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WORD COUNT 2618
TIME SUBMITTED 17-JAN-2023 02:42PM
PAPER ID 95614506

Name of Journal: *World Journal of Hepatology*

Manuscript NO: 80627

Manuscript Type: ORIGINAL ARTICLE

Observational Study

Outcomes of Gout in Patients with Cirrhosis, a National Inpatient Sample-Based Study

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 non-alcoholic 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 is a cross-sectional study. The National Inpatient Sample (NIS) 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 (ICD-9 CM) codes. Primary outcomes were mortality, gout complications and joint interventions. Chi-squared and independent t-tests were done 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 $p<0.05$). Cirrhotics 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 $p=0.677$). Non-cirrhotics 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; Non-alcoholic fatty liver disease; Arthropathy

Khrais A, Kahlam A, Tahir A, Shaikh A, Ahlawat S. Outcomes of Gout in Patients with Cirrhosis, a NIS-Based Study. *World J Hepatol* 2023; In press

Core Tip: Patients with cirrhosis had higher rates of gout-related complications including rates of flares. This could be due to the possibility that patients with cirrhosis have 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 elevated risk of bleeding in 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 (MSUA) 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. MSUA 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 that alter serum urate levels, including thiazide diuretics[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.

Uric acid 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 uric acid 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 non-alcoholic fatty liver disease (NAFLD)[9-12].

Multiple studies have shown a positive correlation between serum urate levels and hepatic steatosis & NAFLD[12,13,14]. 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 aim to analyze 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 U.S. 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 is a cross-sectional study. Inclusion criteria consisted of patients 18 years old or older hospitalized in the U.S. 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, uric acid 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, USA) software was used to conduct statistical analyses. Independent *t*-tests and Chi-squared 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, HIV, HTN, peripheral vascular disease and renal failure. Statistical

significance was determined with a *p*-value <0.05. Adjusted odds ratios (AOR) and associated 95% confidence intervals (CI) were calculated.

RESULTS

Of patients hospitalized from 2001 to 2013 with gout, 1,491,829 did not have a diagnosis of cirrhosis while 36,948 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 older and had a greater percentage of males than patients without cirrhosis.

Racial distribution was similar across both non-cirrhotic and cirrhotic groups, with Caucasians making up most of the sample size (71% *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 then Native Americans (0.3% *vs* 0.4%), all with statistical significance (*p*<0.05) (Table 3).

In terms of in-hospital outcomes, cirrhotic patients 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. Non-cirrhotic patients 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 non-cirrhotic patients and cirrhotic patients; adjusted *p*=0.977), nephropathy (0.02% in non-cirrhotic patients *vs* 0.01% in cirrhotic patients; adjusted *p*=0.19) and uric acid 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. 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, however it may be clinically irrelevant. The aforementioned positive correlation may be attributed to the elevated serum uric acid 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]. Uric acid 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 & inflammasome formation, and promotes hepatic lipid aggregation[19,20,21]. Therefore, intra-hepatocytic uric acid 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 uric acid levels[23]. The mechanism of NAFLD-induced hyperuricemia is unclear, yet this interrelationship is strong enough to have incentivized clinicians into investigating uric acid-lowering medications as a potential therapy for patients with fatty liver disease, especially xanthine oxidase inhibitors[24,25]. Other therapies designed to lower intra-hepatocyte 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 raised intracellular uric acid 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 can 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, cirrhotic patients 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 is expected, as cirrhosis has a poor prognosis and patients are at risk for significant complications resulting from their end stage liver disease, including bleeding, infection and hemodynamic instability[20,27].

This study is limited by the fact that risk factors for cirrhosis, such as metabolic syndrome and chronic alcohol use, are independently associated with elevated serum uric acid levels and gout[29,30]. The population of patients with cirrhosis examined in this study encompassed both alcoholic and non-alcoholic 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 is 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 cirrhotic patients may clarify factors leading to our finding of lower rates in patients with cirrhosis. We did not stratify cirrhotic patients by subtype of cirrhosis (ie, viral *vs* alcoholic *vs* NAFLD) as there were no specific ICD-9 codes distinguishing viral cirrhosis from NAFLD.

Alternate avenues of research worth exploring can 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 not only clarify the relationship between gout and cirrhosis, but it would also 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 can include studying rates of gout complications in patients diagnosed with virus-related cirrhosis, including hepatitis B virus (HBV) and hepatitis C virus (HCV). 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 HCV or HBV 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 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 levels and cirrhosis.

Research motivation

The relationship between gout and cirrhosis has not been adequately explored, despite their common risk factors, and the possible relationship between hyperuricemia and liver disease. We aim 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 uric acid levels, as determined in prior research endeavors, in patients with cirrhosis. The reduced rate of joint interventions could be due to clinician hesitancy with performance of 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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