



## **Impact of gout on in-hospital outcomes of acute coronary syndrome-related hospitalizations and revascularizations: Insights from the national inpatient sample.**

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## Retrospective Study

**Impact of gout on in-hospital outcomes of acute coronary syndrome-related hospitalizations and revascularizations: Insights from the national inpatient sample**

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**Abstract****BACKGROUND**

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations

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and post-revascularization is inadequate.

### AIM

To evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

### METHODS

We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

### RESULTS

We identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ( $P < 0.001$ ). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44, CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ( $P < 0.001$ ). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ( $P < 0.001$ ). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

### CONCLUSION

Although gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS, it did increase post-revascularization complications.

**Key words:** Gout; Serum uric acid; Acute coronary syndrome; Unstable angina; Myocardial infarction; Revascularization; Percutaneous coronary intervention; Coronary artery bypass grafting; In-hospital outcomes

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**Core tip:** Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate. In this largest nationwide cohort, we identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization (percutaneous coronary intervention/coronary artery bypass grafting) complications including cardiovascular (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher and raised the mortality odds whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort. Mean length of stay, transfers and hospital charges were higher in the ACS-gout cohort.

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## INTRODUCTION

Acute coronary syndrome (ACS) comprises a range of diseases including unstable angina (UA), non-ST segment elevation myocardial infarction, and acute ST-elevation myocardial infarction (STEMI)<sup>[1]</sup>. It is one of the major causes of mortality around the world. Several independent predictors including advanced age, gender, history of diabetes or hypertension, obesity, and socioeconomic status have been determined for the unfavorable outcomes and rise in the overall mortality in ACS patients<sup>[2,3]</sup>. Gout is a common inflammatory disease associated with hyperuricemia and has shown to be associated with almost 410% increase in the hospitalizations in the last two decades in the United States<sup>[4]</sup>. The clinical evidence has shown that uric acid (UA) may have a pro-inflammatory effect on the vascular cells contributing to the negative effects of hyperuricemia in cardiovascular diseases (CVD) including ACS<sup>[5,6]</sup>. Previous studies have also suggested that gout patients have two to five-fold higher mortality risk in patients with CVD<sup>[7,8]</sup>. Recent studies have also established the crucial role of high UA levels in predicting the higher odds of MI and subsequent in-hospital mortality in ACS and STEMI hospitalizations<sup>[9,10]</sup>. Furthermore, microvasculature is becoming a key prognostic factor in patients undergoing percutaneous coronary intervention (PCI) since UA has been found to induce microvascular lesions, accounting for vascular dementia and allograft vasculopathy post-cardiac transplantation<sup>[11]</sup>. While quick restoration of blood flow through an infarct-related artery is important, the presence of distal microvascular disease can result in impaired myocardial flow leading to an increased risk of major adverse cardiac events after acute MI<sup>[12,13]</sup>. Nevertheless, the relationship between gout and healthcare resource utilization and post-revascularization outcomes in ACS hospitalizations has not been previously studied on a large scale in the United States. Therefore, in this retrospective population-based study, we aim to evaluate the impact of gout on the in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality using the largest nationwide cohort from January 2010 through December 2014.

## MATERIALS AND METHODS

### Source of data

The study cohort was derived from the national inpatient sample (NIS) database from January 2010 through December 2014, which is a part of the Healthcare Cost and Utilization Project held by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest publicly accessible all-payer inpatient database in the United States and incorporates diverse identifiers for the hospitalization and clinical data for each visit including up to 25 discharge diagnoses and 15 procedures<sup>[14]</sup>. It includes discharge statistics from 20% inpatient discharges of all non-federal United States hospital facilities (not including rehabilitation and long-term acute care hospitals), disclosing up to 95% of hospital releases across the country. Nationwide assessments were generated utilizing discharge weights provided by AHRQ.

### Study population

All ACS-related adult hospitalizations were recognized by applying International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) codes 410.1x and 411.1 for the primary discharge diagnosis. These codes have been successfully utilized in earlier studies<sup>[15]</sup>. We then divided ACS population into the two cohorts: one who had baseline gout and another without gout by using ICD-9 CM codes 274.x or 274.xx in any of the secondary discharge diagnoses.

### Study variables

Patient and hospital-level variables including age, gender, race, median household income, primary payer, hospital location/teaching status, bed size, and regions were studied and compared between ACS hospitalizations with *vs* without gout. Underlying comorbid illnesses were also compared between the ACS population with *vs* without gout. Revascularization comprised of thrombolysis (ICD-9 CM diagnosis code V45.88 or procedure code 99.10), PCI (ICD-9 CM procedure codes 00.66, 36.01, 36.02, 36.05, 36.06, and 36.07, 17.55) OR CABG (ICD-9 CM procedure codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.3, 36.31, 36.32, 36.33, 36.34, 36.39). Since the NIS is an openly available database with de-identified data, our study was exempt from an Institutional Review Board authorization.

### Study outcomes

The primary outcomes of interest were all-cause in-hospital mortality, revascula-

rization (thrombolysis, PCI or CABG) rates, discharge disposition, length of hospital stay (LOS), and total hospital charges (denotes the total amount payable for service rather than the actual payment received). The secondary outcomes were post-revascularization complications in ACS-hospitalizations including all-cause in-hospital mortality, hemorrhage, blood transfusion, hypotension/shock, cardiac complications, postoperative myocardial infarction, stroke, respiratory complications, gastrointestinal complications including gastrointestinal hemorrhage, acute kidney injury (AKI) requiring dialysis, urinary complications, postoperative infections, and predictors of in-hospital mortality. Comorbidities and postoperative complications were identifying from the secondary discharge diagnoses. The codes used in the study to identify comorbidities and post-revascularization complications are mentioned in Supplementary [Table 1](#).

### Statistical analyses

We integrated the discharge weights to unweighted records, to generate the national estimates. The missing data (< 10% for any variable) were omitted from the analysis. The baseline characteristics were compared amongst ACS patients with gout and without gout by applying Pearson's Chi-square test for categorical and Student's t-test for the continuous variable where appropriate. We developed a two-step hierarchical multivariate logistic regression model to evaluate for the patient and hospital level components, and in-hospital outcomes such as in-hospital mortality and procedural complications related to the ACS. This model permitted us to represent the possible relationship of insights into each hospital visit. Both patient and hospital level components along with all relevant comorbidities were incorporated into the multivariable model to control confounders. In addition to unadjusted analysis, post-revascularization outcomes were also analyzed using a propensity score-matched analysis with a caliper width of 0.01 without replacement and adjusting for demographics and all relevant comorbid conditions (Supplementary [Tables 2 and 3](#)). A two-tailed *P*-value of < 0.5 was considered statistically significant. All statistical analyses were completed utilizing SPSS Statistics 24 (IBM Corp., Armonk, NY).

## RESULTS

### Population demographics and comorbidities

We identified 3144744 ACS-related hospitalizations during the study period, of whom 3.34% ( $n = 105198$ ) also had gout as comorbidity ([Table 1](#)). Patients with gout were older with more than two-thirds being > 65 years old (mean age 71.3 years), white (71.8%), mostly males (74%), and Medicare enrollees (69.1%). Interestingly, the ACS-gout cohort consisted of comparatively higher median household income population (76-100<sup>th</sup> percentile: 21.9% *vs* 19.1%,  $P < 0.001$ ), and were more likely to be admitted to urban-teaching (54.3% *vs* 50.5%,  $P < 0.001$ ) and Southern region hospitals (20.6% *vs* 17.7%,  $P < 0.001$ ) as compared to those without gout. The majority (94.1%) of admissions was non-elective, and 74.4% of admissions occurred on the weekdays. As compared to ACS patients without gout, those with gout had a higher prevalence of baseline comorbidities, except CHF and previous history of cardiac arrest ([Table 2](#)). The ACS-gout patients had higher frequency of traditional comorbid risk factors such as: hypertension (83.3% *vs* 71.4%,  $P < 0.001$ ), dyslipidemia (71.0% *vs* 61.8%,  $P < 0.001$ ), diabetes (46.7% *vs* 36.6%,  $P < 0.001$ ), and obesity (21.9% *vs* 14.6%,  $P < 0.001$ ). They also had the higher prevalence of chronic kidney disease (45.5% *vs* 19.0%,  $P < 0.001$ ), AKI (45% *vs* 18.7%,  $P < 0.001$ ), and deficiency anemias (26.7% *vs* 16.0%,  $P < 0.001$ ).

### Revascularization rates and in-hospital outcomes in ACS-related hospitalizations with vs. without gout

As shown in [Table 2](#), the ACS patients with gout had a higher rate of undergoing CABG (9.2% *vs* 8.1%,  $P < 0.001$ ) as compared to those without gout. All-cause in-hospital mortality associated with revascularization was lower in the ACS patients with gout compared to those without gout (4.3% *vs* 5.0%,  $P < 0.001$ ). Gout patients were more likely to be discharged to skilled nursing facilities, intermediate care facility or similar facilities (14.8% *vs* 12.1%,  $P < 0.001$ ) and were less likely to be discharged routinely (56.7% *vs* 61.8%,  $P < 0.001$ ). The average LOS was higher (5.1 d *vs* 4.5 d,  $P < 0.001$ ) and mean total hospital charges were higher (\$72328 *vs* \$71312,  $P < 0.001$ ) for ACS patients with gout compared to those without gout ([Table 3](#)).

### Post-revascularization outcomes in ACS hospitalizations with gout

The ACS-gout cohort undergoing PCI or CABG demonstrated a higher number of postoperative complications including cardiovascular, respiratory, stroke,

**Table 1** Baseline characteristics of acute coronary syndrome hospitalizations without vs with gout (*n* = 3144744)

| Variables  | Without gout( <i>n</i> = 3039546) | With gout( <i>n</i> = 105198) | P value              |
|--|-----------------------------------|-------------------------------|----------------------|
| Age (yr) at hospitalization  |                                   |                               | < 0.001 <sup>a</sup> |
| mean (± SD)  | 66.9 (± 14.2)                     | 71.3 (± 12.5)                 |                      |
| 18-44  | 171857 (5.7)                      | 2337 (2.2)                    |                      |
| 45-64  | 1178621 (38.8)                    | 28567 (27.2)                  |                      |
| 65-84  | 1288783 (42.4)                    | 57054 (54.2)                  |                      |
| ≥ 85   | 400285 (13.2)                     | 17240 (16.4)                  |                      |
| Sex  |                                   |                               | < 0.001 <sup>a</sup> |
| Male   | 1830228 (60.2)                    | 77834 (74.0)                  |                      |
| Female   | 1209120 (39.8)                    | 27355 (26.0)                  |                      |
| Race   |                                   |                               | < 0.001 <sup>a</sup> |
| White  | 2102509 (75.4)                    | 69431 (71.8)                  |                      |
| African American   | 302121 (10.8)                     | 14798 (15.3)                  |                      |
| Hispanic   | 218605 (7.8)                      | 4833 (5.0)                    |                      |
| Asian and Pacific Islander   | 61156 (2.2)                       | 4799 (5.0)                    |                      |
| Native American  | 16624 (0.6)                       | 394 (0.4)                     |                      |
| Others   | 88091 (3.2)                       | 2477 (2.6)                    |                      |
| Admission type   |                                   |                               | < 0.001              |
| Non-elective   | 2847182 (93.9)                    | 98886 (94.1)                  |                      |
| Elective   | 185903 (6.1)                      | 6149 (5.9)                    |                      |
| Median household income percentile for patient's zip code <sup>1</sup> |                                   |                               | < 0.001 <sup>a</sup> |
| 0-25 <sup>th</sup>   | 894564 (30.1)                     | 29758 (28.8)                  |                      |
| 26-50 <sup>th</sup>  | 807784 (27.2)                     | 26606 (25.8)                  |                      |
| 51-75 <sup>th</sup>  | 701363 (23.6)                     | 24152 (23.4)                  |                      |
| 76-100 <sup>th</sup>   | 566069 (19.1)                     | 22637 (21.9)                  |                      |
| Primary expected payer   |                                   |                               | < 0.001 <sup>a</sup> |
| Medicare   | 1709250 (56.4)                    | 72559 (69.1)                  |                      |
| Medicaid   | 218428 (7.20)                     | 4232 (4.0)                    |                      |
| Private including HMO  | 803459 (26.5)                     | 22757 (21.7)                  |                      |
| Self-pay/no charge/others  | 301827 (10.0)                     | 5433 (5.2)                    |                      |
| Control/ownership of hospital  |                                   |                               | < 0.001 <sup>a</sup> |
| Government, nonfederal   | 305519 (10.1)                     | 9697 (9.3)                    |                      |
| Private, non-profit  | 2258936 (74.7)                    | 81175 (77.4)                  |                      |
| Private, invest-own  | 459942 (15.2)                     | 13962 (13.3)                  |                      |
| Bed size of hospital   |                                   |                               | 0.157                |
| Small  | 351544 (11.6)                     | 12101 (11.5)                  |                      |
| Medium   | 767625 (25.4)                     | 26387 (25.2)                  |                      |
| Large  | 1905229 (63.0)                    | 66346 (63.3)                  |                      |
| Location/teaching status   |                                   |                               | < 0.001 <sup>a</sup> |
| Rural  | 312292 (10.3)                     | 10030 (9.6)                   |                      |
| Urban non-teaching   | 1183544 (39.1)                    | 37858 (36.1)                  |                      |
| Urban teaching   | 1528562 (50.5)                    | 56946 (54.3)                  |                      |
| Region of hospital   |                                   |                               | < 0.001 <sup>a</sup> |
| Northeast  | 575864 (18.9)                     | 19077 (18.1)                  |                      |
| Midwest  | 705042 (23.2)                     | 24946 (23.7)                  |                      |
| South  | 1219352 (40.1)                    | 39502 (37.5)                  |                      |
| West   | 539288 (17.7)                     | 21672 (20.6)                  |                      |

<sup>a</sup>*P* < 0.05 indicates clinical significance. The bed size cutoff points are derived from [https://www.hcup-us.ahrq.gov/db/vars/hosp\\_bedsizes/nisnote.jsp](https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsizes/nisnote.jsp).<sup>1</sup>Represents a quartile classification of the estimated median household income of residents in the patient's ZIP Code, derived from [https://www.hcup-us.ahrq.gov/db/vars/zipinc\\_qrtl/nisnote.jsp](https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp). HMO: Health maintenance organization; SNF: Skilled nursing facility; ICF: Intermediate care facility.

hemorrhage, hypotension/shock, need of blood transfusion, AKI requiring dialysis,

**Table 2 Comorbidities in acute coronary syndrome without vs with gout**

| Comorbidities                                   | ACS + no gout  | ACS + gout   | P value              |
|---|----------------|--------------|----------------------|
| Alcohol abuse                                   | 95449 (3.1)    | 3768 (3.6)   | < 0.001 <sup>a</sup> |
| Deficiency anemias                              | 487126 (16.0)  | 28065 (26.7) | < 0.001 <sup>a</sup> |
| Rheumatoid arthritis/collagen vascular diseases | 72214 (2.4)    | 3343 (3.2)   | < 0.001 <sup>a</sup> |
| Congestive heart failure                        | 24213 (0.8)    | 811 (0.8)    | 0.357                |
| Chronic pulmonary disease                       | 634046 (20.9)  | 22789 (21.7) | < 0.001 <sup>a</sup> |
| Coagulopathy                                    | 152932 (5.0)   | 7283 (6.9)   | < 0.001 <sup>a</sup> |
| Diabetes, uncomplicated                         | 911629 (30.0)  | 36556 (34.7) | < 0.001 <sup>a</sup> |
| Diabetes with chronic complications             | 200881 (6.6)   | 12597 (12.0) | < 0.001 <sup>a</sup> |
| Drug abuse                                      | 95449 (3.1)    | 1519 (1.4)   | < 0.001 <sup>a</sup> |
| Hypertension                                    | 75189 (2.5)    | 87598 (83.3) | < 0.001 <sup>a</sup> |
| Hypothyroidism                                  | 2170519 (71.4) | 15366 (14.6) | < 0.001 <sup>a</sup> |
| Liver disease                                   | 334044 (11.0)  | 2013 (1.9)   | < 0.001 <sup>a</sup> |
| Fluid and electrolyte disorders                 | 43749 (1.4)    | 26081 (24.8) | < 0.001 <sup>a</sup> |
| Other neurological disorders                    | 636496 (20.9)  | 6138 (5.8)   | < 0.001 <sup>a</sup> |
| Obesity   | 186097 (6.1)   | 23082 (21.9) | < 0.001 <sup>a</sup> |
| Peripheral vascular disorders                   | 443723 (14.6)  | 16964 (16.1) | < 0.001 <sup>a</sup> |
| Renal failure                                   | 355484 (11.7)  | 47359 (45.0) | < 0.001 <sup>a</sup> |
| Valvular disease                                | 568903 (18.7)  | 327 (0.3)    | < 0.001 <sup>a</sup> |
| Dyslipidemia                                    | 7101 (0.2)     | 74674 (71.0) | < 0.001 <sup>a</sup> |
| Coronary atherosclerosis                        | 1879620 (61.8) | 89777 (85.3) | < 0.001 <sup>a</sup> |
| Previous history of MI                          | 2500606 (82.3) | 16972 (16.1) | < 0.001 <sup>a</sup> |
| Family history of CAD                           | 359298 (11.8)  | 8442 (8.0)   | < 0.001 <sup>a</sup> |
| Previous PCI                                    | 298852 (9.8)   | 18591 (17.7) | < 0.001 <sup>a</sup> |
| Previous CABG                                   | 439722 (14.5)  | 13165 (12.5) | < 0.001 <sup>a</sup> |
| Previous history of cardiac arrest              | 247161 (8.1)   | 405 (0.4)    | 0.786                |
| Smoking   | 11543 (0.4)    | 34019 (32.3) | < 0.001 <sup>a</sup> |
| History of venous thromboembolism               | 1210142 (39.8) | 3146 (3.0)   | < 0.001 <sup>a</sup> |
| Chronic kidney disease                          | 66017 (2.2)    | 47909 (45.5) | < 0.001 <sup>a</sup> |
| Dialysis status                                 | 576268 (19.0)  | 4388 (4.2)   | < 0.001 <sup>a</sup> |

<sup>a</sup> $P < 0.05$  (bold value) indicates clinical significance. ACS: Acute coronary syndrome; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

and gastrointestinal and urinary complications as compared to those without gout (Table 3). However, overall in-hospital mortality was lower (2.2% vs 3.0%,  $P < 0.001$ ) in patients with gout and there were no significant differences in the post-revascularization myocardial infarction and infection rates between both the cohorts. We also confirmed the comparable results with a comprehensive propensity-score matched analysis (Supplementary Tables 2 and 3).

#### Predictors of in-hospital mortality

On multivariable analysis, advanced age (> 85 years vs 18-44 years: OR 15.63, 95%CI: 5.51-44.39;  $P < 0.001$ ), non-elective admissions (OR 2.00, 95%CI: 1.44-2.79;  $P < 0.001$ ), and lower household income (OR 1.44; 95%CI: 1.17-1.78;  $P < 0.001$ ) had significantly higher odds of in-hospital mortality in ACS patients with gout undergoing PCI or CABG (Table 4). Among ACS-gout cohort, Hispanics (OR 0.45, CI: 0.31-0.67;  $P < 0.001$ ) and Asians (OR 0.65, CI: 0.45-0.94;  $P < 0.001$ ) undergoing PCI or CABG demonstrated significantly lower odds of in-hospital mortality as compared to whites (Table 5). Rheumatoid arthritis/collagen vascular diseases, valvular heart diseases, CHF, fluid and electrolyte disorders, coagulopathy, drug abuse, neurological disorders, peripheral vascular disorders, and renal failure independently predicted a greater risk of in-hospital mortality. Additionally, ACS-gout cohort undergoing PCI or CABG revealed highest odds of in-hospital mortality due to postoperative infections followed by hypotension/shock, postoperative myocardial infarction, and postoperative stroke, respiratory, AKI, and cardiac complications.

**Table 3** Revascularization rates and outcomes in acute coronary syndrome with vs without gout

| Outcomes                                 | ACS + no gout(n = 3039546) | ACS + gout(n = 105198) | P value              |
|--|----------------------------|------------------------|----------------------|
| <b>Revascularization</b>                 |                            |                        |                      |
| Thrombolysis                             | 56694 (1.9)                | 1408 (1.3)             | < 0.001 <sup>a</sup> |
| PCI                                      | 1369759 (45.1)             | 38301 (36.4)           | < 0.001 <sup>a</sup> |
| CABG                                     | 245983 (8.1)               | 9657 (9.2)             | < 0.001 <sup>a</sup> |
| <b>All-cause in-hospital mortality</b>   | 151213 (5.0)               | 4539 (4.3)             | < 0.001 <sup>a</sup> |
| <b>Disposition</b>                       |                            |                        |                      |
| Routine                                  | 1878724 (61.8)             | 59605 (56.7)           |                      |
| Transfer to short-term hospital          | 290145 (9.6)               | 10506 (10.0)           |                      |
| Other transfers (SNF, ICF, other)        | 367183 (12.1)              | 15586 (14.8)           |                      |
| Home Health Care                         | 318501 (10.5)              | 14208 (13.5)           |                      |
| Against Medical Advice                   | 30531 (1.0)                | 681 (0.6)              |                      |
| <b>Length of stay (d) mean (± SD)</b>    | 4.5 (± 5.2)                | 5.1 (± 5.0)            | < 0.001 <sup>a</sup> |
| <b>Hospital charges (\$) mean (± SD)</b> | 71312.73 (± 85186.10)      | 72328.21 (± 86223.92)  | < 0.001 <sup>a</sup> |

<sup>a</sup>P < 0.05 indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SNF: Skilled nursing facility; ICF: Intermediate care facility.

## DISCUSSION

This is the first large scale study that evaluates the impact of gout on in-patient mortality in ACS patients and post-revascularization outcomes, predictors of in-hospital mortality during the post-revascularization period and healthcare resource utilization using the largest nationally representative cohort of ACS hospitalizations.

We found that ACS hospitalizations with gout comprised of older white men with a higher median household income, mostly Medicare beneficiaries, and were likely to be admitted to urban-teaching and Southern region hospitals more frequently. These patients also had a higher prevalence of comorbidities. Furthermore, the average LOS and total hospitalization charges were significantly higher. ACS patients with gout underwent CABG more often whereas the PCI revascularizations were comparable between both the cohorts. Those who underwent revascularizations (PCI or CABG) had shown higher overall complications; however lower all-cause in-hospital mortality compared to those without gout. A multivariate analysis demonstrated that older age, Hispanic and Asian race, lower household income, non-elective admissions, a previous history of CHF, valvular diseases, septicemia, shock, and cardiovascular complications were independent predictors of in-hospital mortality in ACS hospitalizations with gout post-revascularization.

In the study, the prevalence of gout among ACS patients was about 3.35% similar to the prevalence of gout among healthy United States population to be 3%-5%, with the age-standardized prevalence of hyperuricemia being 12%-15%<sup>[16]</sup>. In this study, gout has been prevalent in ACS patients with lower all-cause mortality compared to without gout. More recently, Latif *et al*<sup>[17]</sup> indicated that higher UA levels are associated with lower all-cause and cardiovascular mortality, however, they included only hemodialysis patients. Similarly, another study using the NIS suggested that co-occurring gout is associated with reduced in-hospital mortality among postmenopausal women admitted for AMI<sup>[18]</sup>. The paradoxical association with mortality could be due to focus on the short-term post-revascularization in-hospital outcomes, residual confounding factors in administrative data, or missed diagnosis in patients without gout. As shown with previous studies, our findings also showed that ACS hospitalizations with gout consisted of older white men, with higher co-existing comorbid conditions, mostly Medicare enrollees, and a lower median income quartile<sup>[19-21]</sup>. Surprisingly, Harrold *et al*<sup>[22]</sup> found that older women with gout more often had coronary heart disease. The results of our study suggest that ACS patients with gout had prolonged hospital stays post-revascularizations and management costs. A few other studies have also confirmed similar findings<sup>[23,24]</sup>. These studies have given a possible explanation for a prolonged stay and increased hospital cost due to increased risk of recurrent events and complications; however, the results were limited to the economic impact of ACS in general. This would be one of the few studies to describe the impact of gout on outcomes of ACS hospitalizations in terms of healthcare resource utilization including revascularization, the ensuing economic impact and the predictors of post-revascularization inpatient mortality.



**Table 4 Post-revascularization (percutaneous coronary intervention or coronary artery bypass grafting) complications in acute coronary syndrome patients with vs without gout**

| Complications                       | No gout(n = 1592156) | Gout(n = 47307) | P value              |
|-------------------------------------|----------------------|-----------------|----------------------|
| All-cause in-hospital mortality     | 47466 (3.0)          | 1038 (2.2)      | < 0.001 <sup>a</sup> |
| Hemorrhage                          | 43541 (2.7)          | 1470 (3.1)      | < 0.001 <sup>a</sup> |
| Blood transfusion                   | 12272 (0.8)          | 524 (1.1)       | < 0.001 <sup>a</sup> |
| Hypotension/shock                   | 7319 (0.5)           | 261 (0.6)       | 0.004 <sup>a</sup>   |
| Cardiac complications               | 46511 (2.9)          | 1523 (3.2)      | < 0.001 <sup>a</sup> |
| Postoperative myocardial infarction | 27176 (1.7)          | 798 (1.7)       | 0.74                 |
| Stroke                              | 3926 (0.2)           | 140 (0.3)       | 0.033 <sup>a</sup>   |
| Respiratory complications           | 46531 (2.9)          | 1642 (3.5)      | < 0.001 <sup>a</sup> |
| Gastrointestinal complications      | 25573 (1.6)          | 980 (2.1)       | < 0.001 <sup>a</sup> |
| AKI requiring dialysis              | 7843 (0.5)           | 628 (1.3)       | < 0.001 <sup>a</sup> |
| Urinary complications               | 4641 (0.3)           | 307 (0.6)       | < 0.001 <sup>a</sup> |
| Post procedural infections          | 24473 (1.5)          | 687 (1.5)       | 0.139                |

<sup>a</sup>P < 0.05 indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AKI: Acute kidney injury.

We found that age, race, median income, relevant comorbidities, and post-revascularization outcomes/postoperative complications in ACS patients undergoing PCI or CABG were independently predictive of in-hospital mortality in ACS patients with gout. Conversely, no association was observed in gender, which is consistent with a previous meta-analysis<sup>[25]</sup>. The gender-specific relative risk for congestive heart diseases (CHD) in that meta-analysis for each increase of 1 mg/dL in serum UA was similar, but not statistically significant. However, subgroup analysis showed a significant association between hyperuricemia and CHD incidence in men, but increased risk of CHD mortality in women. The result differs from the previous studies that showed both men and women with gout have increased the risk of cardiovascular mortality compared with those without gout<sup>[26-28]</sup>. A retrospective study of STEMI patients who underwent PCI reported that one in every five patients had higher UA levels and it was independently associated with increased risk of in-hospital mortality<sup>[10]</sup>. Ndrepepa *et al*<sup>[29]</sup> reported that every 1 mg/dL rise in UA increased by 12% in the adjusted risk for 1-year mortality in an unselected cohort. Alcohol consumption and dyslipidemia have been associated with significantly increase the risk of hyperuricemia<sup>[30,31]</sup>, which could further precipitate or increase the severity of gout. Interestingly, we observed the lower odds of in-hospital mortality with alcohol abuse, dyslipidemia, and obesity in ACS patients with gout undergoing revascularization. The implication of our findings is important for targeted preventive intervention in a certain population at the risk of gout and ACS.

Several potential mechanisms including causal role of UA in hypertension and atherosclerosis development, vasoconstriction, role of UA as pro-oxidant or gout per se promoting atherosclerosis, explain the increased risk of cardiovascular mortality in patients with gout<sup>[32,33]</sup>. However, whether gout is an independent factor with a pathogenic role in ACS or only attributing for associated risk factors of ACS, such as obesity, renal diseases, and diabetes, remains debatable<sup>[26,34]</sup>. In several large sample studies, gout was linked to increased all-cause and CV mortality rates<sup>[28,35,36]</sup>, nonetheless, data on the impact of gout on post-revascularization remains limited in the literature.

Our study extends on the impact of gout on ACS patients with other comorbid conditions and revascularization complications. The study showed that cardiac, renal, pulmonary and vascular comorbidities are the risk factors for post-revascularization complications as well. Previous studies have shown an association of gout and hyperuricemia with many comorbid conditions. Demir *et al*<sup>[37]</sup> showed increased serum UA levels in calcific aortic valve stenosis (AS), with a positive correlation in the severity of the disease. Raised serum UA level may initiate calcification in the aortic valve and accelerate the progression by causing endothelial dysfunction<sup>[32]</sup>. Similarly, a prospective longitudinal study with a large cohort of 11681 men also concluded that CHF decompensation is independently associated with increased risk of hyperuricemia and likely gout, by increased urate production and decreased renal urate excretion<sup>[38]</sup>. Our study also shows an increased risk of in-hospital mortality in ACS patients with gout who are drug abusers that have never been evaluated in the

**Table 5 Predictors of in-hospital mortality in acute coronary syndrome patients with gout undergoing revascularization**

| Predictor   | Adjusted odds ratio | 95%CI (LL-UL) | P value              |
|---|---------------------|---------------|----------------------|
| <b>Age in years at admission</b>  |                     |               | < 0.001 <sup>a</sup> |
| 45-64 vs 18-44  | 2.99                | 1.08-8.30     | 0.036 <sup>a</sup>   |
| 65-84 vs 18-44  | 5.72                | 2.04-16.01    | 0.001 <sup>a</sup>   |
| ≥ 85 vs 18-44   | 15.63               | 5.51-44.39    | < 0.001 <sup>a</sup> |
| <b>Male vs female</b>   | 0.89                | 0.75-1.05     | 0.155                |
| <b>Race</b>   |                     |               | < 0.001 <sup>a</sup> |
| African American vs white   | 1.09                | 0.88-1.35     | 0.413                |
| Hispanic vs white   | 0.45                | 0.31-0.67     | < 0.001 <sup>a</sup> |
| Asian vs white  | 0.65                | 0.45-0.94     | 0.022 <sup>a</sup>   |
| <b>Non-elective vs elective admission</b>   | 2.00                | 1.44-2.79     | < 0.001 <sup>a</sup> |
| <b>Median household income quartile 0-25<sup>th</sup> vs 76-100<sup>th</sup>#</b> | 1.44                | 1.17-1.78     | 0.001 <sup>a</sup>   |
| <b>Comorbidities</b>  |                     |               |                      |
| Alcohol abuse   | 0.49                | 0.31-0.79     | 0.003 <sup>a</sup>   |
| Rheumatoid arthritis/collagen vascular diseases                                   | 1.57                | 1.09-2.25     | 0.016 <sup>a</sup>   |
| Congestive heart failure  | 5.91                | 3.54-9.86     | 0.000 <sup>a</sup>   |
| Coagulopathy  | 1.29                | 1.05-1.58     | 0.014 <sup>a</sup>   |
| Drug abuse  | 2.33                | 1.34-4.05     | 0.003 <sup>a</sup>   |
| Fluid and electrolyte disorders   | 2.88                | 2.49-3.35     | < 0.001 <sup>a</sup> |
| Other neurological disorders  | 1.72                | 1.33-2.23     | < 0.001 <sup>a</sup> |
| Obesity   | 0.79                | 0.66-0.95     | 0.012 <sup>a</sup>   |
| Peripheral vascular disorders   | 1.60                | 1.36-1.88     | < 0.001 <sup>a</sup> |
| Renal failure   | 2.04                | 1.13-3.70     | 0.019 <sup>a</sup>   |
| Valvular disease  | 8.15                | 3.87-17.15    | < 0.001 <sup>a</sup> |
| Dyslipidemia  | 0.63                | 0.54-0.72     | < 0.001 <sup>a</sup> |
| <b>Outcomes/postoperative complications</b>                                       |                     |               |                      |
| Hypotension/shock   | 2.97                | 1.93-4.56     | < 0.001 <sup>a</sup> |
| Cardiac complications   | 1.59                | 1.19-2.11     | 0.002 <sup>a</sup>   |
| Postoperative myocardial infarction   | 2.53                | 1.74-3.68     | < 0.001 <sup>a</sup> |
| Perioperative stroke  | 2.48                | 1.20-5.10     | 0.014 <sup>a</sup>   |
| Respiratory complications   | 1.80                | 1.41-2.30     | < 0.001 <sup>a</sup> |
| Postoperative acute kidney injury   | 1.48                | 1.26-1.74     | < 0.001 <sup>a</sup> |
| Infections/septicemia   | 3.94                | 3.01-5.16     | < 0.001 <sup>a</sup> |

<sup>a</sup>P < 0.05 indicates clinical significance. CI: Confidence interval; LL: Lower level; UL: Upper level, Multivariate regression model was adjusted for age, gender, race, admission type, median household income, payer status, hospital characteristics and all relevant comorbidities and prior medical history.

past.

Systemic (kidney, respiratory and vascular) complications of revascularization in ACS patients with gout were likely to increase in-hospital mortality compared to patients without gout. This could also be the reason for prolonged hospitalization and increased treatment cost. Ejaz *et al*<sup>[39]</sup> showed that the UA is associated with a five to eight-fold increase in the post-cardiac surgery AKI. A study from the United Kingdom found 1.71 times higher risk of stroke in patients with gout than in the general population<sup>[40]</sup>. A nationwide population-based cohort study showed that gout was associated with an increased risk of pulmonary embolism by almost 53%<sup>[41]</sup>. Several studies have shown an association between gout and collagen vascular diseases, such as systemic sclerosis and rheumatoid arthritis<sup>[42,43]</sup>. Our findings would be prospective to initiate the discussion of screening and appropriate treatment of gout in ACS patients, and other dynamics responsible for gout should be considered when targeting new therapeutic strategies to prevent postoperative complications. In addition, appropriate screening for CVD in patients with gout is suggested as these patients have worse cardiovascular outcomes.

Our retrospective database study has few limitations which need to be mentioned. Due to the administrative nature of this database, some baseline patient's data might be missing, and follow up data was not available. There is a possibility of a misclassification bias from the use of diagnostic codes to define gout based on the clinical

findings by physicians or to diagnose ACS, with a possible change in terminology and use of generalized diagnostic codes by the clinicians. The NIS database does not contain information on serum uric acid level in gout patients so the severity and the extent of worse outcomes in ACS and post-revascularization outcomes with a unit increase in uric acid levels are not possible to be evaluated. In addition, each hospitalization is considered separately in the NIS, which could result in overestimation of the number of admissions for the same patient. Furthermore, the study emphasizes the short-term in-hospital impact of gout, lacking long-term follow-up outcomes. Nevertheless, the current study showed several important strengths, including nationwide large sample size, standardized methods, and absence of selection bias.

In conclusion, although gout did not increase the in-hospital mortality in ACS-related hospitalizations, the findings from this nationwide cohort highlight the significant impact of gout on in-hospital outcomes in ACS patients in terms of higher cardiovascular comorbidities, CABG frequency, post-revascularization complications, hospital stay, and total hospital charges.

## ARTICLE HIGHLIGHTS

### Research background

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate.

### Research motivation

Limited data exist on impact of gout on in-hospital outcome of ACS in terms of healthcare utilization and post-revascularization outcomes.

### Research objective

The study aimed to evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

### Research methods

We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

### Research results

Out of 3144744 ACS-related hospitalizations, 105198 (3.35%) patients had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. ACS-gout cohort showed comparatively higher prevalence of Coronary artery bypass grafting. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ( $P < 0.001$ ). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44; CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ( $P < 0.001$ ). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ( $P < 0.001$ ). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

### Research conclusions

Gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS. However, gout did increase post-revascularization complications.

### Research perspectives

This study may help clinicians making evidence-based decision in patients with history of gout who are admitted with primary diagnosis of ACS and have undergone re-vascularization.

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