



## Non-traditional risk factors and the risk of myocardial infarction in the young in the US population-based cohort



Chayakrit Krittanawong<sup>a,b,f,\*</sup>, Yiming Liu<sup>c</sup>, Dhruv Mahtta<sup>a</sup>, Bharat Narasimhan<sup>f</sup>, Zhen Wang<sup>d,e</sup>, Hani Jneid<sup>a,b</sup>, Jacqueline E. Tamis-Holland<sup>f</sup>, Alam Mahboob<sup>a</sup>, Usman Baber<sup>f</sup>, Roxana Mehran<sup>f</sup>, W.H. Wilson Tang<sup>g</sup>, Christie M. Ballantyne<sup>a</sup>, Salim S. Virani<sup>a,b</sup>

<sup>a</sup> Michael E. DeBakey VA Medical Center, Houston, TX, USA

<sup>b</sup> Section of Cardiology, Baylor College of Medicine, USA

<sup>c</sup> National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

<sup>d</sup> Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA

<sup>e</sup> Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

<sup>f</sup> Department of Cardiology, Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, New York, NY, USA

<sup>g</sup> Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA

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### ABSTRACT

Although most prevalent in elderly, myocardial infarction (MI) also affects younger adults. We sought to investigate baseline characteristics in young patients (<55 years) with MI using the National Inpatient Sample (NIS) database between 2004 and 2015. Multivariable logistic regression models were used to assess factors associated with acute myocardial infarction (AMI) in young patients. After multivariable analyses adjusted for age, sex, race, family history of atherosclerosis, body mass index (BMI), diabetes, hypertension, hyperlipidemia, chronic kidney disease, and current cigarette smoking; novel risk factors such as human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE), and obstructive sleep apnea (OSA) were associated with a higher risk of developing an AMI in the young (adjusted OR for HIV 4.06; 95 CI 3.48–4.71,  $p < 0.001$ ), (adjusted OR for SLE 2.12; 95 CI 1.89–2.39,  $p = 0.04$ ), and (adjusted OR for OSA 1.16; 95 CI 1.12–1.20,  $p < 0.001$ ), respectively. Rheumatoid arthritis was associated with a lower risk of AMI (adjusted OR 0.83; 95 CI 0.76–0.89,  $p < 0.001$ ). After multivariable analyses, cigarette smoking (adjusted OR 1.98; 95 CI 1.95–2.02,  $p < 0.001$ ), obesity (adjusted OR 1.37; 95 CI 1.33–1.41,  $p = 0.003$ ), hyperlipidemia (adjusted OR 1.07; 95 CI 1.04–1.08,  $p < 0.001$ ) and a family history of CAD (adjusted OR 1.35; 95 CI 1.3–1.4,  $p < 0.001$ ) were also associated with a higher risk of developing an AMI in the young. In conclusion, young patients with AMI have both traditional risk factors and non-traditional risk factors. In addition to traditional risk factors, close attention should be paid to emerging risk factors such as SLE, HIV and OSA.

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## 1. Introduction

In young individuals, acute myocardial infarction (AMI) remains a major cause of morbidity and mortality worldwide. Due to lack of reporting, there is paucity of information regarding this patient population. Traditional risk factors such as, smoking, hyperlipidemia, hypertension, family history of atherosclerosis, obesity and diabetes mellitus (DM), which are well recognized risk factors for AMI are becoming more prevalent in the younger population [1–3]. In addition, relatively uncommon syndromes of adults including rheumatoid arthritis (RA), systemic lupus erythematosus

(SLE) and obstructive sleep apnea (OSA) are more prevalent in younger patients with AMI. The novel risk factors are not well studied in large national datasets. This study sought to investigate baseline characteristics in young patients with AMI using the National Inpatient Sample (NIS) database between 2004 and 2015. We also evaluated independent associations of traditional and non-traditional risk factors with risk of AMI in this population.

## 2. Methods

### 2.1. Data source

The study sample originated from the NIS database which includes data from hospitalized patients in the United States (US) from January 1, 2004, to September 30, 2015. This registry is part

\* Corresponding author at: Baylor College of Medicine, Section of Cardiology, 1 Baylor Plaza, Houston, TX 77030, USA.

E-mail address: [Chayakrit.Krittanawong@bcm.edu](mailto:Chayakrit.Krittanawong@bcm.edu) (C. Krittanawong).

of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality. The NIS is derived from billing data submitted by hospitals from a total of 46 states, which serve 97% of the national population, to statewide data organizations. These reports are published on the NIS website (<http://www.hcup-us.ahrq.gov/db/nation/nis/nisrelatedreports.jsp>).

## 2.2. Data extraction

Data were extracted from the Nationwide Inpatient Sample (NIS) from January 1, 2004, to September 30, 2015, using ICD-9 codes. Young patients (<55 years) with the principal diagnosis of acute myocardial infarction were identified, defined as either STEMI (ICD-CM 9 codes of 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.81, and 410.91) and NSTEMI (ICD-9-CM code of 410.7x). All comorbidities (e.g., hypertension, diabetes, overweight, obesity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, current cigarette smoking etc.) were identified. The methodological standards comply with the Agency for Healthcare Research and Quality's recommendations (Online supplementary Table 1).

## 2.3. Study definitions

Demographics, conventional risk factors, and in-hospital outcomes were evaluated. Most of the included variables were readily available in the NIS database including age, sex, race (white, African American, Hispanic, Asian, Native American, and other) and comorbidities (e.g., hypertension, diabetes, overweight, obesity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, current cigarette smoking, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, obstructive sleep apnea) were included in the analysis using their specific ICD-9-CM codes. A list of ICD-9-CM codes for the covariables included in the current analysis is described in the online supplementary Table 2

## 2.4. Statistical analysis

Spread of variables was assessed across young patients with AMI and young patients without AMI (control group). Percentages and means  $\pm$  standard deviations were computed for categorical and continuous variables, respectively. Categorical variables were compared using the Chi-square test or Fisher's exact tests, when

appropriate, while continuous variables were analyzed using the two-tailed Student's *t* test or the Mann-Whitney-*U* test, when appropriate. Univariable and multivariable logistic regression modeling were performed to determine traditional and non-traditional risk factors associated with AMI among young patients. All analyses were conducted using R 3.4.0 and Stata version 14.2. All p-values were two-sided, and statistical significance was determined at the level of  $p < 0.05$ .

## 3. Results

### 3.1. Baseline characteristics

The study population comprised of 5,764,755 hospitalized young individuals (<55 years), among which 1,149,185 (19.9%) were found to have AMI as outlined in Table 1. At baseline, the AMI cohort had a male predominance (66.6% vs 57.7%) with mean age of  $45.1 \pm 7.8$  years old with a greater proportion of African Americans (11.5% vs 6.4%) and Hispanics (8.5% vs 5.4%) than the non-AMI group. Patients with AMI had a higher prevalence of obesity (5.7% vs. 3.7%), human immunodeficiency virus (HIV) (0.17% vs. 0.04%), and obstructive sleep apnea (2.6% vs. 2.1%). Smoking (12.8% vs 6.4%) as well as a family history of coronary artery disease (2.3% vs 1.4%) were nearly twice as prevalent among patients with AMI than those without. Rheumatic conditions such as, SLE (0.22% vs 0.12%) predominated among patients with AMI while RA was significantly more common among non-AMI patients. (all  $p$  values  $< 0.001$ ) With regards to traditional cardiovascular risk factors, diabetes mellitus was significantly more common in patients without AMI (19.2% vs 15.4%). Hypertension (28.7% vs 25.3%) as well as hyperlipidemia (37.8% vs 33%) though statistically significant, were only slightly more common in the AMI cohort.

### 3.2. Emerging risk factors for AMI in young

In the univariable analyses, HIV (OR 3.9; 95 CI 3.3–4.6,  $p < 0.001$ ), SLE (OR 1.69; 95 CI 1.5–1.8,  $p < 0.001$ ) and OSA (OR 1.08; 95 CI 1.05–1.12,  $p < 0.001$ ) were associated with a higher risk of AMI in the young. In contrast, RA (OR 0.70; 95 CI 0.64–0.74,  $p < 0.001$ ) was associated with lower risk of developing an AMI in the young. After multivariable analyses for adjusted for age, sex, race, family history, BMI, diabetes, hypertension, hyperlipidemia, chronic kidney disease, current cigarette smoking, HIV emerged as the strongest risk factor (adjusted OR 4.06; 95 CI

**Table 1**  
Demographic and baseline characteristics among young patients with acute myocardial infarction in young.

	Young patients without AMI (n = 4,615,570)	Young Patients with AMI (n = 1,149,185)	P-Values
Female	42.3%	33.4%	<0.0001
White	55.7%	51%	<0.0001
Black	6.4%	11.5%	<0.0001
Hispanic	5.4%	8.5%	<0.0001
Overweight	0.2%	0.3%	<0.0001
Obesity	3.7%	5.7%	<0.0001
Smoking	6.4%	12.8%	<0.0001
Hyperlipidemia	33%	37.8%	<0.0001
Family history of coronary artery disease	1.4%	2.3%	<0.0001
Hypothyroidism	5.6%	3.2%	<0.0001
Rheumatoid Arthritis	0.6%	0.45%	<0.0001
Systemic Lupus erythematosus	0.12%	0.22%	<0.0001
HIV	0.05%	0.17%	<0.0001
Obstructive sleep apnea	2.1%	2.6%	<0.0001
Diabetes mellitus	15.4%	18.2%	<0.0001
Hypertension	25.3%	28.7%	<0.0001
Chronic kidney disease	6.1%	6.8%	<0.0001
Chronic obstructive pulmonary disease	10.6%	9.2%	<0.0001

**Table 2**

Multivariate logistic regression analyses for non-traditional risk factors in young patients with acute myocardial infarction.

Variable	Adjusted OR [95% CI]	P value
<b>Systemic Lupus erythematosus</b>		
No adjustment	1.69 (1.5–1.8)	<0.001
Multivariable adjusted	2.12 (1.89–2.39)	0.04
<b>HIV</b>		
No adjustment	3.90 (3.3–4.6)	<0.001
Multivariable adjusted	4.06 (3.48–4.71)	<0.001
<b>Obstructive sleep apnea</b>		
No adjustment	1.08 (1.05–1.12)	<0.001
Multivariable adjusted	1.16 (1.12–1.20)	<0.001
<b>Rheumatoid Arthritis</b>		
No adjustment	0.70 (0.64–0.74)	<0.001
Multivariable adjusted	0.83 (0.76–0.89)	<0.001

Multivariable logistic regression models adjusted for age, sex, race, family history, body mass index, diabetes, hypertension, hyperlipidemia, chronic kidney disease, current cigarette smoking.

3.48–4.71,  $p < 0.001$ ) followed by SLE (adjusted OR 2.12; 95 CI 1.89–2.39,  $p = 0.04$ ) and OSA (adjusted OR 1.16; 95 CI 1.12–1.20,  $p < 0.001$ ). Rheumatoid arthritis was associated with a lower risk of developing AMI (adjusted OR 0.83; 95 CI 0.76–0.89,  $p < 0.001$ ) (Table 2).

### 3.3. Traditional risk factors for AMI in young

Among traditional cardiovascular risk factors, hypertension (OR 1.13; 95 CI 1.1–1.14,  $p < 0.001$ ), cigarette smoking (OR 3.24; 95 CI 3.18–3.3,  $p < 0.001$ ), obesity (OR 1.6; 95 CI 1.55–1.65,  $p < 0.001$ ), hyperlipidemia (OR 1.1; 95 CI 1.09–1.11,  $p < 0.001$ ) and a family history of CAD (OR 1.39; 95 CI 1.34–1.43,  $p < 0.001$ ) were all associated with higher risk of AMI in the young. All the aforementioned variables remained significant after multivariable analyses. After adjustment for all covariates, current cigarette smoking, (adjusted OR 1.98; 95 CI 1.95–2.02,  $p < 0.001$ ), obesity (adjusted OR 1.37; 95 CI 1.33–1.41,  $p = 0.003$ ), hyperlipidemia (adjusted OR 1.07; 95 CI 1.04–1.08,  $p < 0.001$ ) and a family history of CAD (adjusted OR 1.35; 95 CI 1.3–1.4,  $p < 0.001$ ) were independently associated with higher odds of AMI. Although diabetes mellitus was associated with higher odds of developing an AMI in the young (OR 1.03; 95 CI 0.99–1.08,  $p = 0.08$ ) in the univariate analysis, the result became

**Table 3**

Multivariate logistic regression analyses for traditional risk factors in young patients with acute myocardial infarction.

Variable	Adjusted OR [95% CI]	Adjusted P value
<b>Family history of coronary artery disease</b>		
No adjustment	1.39 (1.34–1.43)	<0.001
Multivariable adjusted	1.35 (1.30–1.40)	<0.001
<b>Cigarette smoking</b>		
No adjustment	3.24 (3.18–3.3)	<0.001
Multivariable adjusted	1.98 (1.95–2.02)	<0.001
<b>Diabetes</b>		
No adjustment	1.03 (0.99–1.08)	0.08
Multivariable adjusted	0.76 (0.75–0.78)	<0.001
<b>Hyperlipidemia</b>		
No adjustment	1.10 (1.09–1.11)	<0.001
Multivariable adjusted	1.07 (1.04–1.08)	<0.001
<b>Hypertension</b>		
No adjustment	1.13 (1.10–1.14)	<0.001
Multivariable adjusted	0.93 (0.91–0.94)	<0.001
<b>Obesity</b>		
No adjustment	1.60 (1.55–1.65)	<0.001
Multivariable adjusted	1.37 (1.33–1.41)	0.003

Multivariable logistic regression models adjusted for age, sex, race, family history, body mass index, diabetes, hypertension, hyperlipidemia, chronic kidney disease, current cigarette smoking.

significant after adjusting for all covariates (adjusted OR 0.76; 95 CI 0.75–0.78,  $p < 0.001$ ) as described in Table 3.

## 4. Discussion

Based on our nationwide population-based analysis of young patients with AMI, we highlight two key findings. First, non-traditional risk factors such as HIV infection, SLE and OSA were associated with increased risk of AMI in young patients. Second, rheumatoid arthritis (RA) was associated with a decreased risk of AMI in young patients.

### 4.1. HIV and AMI

Large population studies have demonstrated an increased adjusted risk of MI among patients with HIV [4]. Several studies have also shown at least 1.5-fold higher risk of MI among patients with HIV [5–7]. This is also consistent with the results of our study. In fact, low CD4 count and high plasma HIV RNA levels have been associated with an increased risk of premature MI. This risk appears to be independent of the deleterious metabolic effects of antiretroviral therapy as well as traditional atherosclerotic risk factors [4,8]. HIV infection related chronic inflammation, immune activation, and ensuing endothelial dysfunction have been hypothesized as mechanisms driving the elevated risk of premature MI [9–12]. The Veterans Aging Cohort Study Virtual Cohort demonstrated that HIV infection may confer similar adjusted risk of MI as compared to that of diabetes [4]. Therefore, HIV infection may be considered as important risk factor for MI in young individuals, similar to some of the traditional risk factors such as hypertension and smoking. Therefore, besides optimization of HIV infection, aggressive measures targeting primary prevention of ischemic heart disease should be considered in these individuals.

### 4.2. SLE and AMI

SLE, a heterogeneous autoimmune disease, has a well-established association with endothelial dysfunction and systematic inflammation in multiple organs, thereby promoting accelerated atherosclerosis. Common comorbidities associated with SLE include MI and may be observed in up to 16% of SLE patients [13]. In the absence of coronary atherosclerosis on coronary angiography, patients with SLE may be predisposed to MI via a mechanism of coronary artery thrombosis or embolization, or coronary arteritis [14–17]. Several studies have suggested that patients with SLE had higher adjusted risk of MI compared with non-SLE control [18]. Most importantly, in the Framingham Offspring Study, Manzi et al. [19] found that patients with SLE in the 35 to 44-year age group were over 50 times more likely to have a MI compared with healthy controls. In the Nurses' Health Study of 119,332 which primarily consisted of Caucasian women with 28 years of follow-up, presence of SLE (mean age at diagnosis of 53 years) was associated with a 2-fold increased risk of cardiovascular end points including fatal and nonfatal MI (2.26; 95% CI 1.45 to 3.52,  $p = 0.001$ ) [20]. The findings from our analyses are in line with data from aforementioned studies and provide evidence from a nationwide scale to consider patients with SLE at an elevated risk for premature MI despite the lack of traditional atherosclerotic risk factors.

### 4.3. RA and AMI

RA is an independent risk factor for MI in young adults [21,22]. A recent meta-analysis demonstrated that patients with RA had significantly increased risk of CAD (RR = 1.26 [95% CI 1.04–1.52];

$p = 0.021$ ) compared to controls [23]. Interestingly, our analyses demonstrated that patients with RA had a lower likelihood of MI after adjustment for traditional atherosclerotic risk factors. Although these findings are in contrast to what data from prior analyses have suggested, we suspect there are several reasons behind our contrasting results. Firstly, on average patients with RA are diagnosed in the fifth to sixth decade of their life [24]. As compared to these patients, patients who are diagnosed with young onset rheumatoid arthritis have been shown to have lower disease activity which may explain why young patients with RA in our cohort had a lower likelihood of MI [25]. Additionally, the mechanisms hypothesized behind AMI in patients with RA are those of vascular dysfunction and plaque destabilization due to a chronic inflammatory state [26]. Disease duration has been demonstrated to be an independent risk factor for cardiovascular disease among patients with RA [27]. Hence, we suspect that young patients from our cohort may have had an overall lower disease duration (secondary to their young age) contributing to the lower likelihood of AMI. Finally, given the nationwide inpatient hospital admissions database, we suspect that patients included in our study may include patients with optimal treatment with anti-rheumatic drugs such as ASA or disease-modifying antirheumatic drugs (DMARDs). Aspirin was the mainstay of RA treatment, but aspirin doses for CAD prevention are much lower than anti-rheumatic drug usage [28]. Evidence indicates that treatment with DMARDs reduces the risk of cardiovascular disease. DMARDs are involved in anti-cytokine activities such as an inhibition of tumor necrosis factor- $\alpha$ , interleukin-6 (IL-6), and interleukin-1 (IL-1) [29,30]. A case control study showed that DMARD use could suppress inflammation, leading to a reduction of the development of atherosclerosis [31]. Tight control of systemic inflammation among patients with RA may also reduce MI risk, which may have contributed to the findings represented in our study. Since our control group included young hospitalized patients without MI as opposed to community controls, it is also possible that young patients with RA may have been hospitalized more often for non-MI related conditions. This could lead to an increased prevalence of RA in patients without MI in our cohort giving the appearance of RA being a protective risk factor for MI.

#### 4.4. OSA and AMI

Prior studies have demonstrated a high prevalence of previously undiagnosed OSA in patients admitted with MI and up to 42% of the patients admitted with STEMI have undiagnosed severe OSA [32,33]. The independent association between OSA and MI, although a subject of initial conflicting data, has been well recognized and attributed to the oxidative stress secondary to reactive oxygen species thereby leading to coronary microvascular injury and endothelial injury [34]. One study concluded that OSA increases the risk of MI regardless of traditional atherosclerotic risk factors [35], while another study reported that OSA was an independent predictor of the risk of recurrent MI [36]. Data from our analyses are in line with prior investigations and highlight the importance of OSA in young patients who are at increased risk for higher accrued lifetime risk for cardiovascular comorbidity related to AMI.

Apart from novel risk factors such as SLE, OSA, and HIV, our analyses also emphasize the high prevalence and importance of traditional atherosclerotic risk factors including tobacco use, hypertension, and family history of CAD. Although we bring to attention the role of the above-mentioned non-traditional risk factors, it is important to recognize and accordingly optimize young patients with traditional risk factors and especially those with concomitant disease states such as HIV, OSA, and SLE. Finally, the magnitude of the adjusted risk of AMI among young individuals with

HIV, OSA, and SLE not only calls for increased importance of optimal management of these respective disease states but also emphasizes the need for proper screening and prevention measures even among the young population. Similar to RA, young patients with DM may have been hospitalized more often for non-MI related conditions (e.g., diabetic ketoacidosis), resulting in an increased prevalence of DM in patients without MI.

#### 4.5. Study limitations

Our study has certain limitations. First, given the observational nature of our analyses, we were unable to adjust for unmeasured confounders. Second, we did not have data on some known confounders such as ApoB/ApoA1 ratio, factor V Leiden, or hs-CRP. Third, we were unable to adjust for other potential confounders such as, duration of rheumatic diseases and control of these disease states (CPAP use in patients with OSA, DMARD use in patients with SLE, antiretroviral therapy in patients with HIV). Fourth, we compared to a control of hospitalized patients but did not compare to a community control. Fifth, data on long-term survival and other outcomes were not available. Sixth, the association between non-traditional risk factors and AMI might not necessarily reflect a causal relation; patients with and without AMI differed for most variables and statistical adjustments in this condition can be subject to errors. Finally, given that our control group includes patients hospitalized for various medical conditions, further studies are needed to validate the results in using community controls. Moreover, the criteria for the diagnosis of AMI have changed over time and it might this have influenced the results. For example, with the new Universal definition of AMI, small changes in troponin levels might have been classified as AMI in patients with inflammatory disease (e.g., SLE and HIV), when, instead, they might have been related to myocardial inflammation and injury.

### 5. Conclusion

In our nationwide analysis, we demonstrate that young patients with AMI have a higher preponderance of both traditional and non-traditional risk factors. We also demonstrate that HIV, SLE, and OSA were all associated with an elevated risk of AMI, independent of traditional atherosclerotic risk factors. Although, young patients are often screened and medically optimized for traditional atherosclerotic risk factors, the magnitude of attributable risk of AMI due non-traditional risk factors (SLE, HIV, and OSA) should urge screening and optimization of these risk factors in contemporary cardiovascular practice. Prospective studies with age and sex-matched cohorts are needed to investigate the mechanistic relationship between RA and AMI. Finally, the impact of traditional risk factors should not be underestimated in the young population.

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#### Disclosure

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### Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100634>.

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