Acute Myocardial Infarction in Autoimmune Rheumatological Disease: A Nationwide Analysis of Clinical outcomes and Predictors of Management Strategy

Short title: AMI outcomes in rheumatological diseases

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Abstract

Objectives: The present study sought to examine national-level differences in management strategies and outcomes in patients with autoimmune rheumatic disease (AIRD) with acute myocardial infarction (AMI) between 2004 and 2014.

Methods: All AMI hospitalizations were analyzed from National Inpatient Sample, stratified according to AIRD diagnosis into four groups; No AIRD, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSC). The associations between AIRD subtypes and 1) receipt of coronary angiography (CA) and percutaneous coronary intervention (PCI) and 2) clinical outcomes were examined in comparison to patients without AIRD.

Results: Out of 6,747,797 AMI hospitalizations, 109,983 patients (1.6%) had an AIRD diagnosis (RA:1.3%, SLE:0.3% and SSC:0.1%). The prevalence of RA has risen from 1.0% (2004) to 1.5% (2014) while SLE and SSC remained stable. Patients with SLE were less likely to receive invasive management (odds ratio (OR) CA:0.87; 95% confidence interval (CI) 0.84,0.91, PCI:0.93 0.90,0.96) whereas no statistically significant differences were found in RA and SSC groups. Subsequently, the odds of mortality and bleeding were increased in patients with SLE (OR 1.15; 1.07,1.23 and 1.24; 1.16,1.31, respectively). SSC was associated with increased odds of MACCE and mortality (OR 1.52; 1.38,1.68 and 1.81; 1.62,2.02, respectively) but not bleeding or stroke, whereas the RA group was at no increased risk of any complication.

Conclusion: In a nationwide cohort of AMI hospitalizations we demonstrate lower utilization of invasive management in patients with SLE and worse outcomes after AMI in SLE and SSC patients compared to those without AIRD.

Key Words: acute myocardial infarction, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, outcomes, revascularization

Abbreviations

AMI	Acute myocardial infarction
AIRD	Autoimmune rheumatic disease
CABG	Coronary artery bypass grafting
MACCE	Major Adverse Cardiovascular and Cerebrovascular Events
NIS	National Inpatient Sample
OR	Odds Ratio
PCI	Percutaneous coronary intervention
RA	Rheumatoid arthritis
STEMI	ST-Elevation Myocardial Infarction
SLE	Systemic Lupus Erythematosus
SSC	Systemic Sclerosis
NSTEMI	non- ST-Elevation Myocardial Infarction

Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality globally.[1-4] Patients with autoimmune rheumatic disease (AIRD), including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSC), are at an increased risk of CVD owing to numerous risk factors, including accelerated atherosclerosis and underlying inflammation, as well as the use of disease modifying pharmacotherapy that are also implicated in the progression of coronary artery disease (CAD).[5, 6]

Patients with AIRD are at increased risk of acute myocardial infarction (AMI)[1, 7] and, whilst several studies have examined the clinical outcomes in patients with AIRD following AMI, they have been subject to several limitations such as the study of specific disease subtypes (e.g. RA), use of specific AMI cohorts (e.g. only first-time AMI) or small sample size that may be underpowered to detect clinically significant differences in outcomes, making them less generalizable to the wider population of interest.[5, 8-10] It is possible that differences in these AMI-related outcomes exist between AIRD subtypes, however, the evidence base to support such a hypothesis is limited.

The present study was designed to examine the prevalence, characteristics and in-hospital clinical outcomes of patients with pre-existing AIRD presenting with AMI in a national cohort of United States (US) hospitalizations.

Methods

Data Source

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the US and is sponsored by the Agency for Healthcare Research and

Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[11] NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population.

Study Design and Population

All records for AMI hospitalizations between 2004 and 2014 were included in this study, as identified using the International Classification of Diseases, ninth revision (ICD-9) codes given in Table S1 (Supplemental Material). Records with missing data on the following variables were excluded as they did not account for more than 3% of the original dataset and thereby would not affect any statistical inferences: age, sex, sex, elective and weekend admissions, primary expected payer, median household income, and hospital bed size and location.[12] (Figure S1)

Patient characteristics, comorbidities, and clinical outcomes were extracted using the ICD-9 procedure and diagnosis codes provided in Table S1 (Supplemental Material); bleeding, cardiac complications (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis) and acute stroke or transient ischemic attack (TIA) were also extracted. Bleeding was defined as any post-procedural hemorrhage or anemia requiring blood transfusion according to ICD-9 diagnosis codes. (Table S1)

Outcomes

The main outcomes were to compare 1) the receipt of invasive management (coronary angiography (CA), PCI and CABG) for AMI and 2) differences in in-hospital adverse events between patients with and without AIRD. In-hospital adverse events included major acute cardiovascular and cerebrovascular events (MACCE), all-cause mortality, bleeding, cardiac

complications and acute ischemic stroke. In-hospital MACCE was defined as a composite of all-cause mortality, cardiac complications, and thoracic complications.

Statistical Analysis

For exploratory analysis, the cohort was stratified by presence or absence of AIRD in to 4 groups: No AIRD, RA, SLE and SSC. Continuous variables were summarized using median and interquartile range (IQR) and compared using the Kruskal-Wallis test. Categorical variables were summarized as percentages and analyzed using the chi-squared (X^2) test.

Several multivariable logistic regression models were constructed to examine the independent association between the type of AIRD and our outcomes of interest in patients hospitalized for AMI using the 'No AIRD' group as a reference; first, receipt of invasive management (CA, PCI and CABG) and second, all the procedure-related adverse events that we considered. A subgroup analysis of outcomes was performed according to the type of coronary syndrome (non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)). All multivariable models adjusted for differences in socioeconomic, clinical, and hospital-level covariates that may directly influence in-hospital outcomes (all variables listed in Appendix A in Supplemental Material). All associations were summarized from the multivariable logistic regression models using odds ratios (ORs) and associated 95% confidence intervals (CI). To adjust for multiple comparisons, a Benjamini–Hochberg test was performed adjusting for the number of tests performed (18 in total), with comparison of the p-value for each outcome against the critical value generated from the test.

All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY). Additionally, all analyses used the sampling weights provided by the AHRQ, which are required because the design of the study means that different observations may have different probabilities

of selection. The sampling weights for each individual discharge were hence incorporated into the relevant SPSS commands for each analysis.

Patient and Public Involvement

It was not possible to involve patients or the public in the design, conduct, reporting or dissemination plans of this research as this is an administrative dataset derived research based on a stratified sample of anonymized patients from the United States.

Results

A total of 6,747,797 hospitalizations for AMI were recorded in U.S. hospitals between 2004 and 2014, of which 109,983 patients (1.6%) had an AIRD diagnosis. The number of patients with concomitant RA, SLE and SSC were: 85,335 (1.3%), 20,207 (0.3%) and 4,441 (0.1%), respectively (Table 1). The prevalence of RA amongst people hospitalized with AMI has risen from 2004 (1.0%) to 2014 (1.5%) while SLE and SSC remained relatively stable (2004 to 2014: SLE 0.3% to 0.4% and SSC 0.1% throughout).

Several differences were observed between the study groups. The prevalence of women was much higher in the AIRD groups (RA: 62%, SLE 79.6%, SSC: 76.7%) compared to the group without AIRD (39.3%). (Table 1). Patients with AIRD had a higher prevalence of anemia, hypothyroidism and chronic pulmonary disease, and chronic renal failure was most prevalent amongst patients with SLE (23.5%) compared to all other groups (15.5-18.7%). However, rates of previous MI (9.0-10.4%) and prior PCI (11.1-11.7%) were similar across all groups, and patients with SSC were less likely to have had prior CABG (4.5%) than patients without AIRD (7.5%). Patients with AIRD had a significantly higher mean Charlson Comorbidity Index (CCI) score compared to those without (RA: 2.32 (±1.46), SLE: 2.42 (±1.49) and SSC: 2.21 (±1.46) vs. no

AIRD: 1.35 (±1.55)). At least a third of patients with AIRD had a CCI score ≥3 (ranging from 32.5-40.5%) compared to 18.9% in patients without AIRD.

In-hospital revascularization

The crude rates of CA were lower in patients with RA (61.8%) and SSC (60.2%) compared to those with SLE (65.4%) and those without AIRD (64.5%) (p<.001). (Table 2, Figure 1a) However, all AIRD groups (RA, SLE and SSC) were less likely to undergo PCI (36.2-40.3%) and CABG (6.2-7.0%) compared to those without AIRD (PCI: 42.9% and CABG: 8.9%), while the rates of thrombolysis did not differ between patients with and without AIRD. These findings remained significant after adjustment for multiple comparisons (Table S2). This pattern was observed both in STEMI and NSTEMI subgroups, with higher rates of utilization of invasive strategies in the STEMI group. (Table S3)

In multivariable analysis, patients with SLE were associated with reduced odds of receipt of CA (OR 0.87 95% CI 0.84, 0.91) and PCI (OR 0.93 95% CI 0.90, 0.96), compared to those without AIRD, whereas no difference was found in RA (OR CA: 1.02 95% CI 0.97, 1.08 and PCI: 1.02 95% CI 0.94, 1.10) and SSC groups (OR CA: 1.01 95% CI 0.94, 1.08 and PCI: 0.98 95% CI 0.92, 1.05). (Table 3). These findings were consistent in both STEMI and NSTEMI subgroups, with lower odds of receipt of CA and PCI in SLE patients with NSTEMI than in those with STEMI (Table S4).

In-hospital clinical outcomes

The crude rates of MACCE and mortality were significantly higher in the SSC group (11.7%) than in other AIRD groups and patients without AIRD (7.2-7.8%), mainly driven by higher rates of mortality (9.7%) and cardiac complications (0.9%) (Table 2, Figure 1b) The rate of bleeding was highest in the SLE group (6.4%) compared to all other groups. There was no

difference in the rates of stroke between patients with and without rheumatological disease. Although the same pattern was observed in STEMI and NSTEMI groups, there was no difference in cardiac complications when stratified by syndrome type, and stroke was found to be much lower in patients with SLE in the NSTEMI cohort compared to other AIRD groups and those without AIRD (1.5% vs. 1.8-2.0%). (Table S3)

In multivariable analysis, SSC was associated with significantly increased odds of MACCE and mortality compared to those without AIRD (OR 1.52 95% CI 1.38, 1.68 and 1.81 95% CI 1.62, 2.02, respectively), while patients with SLE were only associated with increased odds of mortality (OR 1.15 95% CI 1.07,1.23) with no difference in MACCE (OR 1.01 95% CI 0.96,1.07). (Table 3, Figure 2). Patients with SLE were also associated with significantly increased odds of bleeding (OR 1.24 95% CI 1.16, 1.31) and lower odds of stroke (OR 0.86 95% CI 0.76, 0.96) compared to those without AIRD, but no difference in either complication was found in SSC and RA groups. Several factors other than AIRD were independently associated with increased odds of adverse outcomes after AMI, including STEMI (mortality), female sex (bleeding and stroke), renal and heart failure, AF, STEMI, coagulopathies, peripheral vascular disease and metastatic cancer. (Table 4) PCI and CABG were associated with reduced odds of mortality (OR PCI: 0.44 95% CI 0.43, 0.44; CABG: 0.38 95% CI 0.38, 0.39) and MACCE (OR PCI: 0.62 95% CI 0.61, 0.62; CABG: 0.68 95% CI 0.67, 0.69), but also an increase in odds of major bleeding (OR PCI: 2.04 95% CI 1.99, 2.09; CABG: 8.78 95% CI 8.56, 9.01). and increased odds of acute stroke in the case of CABG (OR 1.37 95% CI 1.34, 1.40) ($p<.001$ for all). These findings remained significant after adjustment for multiple comparisons.

Several differences in outcomes were noted between coronary syndrome subgroups with generally worse outcomes in patients with NSTEMI compared to STEMI (Table S4). The odds of mortality and bleeding were higher in SLE and SSC patients with NSTEMI, compared to STEMI,

as were the odds of MACCE in patients with SSC with NSTEMI. The odds of stroke were lower in SLE patients with NSTEMI (OR 0.86 95% CI 0.75, 0.98) whereas no difference in odds of stroke was found in SLE patients with STEMI (OR 0.84 95% CI 0.69, 1.04). No difference in mortality, bleeding or stroke was found in RA patients with STEMI and NSTEMI.

Discussion

The present study is the largest to report AMI outcomes in over 100,000 patients with AIRD from a contemporary cohort of US hospitalizations, stratified by AIRD subtype. First, we report a rise in the prevalence of RA patients presenting with AMI over an eleven-year period, with no change in prevalence of SLE and SSC groups. The rise in prevalence of RA may reflect physicians' increasing awareness of the independent risk of AMI associated with RA, but also correlates with an overall rise in the incidence of RA in the background population.[13] Second, we demonstrate that patients with AIRD were significantly more comorbid than those without AIRD. More importantly, we observe that patients with SLE were less likely to receive invasive management for both NSTEMI and STEMI, compared to those without AIRD, and were associated with a higher risk of mortality and bleeding. Whilst no difference in receipt of invasive management was found in patients with RA and SSC, the latter remained at a higher risk of mortality compared to those without AIRD.

There is limited data to inform physicians of the rates of utilization of invasive management in patients with AIRD presenting with AMI. Furthermore, the evidence to date does not provide contrast between AIRD subtypes. A recent study by Lai et al. reported no difference in adjusted odds of revascularization in approximately 1000 RA and SLE patients (OR 1.00 95% CI 0.85, 1.18 and OR 1.25 95% CI 0.99, 1.59, respectively) following AMI [10] whilst a study of 1409 patients with first time AMI, the odds of receipt of in-hospital PCI and CABG were lower in patients with AIRD compared to those without (OR: 0.81 95% CI 0.70, 0.94, and OR: 0.52 95% CI 0.39, 0.69,

respectively). The latter analysis did not stratify management strategies by AIRD subtype, and the study findings were derived from a relatively noncontemporary cohort where invasive management was underutilized. [9, 14, 15] Our nationwide level analysis demonstrates a disparity in management strategy between AIRD patients, where SLE patients were less likely to receive invasive management in the form of coronary angiography and PCI compared to those without AIRD, even after adjustment for baseline differences between the groups, whereas no difference in invasive management was found in patients with RA and SSC. Moreover, the lower rates of receipt of PCI in the SLE was observed in NSTEMI as well as STEMI subgroups, despite the high-mortality risk associated with the latter. This could reflect cardiologists' concerns about revascularization in this group, who are also at a high risk of bleeding, as this would mandate the use of dual antiplatelet therapy for a period of at least 6 months according to contemporary guidelines.[16, 17] Furthermore, a proportion of SLE patients may have antiphospholipid syndrome, which is associated with an increased risk of bleeding.[18 19] The greater burden of comorbidities in AIRD patients, as measured by their CCI score, may also be a contributing factor to their low rates of invasive management due to concerns about their higher risk of procedure-related complications.

A myriad of factors predisposes to the advanced and more severe presentation of CAD in patients with AIRD, including accelerated and more severe atherosclerosis and atypical anginal symptoms leading to delayed presentation and increased likelihood of plaque rupture or thrombosis due to severe inflammation.[6] Patients with AIRD are also believed to be at an increased risk of myocardial infarction with non-obstructive coronary arteries (MINOCA), although there is insufficient data to inform us of its incidence in this patient group compared to the background population. [20] While some disease modifying antirheumatic drugs (DMARDs) decrease the risk of cardiovascular mortality in patients with AIRD, other frequently used agents such as non-steroidal

anti-inflammatory drugs (NSAIDs) and glucocorticoid medications could increase this risk.[21] Several studies have reported adverse outcomes in patients with rheumatological disease presenting with AMI, although these have been subject to several limitations.[5, 8-10] Furthermore, studies to date have primarily examined mortality and specific complications such as reinfarction, leaving a gap in evidence on important post AMI complications such as bleeding, cardiac complications in this patient group. Lai. et al reported higher odds of major adverse cardiac events (composite of overall mortality, revascularization and reinfarction) in RA and SLE patients with a first time AMI, primarily driven by higher mortality.[10] Van Doornum et al. reported worse 30-day (OR 1.44 95% CI 1.25, 1.66) and 1-year mortality (OR 1.71 95% CI 1.61, 1.94) in patients with AIRD with a first time AMI between 2001 and 2007.[9] Another study reported worse crude in-hospital (6.1% vs. 4.1%) and adjusted 7-day (hazard ratio (HR) 1.44 95% CI 1.14,1.82) and 30-day mortality (HR 1.36 95% CI 1.13,1.64) in 1135 patients with RA and incident (first-time) ACS compared to a matched cohort from the Swedish registry between 2006 and 2009.[5] This analysis provided important insights in to the outcomes of patients with a specific type of AIRD (RA), but it was based on a small sample size and may not be generalizable to the wide population of interest., both these studies excluded an important patient subgroup, those with previous AMI, who are at a higher risk of further ischemia and mortality.[22]

Our analysis demonstrates that clinical outcomes after AMI vary according to the subtype of AIRD and type of coronary syndrome. Patients with SLE were at an increased risk of major complications (MACCE, mortality and bleeding) except stroke compared to those without AIRD, even after adjustment for differences in baseline comorbidities, and their outcomes were generally worse in the NSTEMI subgroup. This could be possibly explained by their lower rates of invasive management, especially in those with NSTEMI, placing them at a higher risk of further ischemia and mortality. The higher risk of bleeding could be due to differences in pharmacotherapeutic use

(DMARDs, NSAIDs, steroids) that were not adjusted for in our analysis. SLE patients are also more likely to have thrombocytopenia or anti-phospholipid antibody syndrome for which they are on antithrombotic therapy, which may contribute to higher bleeding rates and lower rates of stroke in this group.[23-25] We also observe increased mortality in patients with SSC, especially those with NSTEMI, compared to those without AIRD despite no difference in their receipt of CA and PCI. In the absence of any study on outcomes of AMI in patients with SSC, our results demonstrate for the first time that this patient group is at an independent risk of all-cause mortality. Although SSC is known to be a major occlusive vasculopathy and a multisystemic disease with subclinical cardiac involvement, further study of the specific causes of mortality in this risk group patients is necessary. [26, 27] However, the current data provides important insights into the real-world outcomes of patients with SLE and SSC and should better inform the decision-making of multidisciplinary teams of rheumatologists and cardiologists when deciding on the optimal management strategy of these patients.

Limitations

Administrative datasets such as the NIS are subject to potential selection bias resulting from potential coding inaccuracies or missing data.[28] However, the use of ICD-9 codes for cardiovascular outcomes research has been previously validated.[29-32] While the NIS database contains many variables of interest, data on antithrombotic regimen, severity and degree of systemic involvement of rheumatological disease, and use of disease modifying drugs (e.g. tumor necrosis factor alpha inhibitors, non-steroidal anti-inflammatory drugs, and methotrexate) are not routinely collected and may provide additional information to better stratify risk and procedural outcomes.[21] Furthermore, ICD-9 coding system does not differentiate between Type 2 MI and NSTEMI. Additionally, the NIS only captures in-hospital outcomes and it is possible that longer-term data on mortality and other adverse events such as reinfarction follow a less favorable course

in patients with rheumatological disease. Furthermore, the NIS dataset does not capture platelet or hemoglobin counts, which may influence management. Finally, in keeping with all observational registry work, the possibility of unmeasured or unrecognized confounders may contribute to the adverse outcomes, although capture of a wide range of comorbid conditions in the NIS may help to mitigate this bias.

Conclusion

In this nationwide study of 100,000 AIRD patients presenting with AMI, patients with SLE were less likely to receive invasive management for AMI, compared to those without AIRD, and were associated with a higher risk of mortality and bleeding. Although no difference in management found in patients with RA and SSC, the latter remained at a higher risk of mortality compared to those without AIRD. These findings provide multidisciplinary teams of rheumatologists and cardiologists with insight into the national-level differences in risk profiles, management strategies and outcomes of AIRD subtypes in the context of AMI.

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Figure titles and captions:

Figure 1a. Rate of utilization of invasive management

Legend: †: p<.001 **AIRD:** autoimmune rheumatic disease; **RA:** rheumatoid arthritis**; SLE:** systemic lupus erythematosus**; SSC:** systemic sclerosis; **CA:** coronary angiography; **PCI:** percutaneous coronary intervention; **CABG:** coronary artery bypass grafting

Figure 1b. In-hospital outcomes of study groups

Legend: §: non-significant (p>0.05); †: p<.05; **ǂ**: p<.001; ***MACCE**: composite of all- mortality, cardiac complications and stroke; **RA:** rheumatoid arthritis; **SLE:** systemic lupus erythematosus; **SSC:** systemic sclerosis

Figure 2. Adjusted odds ratios (OR) of adverse events in rheumatological disease groups*

Legend: *reference is no AIRD group; ****MACCE:** composite of all- mortality, cardiac complications and stroke; **AIRD:** autoimmune rheumatic disease; **RA:** rheumatoid arthritis; **SLE:** systemic lupus erythematosus; **SSC:** systemic sclerosis