 0.6 | 1.2 |  |
| Other | 2.9 | 3.6 | 1.5 |  |
| Weekend admission, % | 26.4 | 25.6 | 26.1 | <0.001 |
| Primary expected payer, % |  |  |  | <0.001 |
| Medicare | 57.6 | 54.2 | 66.2 |  |
| Medicaid | 5.9 | 8.2 | 5.8 |  |
| Private Insurance | 27.9 | 28.5 | 19.8 |  |
| Self-pay | 5.5 | 5.7 | 5.1 |  |
| No charge | 0.5 | 0.6 | 0.2 |  |
| Other | 2.7 | 2.8 | 2.9 |  |
| Median Household Income (percentile), % |  |  |  | <0.001 |
| 0-25th | 24.1 | 28.9 | 53.5 |  |
| 26th-50th | 28.1 | 25.5 | 34.5 |  |
| 51st-75th | 26.2 | 24.4 | 10.1 |  |
| 76th-100th | 21.6 | 21.3 | 1.9 |  |
| Bed size of hospital, % |  |  |  | <0.001 |
| Small | 10.2 | 14.4 | 10.5 |  |
| Medium | 25.5 | 29.2 | 13.7 |  |
| Large | 64.3 | 56.4 | 75.8 |  |
| Hospital Region, % |  |  |  | <0.001 |
| Northeast | 13.4 | 24.2 | 13.9 |  |
| Midwest | 19.0 | 24.2 | 29.6 |  |
| South | 43.2 | 36.3 | 48.0 |  |
| West | 24.4 | 15.2 | 8.5 |  |
| Record Characteristics, % |  |  |  |  |
| STEMI | 26.6 | 27.1 | 19.6 | <0.001 |
| Cardiogenic shock | 4.6 | 5.8 | 2.9 | <0.001 |
| Cardiac arrest | 2.9 | 3.1 | 2.2 | <0.001 |
| Ventricular tachycardia | 5.4 | 6.6 | 3.8 | <0.001 |
| Ventricular fibrillation | 2.6 | 3.0 | 1.5 | <0.001 |
| Comorbidities, % |  |  |  |  |
| Atrial fibrillation | 16.2 | 16.4 | 16.4 | <0.001 |
| Dyslipidaemia | 55.5 | 60.2 | 49.1 | <0.001 |
| Thrombocytopenia | 3.1 | 4.1 | 2.3 | <0.001 |
| Smoking | 30.0 | 29.0 | 25.9 | <0.001 |
| Previous PCI | 12.1 | 13.8 | 10.5 | <0.001 |
| Previous CABG | 9.4 | 10.3 | 10.4 | <0.001 |
| Previous CVA | 4.4 | 5.2 | 4.5 | <0.001 |
| Anaemias | 16.0 | 16.4 | 14.0 | <0.001 |
| Heart failure | 30.3 | 31.5 | 32.4 | <0.001 |
| Valvular disease | 1.2 | 2.2 | 1.3 | <0.001 |
| Hypertension | 64.6 | 66.0 | 62.7 | <0.001 |
| Peripheral artery disease | 9.0 | 8.5 | 8.9 | <0.001 |
| Diabetes mellitus | 33.6 | 34.3 | 33.4 | <0.001 |
| Chronic pulmonary disease | 21.2 | 19.4 | 24.5 | <0.001 |
| Coagulopathy | 4.2 | 5.4 | 2.9 | <0.001 |
| Dementia | 6.1 | 4.9 | 7.5 | <0.001 |
| Chronic liver disease | 1.3 | 1.7 | 1.1 | <0.001 |
| Chronic renal failure | 17.0 | 18.6 | 16.6 | <0.001 |
| Metastatic cancer | 0.8 | 0.8 | 0.9 | <0.001 |

**Abbreviations:** CABG – Coronary Artery Bypass Graft; CVA – Cerebrovascular Accidents; IHD – Ischemic Heart Disease; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction.

**Supplementary Table 3.** Unadjusted utilization of invasive management and in-hospital clinical outcomes – sensitivity analysis by teaching status in urban hospitals.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Urban hospitals (N=8,717,241; 89.6%) | Rural hospitals (N=1,011,637; 10.4%) | *P*-value |
| **Non-Teaching (N=3,654,320; 37.6%)** | **Teaching (N=5,062,921; 52.0%)** |
| Invasive management, % |  |  |  |  |
| Coronary angiography | 60.6 | 70.7 | 38.8 | <0.001 |
| PCI | 39.6 | 48.4 | 24.5 | <0.001 |
| Clinical outcomes, % |  |  |  |  |
| All-cause mortality | 5.3 | 5.1 | 5.9 | <0.001 |
| MACCE | 8.5 | 8.0 | 8.8 | <0.001 |
| Major bleeding | 2.3 | 2.4 | 2.2 | <0.001 |
| Ischemic stroke | 3.1 | 2.9 | 2.8 | <0.001 |
| Length of stay (days), median (IQR) | 3 (2-5) | 3 (2-6) | 2 (1-4) | <0.001 |
| Total charges (USD), median (IQR) | 44,365 (21,866-79,847) | 53,060 (29,762-91,832) | 19,389 (8,864-43,154) | <0.001 |

**Abbreviations:** CA – Coronary angiography; PCI - Percutaneous Coronary Intervention; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute ischemic stroke and reinfarction); IQR – Interquartile Range.

**Supplementary Table 4.** Adjusted odds ratios (aOR) of rural invasive management and in-hospital clinical outcomes – sensitivity analysis by teaching status in urban hospitals.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | AMI type | Rural hospitals aOR [95% CI]  | *P*-value |
| Invasive management |  |  |  |
| CA | **STEMI** | 0.32 [0.31-0.32] | <0.001 |
| **NSTEMI** | 0.29 [0.29-0.29] | <0.001 |
| PCI | **STEMI** | 0.44 [0.43-0.44] | <0.001 |
| **NSTEMI** | 0.38 [0.38-0.39] | <0.001 |
| Clinical outcomes |  |  |  |
| All-cause mortality | **STEMI** | 1.11 [1.09-1.13] | <0.001 |
| **NSTEMI** | 1.17 [1.15-1.18] | <0.001 |
| MACCE | **STEMI** | 1.06 [1.04-1.08] | <0.001 |
| **NSTEMI** | 1.04 [1.03-1.05] | <0.001 |
| Major bleeding | **STEMI** | 0.97 [0.94-1.00] | 0.027 |
| **NSTEMI** | 0.89 [0.88-0.91] | <0.001 |
| Ischemic stroke | **STEMI** | 0.85 [0.82-0.88] | <0.001 |
| **NSTEMI** | 0.85 [0.84-0.87] | <0.001 |

**Reference group:** Urban hospitals.

**Abbreviations:** aOR – Adjusted Odds Ratios; CA – Coronary angiography; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute ischemic stroke and reinfarction); NSTEMI – ST-elevation Myocardial Infarction; PCI – Percutaneous Coronary Intervention; STEMI – ST-elevation Myocardial Infarction.

**Multivariable analysis –** the following variables were adjusted for: age, sex, weekend admission, bed size of hospital, cardiogenic shock, cardiac arrest, atrial fibrillation, dyslipidaemia, thrombocytopaenia, smoking, previous PCI, previous coronary artery bypass grafting, previous CVA, anaemia, heart failure, valvular heart disease, hypertension, peripheral artery disease, diabetes, chronic lung disease, coagulopathy, dementia, liver disease, chronic kidney disease, metastatic disease.

# References

1. One in Five Americans Live in Rural Areas [Available from: <https://www.census.gov/library/stories/2017/08/rural-america.html>.

2. Harrington RA, Califf RM, Balamurugan A, Brown N, Benjamin RM, Braund WE, et al. Call to Action: Rural Health: A Presidential Advisory From the American Heart Association and American Stroke Association. Circulation. 2020;141(10):e615-e44.

3. Baldwin LM, MacLehose RF, Hart LG, Beaver SK, Every N, Chan L. Quality of care for acute myocardial infarction in rural and urban US hospitals. J Rural Health. 2004;20(2):99-108.

4. Baldwin LM, Chan L, Andrilla CH, Huff ED, Hart LG. Quality of care for myocardial infarction in rural and urban hospitals. J Rural Health. 2010;26(1):51-7.

5. Alghanem F, Clements JM. Narrowing performance gap between rural and urban hospitals for acute myocardial infarction care. Am J Emerg Med. 2020;38(1):89-94.

6. Loccoh EC, Joynt Maddox KE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-Urban Disparities in Outcomes of Myocardial Infarction, Heart Failure, and Stroke in the United States. J Am Coll Cardiol. 2022;79(3):267-79.

7. Patlolla SH, Pajjuru VS, Sundaragiri PR, Cheungpasitporn W, Sachdeva R, McDaniel MC, et al. Hospital-Level Disparities in the Management and Outcomes of Cardiac Arrest Complicating Acute Myocardial Infarction. Am J Cardiol. 2022;169:24-31.

8. Vallabhajosyula S, Dunlay SM, Barsness GW, Rihal CS, Holmes DR, Prasad A. Hospital-Level Disparities in the Outcomes of Acute Myocardial Infarction With Cardiogenic Shock. Am J Cardiol. 2019;124(4):491-8.

9. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2004-2018. Agency for Healthcare Research and Quality, Rockville, MD. [www.hcup-us.ahrq.gov/nisoverview.jsp](file:///D%3A%5CHB%20Files%5CDesktop%5CResearch%5CMamas%20Team%5CProject%202%5CCRM%20submission%5CRebuttal%5CAM%5Cwww.hcup-us.ahrq.gov%5Cnisoverview.jsp)

10. Ellerbeck EF, Bhimaraj A, Perpich D. Organization of care for acute myocardial infarction in rural and urban hospitals in Kansas. J Rural Health. 2004;20(4):363-7.

11. Graves BA. Access to cardiac interventional services in Alabama and Mississippi: a geographical information system analysis. Perspect Health Inf Manag. 2010;7.

12. Bechtold D, Salvatierra GG, Bulley E, Cypro A, Daratha KB. Geographic Variation in Treatment and Outcomes Among Patients With AMI: Investigating Urban-Rural Differences Among Hospitalized Patients. J Rural Health. 2017;33(2):158-66.

13. James S. Stroke: a rare but devastating procedural complication of PCI. Eur Heart J. 2015;36(25):1571-2.

14. Alkhouli M, Alqahtani F, Tarabishy A, Sandhu G, Rihal CS. Incidence, Predictors, and Outcomes of Acute Ischemic Stroke Following Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2019;12(15):1497-506.

15. Murali S, Vogrin S, Noaman S, Dinh DT, Brennan AL, Lefkovits J, et al. Bleeding Severity in Percutaneous Coronary Intervention (PCI) and Its Impact on Short-Term Clinical Outcomes. J Clin Med. 2020;9(5).

16. Chang KY, Chiu N, Aggarwal R. In-Hospital Mortality for Inpatient Percutaneous Coronary Interventions in the United States. Am J Cardiol. 2021;159:30-5.

17. Jollis JG, Al-Khalidi HR, Roettig ML, Berger PB, Corbett CC, Doerfler SM, et al. Impact of Regionalization of ST-Segment-Elevation Myocardial Infarction Care on Treatment Times and Outcomes for Emergency Medical Services-Transported Patients Presenting to Hospitals With Percutaneous Coronary Intervention: Mission: Lifeline Accelerator-2. Circulation. 2018;137(4):376-87.

18. Healthy People 2030 [Available from: <https://www.cdc.gov/nchs/healthy_people/hp2030/hp2030.htm>.

19. Balamurugan A, Delongchamp R, Im L, Bates J, Mehta JL. Neighborhood and Acute Myocardial Infarction Mortality as Related to the Driving Time to Percutaneous Coronary Intervention-Capable Hospital. J Am Heart Assoc. 2016;5(2).