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***Observational Study***

**Outcomes of gout in patients with cirrhosis: A national inpatient sample-based study**

Khrais A *et al*. Outcomes of gout in cirrhosis

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**Abstract**

BACKGROUND

Hyperuricemia is a prerequisite for the development of gout. Elevated serum uric acid (UA) levels result from either overproduction or decreased excretion. A positive correlation between serum UA levels, cirrhosis-related complications and the incidence of nonalcoholic fatty liver disease has been established, but it is unknown whether hyperuricemia results in worsening cirrhosis outcomes. We hypothesize that patients with cirrhosis will have poorer gout outcomes.

AIM

To explore the link between cirrhosis and the incidence of gout-related complications.

METHODS

This was a cross-sectional study. The national inpatient sample was used to identify patients hospitalized with gout, stratified based on a history of cirrhosis, from 2001 to 2013 *via* the International Classification of Diseases, Ninth Revision, Clinical Modification codes. Primary outcomes were mortality, gout complications and joint interventions*.* The *χ2* test and independent *t*-test were performed to assess categorical and continuous data, respectively. Multiple logistic regression was used to control for confounding variables.

RESULTS

Patients without cirrhosis were older (70.37 ± 13.53 years *vs* 66.21 ± 12.325 years; *P* < 0.05). Most patients were male (74.63% in the cirrhosis group *vs* 66.83%; adjusted *P* < 0.05). Patients with cirrhosis had greater rates of mortality (5.49% *vs* 2.03%; adjusted *P* < 0.05), gout flare (2.89% *vs* 2.77%; adjusted *P* < 0.05) and tophi (0.97% *vs* 0.75%; adjusted *P* = 0.677). Patients without cirrhosis had higher rates of arthrocentesis (2.45% *vs* 2.21%; adjusted *P* < 0.05) and joint injections (0.72% *vs* 0.52%; adjusted *P* < 0.05).

CONCLUSION

Gout complications were more common in cirrhosis. Those without cirrhosis had higher rates of interventions, possibly due to hesitancy with performing these interventions given the higher complication risk in cirrhosis.

**Key Words:** Gout; Cirrhosis; Hyperuricemia; Uric acid; Nonalcoholic fatty liver disease; Arthropathy

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**Core Tip:** Patients with cirrhosis had higher rates of gout-related complications including rates of flares. This could be due to the patients with cirrhosis having higher rates of hyperuricemia, predisposing them to worsening gout. Furthermore, patients with cirrhosis had lower rates of joint interventions, likely due to clinician hesitancy with performing such procedures due to an elevated risk of bleeding in patients with cirrhosis.

**INTRODUCTION**

Gout is an inflammatory joint disease present in approximately 3.9% of adults in the United States, with an increasing yearly incidence[1]. Joint inflammation characteristic of the disease process occurs in reaction to deposition of monosodium uric acid (UA) crystals that form due to elevated serum urate levels[2,3]. Deposition occurs in distal joints, where lower temperature and pH decrease urate solubility, thus favoring crystallization. Monosodium UA crystals are processed by immune cells, including neutrophils and macrophages, which release cytokines, reactive oxygen species and prostaglandins that trigger an inflammatory response, resulting in a gout flare[2,4]. If the hyperuricemia of gout is left untreated, chronic granulomatous inflammation occurs resulting in tophi formation[2,4]. While rarely life-threatening, acute gout attacks and their sequelae are a source of significant morbidity. Patients with gout experience severe joint pain, difficulty with ambulation, chronic joint destruction and potentially systemic manifestations, such as nephropathy and urate nephrolithiasis[5].

Gout flares can be triggered by alcohol, fatty foods, dehydration, trauma and medications, including thiazide diuretics, that alter serum urate levels[6]. Serum urate levels are directly relevant to the development and severity of gout. Management focuses on the reduction of serum urate levels *via* lifestyle modifications and pharmacological interventions.

UA is formed from the breakdown of purine amino acids in the liver, and abnormally elevated serum concentrations occur most commonly due to inefficient elimination[7]. Hyperuricemia itself is prevalent in over 21% of adults in the United States[1,7]. Risk factors for the development of elevated serum UA levels are nearly identical to those that predispose individuals to gout, including metabolic syndrome, diet, chronic kidney disease and certain diuretics[7,8]. Hyperuricemia itself has been described as a possible contributing factor to the development of other diseases besides gout, including cardiovascular disease, atrial fibrillation, kidney disease and nonalcoholic fatty liver disease (NAFLD)[9-12].

Multiple studies have shown a positive correlation between serum urate levels and hepatic steatosis and NAFLD[12-14]. Meanwhile, others depict an inverse relationship between liver fibrosis in NAFLD and hyperuricemia, describing a decreased prevalence of hyperuricemia in individuals with significant hepatic fibrosis[15]. While the relationship between NAFLD and gout has been studied, there are few studies exploring the relationship between gout and liver cirrhosis in general (encompassing NAFLD, alcoholic cirrhosis and viral cirrhosis). In this study we analyzed differences in complication rates and mortality between gout patients with and without cirrhosis using data from the national inpatient sample (NIS).

**MATERIALS AND METHODS**

***Data source***

Patient information found within the NIS, the largest public all-payer inpatient database containing information on more than 7 million hospital stays in the United States, served as the source of the study population. The NIS was developed by the Agency for Healthcare Research and Quality and contains no patient or hospital identifiers, providing a nationally representative set of data representing 20% of all discharges from hospitals within the United States. Sample weight is applied annually, enabling precise estimates. In this study, the NIS was queried for cases from 2001 to 2013 using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes to identify patients with cirrhosis who were hospitalized with gout.

***Study design***

This was a cross-sectional study. Inclusion criteria consisted of patients 18-years-old or older hospitalized in the United States with a diagnosis of gout between 2001 and 2013. These patients were then stratified based on the presence of ICD-9 codes for cirrhosis. Measured outcomes included inpatient mortality, rates of gout flares and complications of gout including flare, tophi, UA nephrolithiasis, nephropathy, septic arthritis as well as rates of arthrocentesis and intra-articular injections. Demographic information such as age, sex at birth and race were analyzed as well.

***Statistical analysis***

The IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, United States) software was used to conduct statistical analyses. Independent *t*-test and *χ2* test were used to analyze outcomes and demographic data for both groups for continuous and categorical data, respectively. Multiple logistic regression was used to characterize primary and secondary outcomes among both groups while controlling for age, sex at birth, race, alcohol use disorder, cardiac arrhythmias, chronic pulmonary disease, heart failure, diabetes, human immunodeficiency virus, hypertension, peripheral vascular disease and renal failure. Statistical significance was determined with a *P* value < 0.05*.* Adjusted odds ratios and associated 95% confidence intervals were calculated.

**RESULTS**

Of patients hospitalized from 2001 to 2013 with gout, 1491829 did not have a diagnosis of cirrhosis, while 36948 had cirrhosis (Table 1). The majority of both groups were male, but the cirrhosis group had a greater number of males compared to the non-cirrhosis group (74.63% *vs* 66.83%) without statistical significance. Patients without cirrhosis were older (70.37 ± 13.53 years *vs* 66.21 ± 12.325 years; *P* < 0.05), while those with cirrhosis were younger in age (Table 2). In effect, patients with cirrhosis were younger and had a greater percentage of males than patients without cirrhosis.

Racial distribution was similar in the non-cirrhosis and cirrhosis groups, with Caucasians making up most of the sample size (71.0% *vs* 69.1%, respectively), followed by Blacks (18.6% *vs* 17.4%, respectively), Hispanics (4.4% *vs* 7.4%, respectively), Asians or Pacific Islanders (3.6% for both groups) and Native Americans (0.3% *vs* 0.4%, respectively), all with statistical significance (*P* < 0.05) (Table 3).

In terms of in-hospital outcomes, patients with cirrhosis with gout had higher rates of mortality (5.49% *vs* 2.03%; adjusted *P* < 0.05), gout flare (2.89% *vs* 2.77%; adjusted *P* < 0.05) and tophi (0.97% *vs* 0.75%; adjusted *P* = 0.677). However, differences in rates of tophi were statistically insignificant. Patients without cirrhosis had higher rates of arthrocentesis (2.45% *vs* 2.21%; adjusted *P* < 0.05) and joint injections (0.72% *vs* 0.52%; adjusted *P* < 0.05) (Table 4). Rates of septic arthritis (0.31% in patients without cirrhosis and patients with cirrhosis; adjusted *P* = 0.977), nephropathy (0.02% in patients without cirrhosis *vs* 0.01% in patients with cirrhosis; adjusted *P* = 0.19) and UA nephrolithiasis (0.02% in both groups; adjusted *P* = 0.915) did not differ significantly among both groups.

**DISCUSSION**

Results from this study demonstrate a significant correlation between gout complications and cirrhosis. The pathophysiologic manifestations of the disease, including rates of gout flare, corresponded positively with the prevalence of cirrhosis, while rates of common diagnostic and therapeutic procedures correlated negatively with rates of cirrhosis. Specifically, the rates of gout flare were higher in patients with cirrhosis. However, the difference in flare rates among both groups was 0.12%. As such, this difference may be statistically significant, but it may be clinically irrelevant. The aforementioned positive correlation may be attributed to the elevated serum UA levels found in patients with cirrhosis.

Hyperuricemia has a direct impact on cardiovascular mortality, insulin resistance, renal disease and NAFLD[16]. This relationship is thought to be secondary to urate-induced radical oxide species formation, resulting in intracellular oxidative damage[17]. UA has differential functions depending on where it is found in relation to the cell. Extracellular urate acts as an antioxidant within the hydrophilic environment, neutralizing reactive oxygen species and thus protecting the plasma membrane[18]. Antithetically, intracellular urate serves a pro-oxidant function when exposed to the hydrophobic environment, stimulating the production of inflammatory cytokines and reactive oxygen species-producing enzymes. Within hepatocytes specifically, urate also increases gluconeogenesis *via* AMPK blockade and inflammasome formation and promotes hepatic lipid aggregation[19-21]. Therefore, intrahepatocytic UA accumulation would result in increased radical oxide formation, insulin resistance and lipid accumulation ultimately promoting liver cell damage and steatosis.

Whether serum urate is a risk factor for cirrhosis or vice versa is still in contention. There is evidence that elevated serum urate is an independent risk factor for hepatic steatosis, a harbinger of cirrhosis[18,22]. Furthermore, a reciprocal relationship between the two conditions has been described. Fatty liver disease has been shown to increase serum UA levels[23]. The mechanism of NAFLD-induced hyperuricemia is unclear, yet this interrelationship is strong enough to incentivize clinicians to investigate UA-lowering medications as a potential therapy for patients with fatty liver disease, especially xanthine oxidase inhibitors[24,25]. Other therapies designed to lower intrahepatocyte radical oxide species formation have also been explored, including blockade of chloride ion channels, which would prevent transport of radicals from the extracellular space to within the cell[26]. Hence radical oxide-induced hepatocyte injury plays a significant role in the development of liver disease and reducing levels of these molecules may slow the progression of cirrhosis. Since increased intracellular UA levels promote formation of these radical oxides, urate-lowering therapy may also delay the progression of liver disease.

The negative relationship between rates of cirrhosis and gout-related interventions found in this study may be due to clinician hesitancy with performance of such procedures in the setting of cirrhosis-induced coagulopathy. This hesitancy may be unfounded. While patients with cirrhosis are coagulopathic and at increased risk of bleeding, significant blood loss following minor procedures is rare in the absence of severe thrombocytopenia[27,28]. On the other hand, patients with cirrhosis are generally sicker than the average hospitalized individual and may be too hemodynamically unstable for such procedures.

We also found that patients with cirrhosis had higher rates of mortality than those without cirrhosis. This finding was expected, as cirrhosis has a poor prognosis and patients are at risk for significant complications resulting from end stage liver disease, including bleeding, infection and hemodynamic instability[20,27].

This study was limited by the fact that risk factors for cirrhosis, such as metabolic syndrome and chronic alcohol use, are independently associated with elevated serum UA levels and gout[29,30]. The population of patients with cirrhosis examined in this study encompassed both alcoholic and nonalcoholic etiologies of cirrhosis. Therefore, alcohol use disorder could represent a significant confounding variable. While alcohol use disorder was controlled for as a confounding variable, its relationship to alcoholic cirrhosis could still pose issues when attempting to independently correlate gout with cirrhosis. Another limitation was that the NIS database could not be used to assess whether the interventions designed to diagnose or treat gout led to any bleeding complications. Further studies analyzing clinician decision making regarding interventions in patients with cirrhosis may clarify factors leading to our finding of lower rates in patients with cirrhosis. We did not stratify patients with cirrhosis by subtype of cirrhosis (*i.e.* viral *vs* alcoholic *vs* NAFLD) as there were no specific ICD-9 codes distinguishing viral cirrhosis from NAFLD.

Alternate avenues of research worth exploring include retrospective chart review of patients hospitalized for gout flares with a history of cirrhosis, further stratifying patients into NAFLD or alcoholic cirrhosis. This proposed study would clarify the relationship between gout and cirrhosis, and it would delineate the differences in gout rates in those with alcoholic cirrhosis, who likely have a significant history of alcohol use, which is an independent risk factor for gout development, and those with NAFLD. Another possible future research endeavor includes studying rates of gout complications in patients diagnosed with virus-related cirrhosis, including hepatitis B virus and hepatitis C virus. We established that there are a limited number of studies assessing the relationship between liver disease and gout; there are even fewer studies correlating viral cirrhosis with gout or hyperuricemia. Since the pathophysiology of hepatitis C virus or hepatitis B virus cirrhosis is not connected to that of hyperuricemia (as opposed to metabolic syndrome in NAFLD and alcohol use in alcoholic cirrhosis), isolating cases of gout in those with viral-induced cirrhosis may provide an objective view into the pathophysiology of cirrhosis-induced hyperuricemia and the subsequent effect on gout exacerbations.

**CONCLUSION**

In summary, patients with cirrhosis may have differential rates of gout exacerbations and potential therapeutic options due to a combination of pathophysiology, cirrhosis-related comorbidities and clinical decision making. As there are few studies connecting both disease states, more investigation is required to further delineate the relationship between liver disease and gout.

**ARTICLE HIGHLIGHTS**

***Research background***

Gout is an inflammatory joint disorder with increasing yearly incidence in the United States. It is affected by factors including diet, alcohol use and obesity, all of which are significant contributors to end stage liver disease. Furthermore, studies suggest a correlation between serum uric acid (UA) levels and cirrhosis.

***Research motivation***

The relationship between gout and cirrhosis and the possible relationship between hyperuricemia and liver disease has not been adequately explored, despite their common risk factors. We aimed to further clarify a possible link between the two disease states.

***Research objectives***

Our objective was to determine if patients with cirrhosis had differential rates of outcomes regarding hospitalizations for gout, including episodes of gout flares, disease complications and possible invasive interventions.

***Research methods***

We utilized data from the national inpatient sample, assessing inpatient cases from 2001 to 2013. Specifically, hospitalized individuals with gout were stratified based on the presence of cirrhosis. Outcomes of gout, including flares, tophus formation and joint interventions were explored. Rates of outcomes were compared between patients with and without cirrhosis.

***Research results***

We found that patients with cirrhosis had greater rates of gout flares, but lower rates of arthrocentesis and joint injections.

***Research conclusions***

Gout recurrence was more common in patients with cirrhosis, and joint interventions were performed more infrequently in these patients. The increased rate of gout flares could be secondary to elevated serum UA levels, as determined in prior research endeavors, in patients with cirrhosis. The reduced rate of joint interventions could be due to clinician hesitancy to perform these procedures, given the increased risk of bleeding in patients with cirrhosis.

***Research perspectives***

A link between cirrhosis and gout flares has been established, yet no significant difference was found between cirrhosis and other gout complications. Further prospective endeavors are required to further characterize this relationship.

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**Footnotes**

**Institutional review board statement:** This study utilized de-identified data from a public database and as such was exempt from institutional review.

**Informed consent statement:** Informed consent was not required.

**Conflict-of-interest statement:** All authors report no relevant conflicts of interest for this article.

**Data sharing statement:** Statistical code and database is available from the national inpatient sample at <https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp>. Consent was not obtained, but the presented data are anonymized, and risk of identification is non-existent as data were obtained from a public database.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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**Table 1 Patient sex at birth for gout with and without a history of cirrhosis**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Patients without cirrhosis, *n* = 1491829** | | **Patients with cirrhosis, *n* = 36948** | | **OR** | **95%CI** | ***P* value** |
| **Percentage** | ***n*** | **Percentage** | ***n*** |
| Sex at birth | Female | 33.17 | 494890 | 25.37 | 9372 | 0.685 | 0.669-0.701 | < 0.05 |
| Male | 66.83 | 996939 | 74.63 | 27576 |

95%CI: 95% Confidence interval;OR: Odds ratio.

**Table 2 Differences in age distribution among patients hospitalized for gout with and without a history of cirrhosis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Patients without cirrhosis** | | | **Patients with cirrhosis** | | | **Mean difference** | **95%CI** | ***P* value** |
| **Mean** | **SD** | **SE mean** | **Mean** | **SD** | **SE mean** |
| Age at admission (yr) | 70.37 | 13.53 | 0.011 | 66.21 | 12.33 | 0.064 | 4.167 ± 0.071 | 4.027-4.306 | < 0.05 |

95%CI: 95% Confidence interval; SD: Standard deviation; SE: Standard error.

**Table 3 Racial characteristics in patients hospitalized for gout with and without a history of cirrhosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Race** | **Patients without cirrhosis** | | **Patients with cirrhosis** | | ***P* value** |
| **%** | ***n*** | **%** | ***n*** |
| Caucasian | 71.0 | 890040 | 69.1 | 22725 | < 0.05 |
| Black | 18.6 | 233005 | 17.4 | 5723 |
| Hispanic | 4.4 | 55174 | 7.4 | 2426 |
| Asian or Pacific Islander | 3.6 | 45217 | 3.6 | 1184 |
| Native American | 0.3 | 4289 | 0.4 | 122 |
| Other | 2.0 | 25351 | 2.1 | 703 |

**Table 4 Primary outcomes in gout among hospitalized patients with and without cirrhosis**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Patients without cirrhosis** | | **Patients with cirrhosis** | | **OR** | **95%CI** | ***P* value** | **AOR** | **ACI** | **Adjusted *P* value** |
| **Percentage** | ***n*** | **Percentage** | ***n*** |
| Mortality | 2.03 | 30286 | 5.49 | 2029 | 2.804 | 2.678-2.937 | < 0.050 | 3.092 | 2.939-3.252 | < 0.05 |
| Gout flare | 2.77 | 41282 | 2.89 | 1066 | 1.044 | 0.982-1.110 | 0. 171 | 0.816 | 0.765-0.871 | < 0.05 |
| Tophi | 0.75 | 11202 | 0.97 | 358 | 1.293 | 1.164-1.438 | < 0.050 | 1.025 | 0.914-1.149 | 0.677 |
| Uric acid nephrolithiasis | 0.02 | 374 | 0.02 | 9 | 0.972 | 0.502-1.882 | 0.932 | 1.037 | 0.530-2.030 | 0.915 |
| Nephropathy | 0.02 | 283 | 0.01 | 5 | 0.713 | 0.295-1.727 | 0.452 | 0.548 | 0.223-1.346 | 0.19 |
| Arthrocentesis | 2.45 | 36611 | 2.21 | 818 | 0.900 | 0.839-0.965 | < 0.050 | 0.741 | 0.686-0.800 | < 0.05 |
| Joint injection | 0.72 | 10673 | 0.52 | 192 | 0.725 | 0.628-0.837 | < 0.050 | 0.713 | 0.610-0.833 | < 0.050 |
| Septic Arthritis | 0.31 | 4637 | 0.31 | 114 | 0.993 | 0.824-1.196 | 0.939 | 0.997 | 0.821-1.211 | 0.977 |

95%CI: 95% Confidence interval; ACI: Adjusted confidence interval; AOR: Adjusted odds ratio; OR: Odds ratio.