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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prevalence of non-alcoholic fatty liver disease in patients with nephrotic syndrome: A population-based study

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a global health concern with a prevalence of about 25% amongst United States adults. Its increased prevalence is attributed to increase in patients with obesity and metabolic syndrome, partly due to similar mechanisms of injury. Nephrotic syndrome (NS) is a clinical entity resulting from extensive proteinuria leading to hypoalbuminemia, hyperlipidemia, edema, and other complications. Given its association with hyperlipidemia, there is concern that patients with NS may be at increased risk of NAFLD.

AIM

To perform a cross-sectional population-based study to investigate the prevalence and risk factors of NAFLD in patients with NS.

METHODS

A large multicenter database (Explorys Inc., Cleveland, OH, United States) was utilized for this retrospective cohort study. A cohort of 49700 patients with a diagnosis of "Non-Alcoholic fatty liver disease" using the Systematized

Nomenclature of Medicine-Clinical Terms (SNOMED-CT) between 1999-2022 was identified. Inclusion criteria were age ≥ 18 years, presence of NAFLD, presence of NS. There were no specific exclusion criteria. Univariate and multivariate analysis were performed to adjust for multiple risk factors including age, gender, Caucasian race, NS, type II diabetes mellitus, hypothyroidism, dyslipidemia, obesity, metabolic syndrome and chronic kidney disease. Statistical analysis was conducted using R, and for all analyses, a 2-sided *P* value of < 0.05 was considered statistically significant.

RESULTS

Among the 78734750 individuals screened in this database, there were a total of 49700 subjects with NAFLD. In univariate analysis, the odds of having NAFLD in patients with NS, type 2 diabetes mellitus, hypothyroidism, dyslipidemia, obesity, metabolic syndrome and chronic kidney disease were 14.84 [95% confidence interval (95%CI) 13.67-16.10], 17.05 (95%CI 16.78-17.32), 6.99 (95%CI 6.87-7.11), 13.61 (95%CI 13.38-13.84), 19.19 (95%CI 18.89-19.50), 29.09 (95%CI 28.26--29.95), and 9.05 (95%CI 8.88-9.22), respectively. In multivariate analysis, the odds of having NAFLD amongst patients with NS were increased to 1.85 (95%Cl 1.70-2.02), while the odds were also remained high in patients that have type 2 diabetes mellitus [odds ratio (OR) 3.84], hypothyroidism (OR 1.57), obesity (OR 5.10), hyperlipidemia (OR 3.09), metabolic syndrome (OR 3.42) and chronic kidney disease (OR 1.33).

CONCLUSION

Patients with NS are frequently found to have NAFLD, even when adjusting for common risk factors. Hence, clinicians should maintain a high index of suspicion regarding presence of NAFLD in patients with NS.

Key Words: Non-alcoholic fatty liver disease; Nephrotic syndrome; Chronic kidney disease; Hyperlipidemia; Population-based study; Database

Core Tip: We conducted a population-based study to investigate the prevalence of non-alcoholic fatty liver disease (NAFLD) in patients with Nephrotic syndrome. We screened over 78 million individuals in a nationwide multicenter database. We performed a comprehensive multivariate analysis accounting for multiple cofounding factors including age ≥ 65 years, gender, Caucasian race, obesity, diabetes mellitus type 2, metabolic syndrome, dyslipidemia, chronic kidney disease and hypothyroidism. We found that patients with nephrotic syndrome had a higher prevalence of NAFLD. However, we could not account for certain confounders such as elevated uric acid levels, hormonal therapy, chemotherapy for tumors, and certain drugs such as corticosteroids, which are known to be risk factors for NAFLD. Further studies are required to confirm these findings and assess the utility of surveillance strategies for NAFLD in patients with nephrotic syndrome.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide with a prevalence of about 25% in the adult world population. It is characterized by excessive hepatic deposition of fat without any other probable explanation including alcohol, viral hepatitis, inherited liver conditions, or protracted use of steatogenic drugs[1]. NAFLD is seen to occur in a progressive manner from steatosis to nonalcoholic steatohepatitis (NASH), which may lead to fibrosis and cirrhosis[2]. Multiple studies have confirmed that NASH and cirrhosis increase the risk of hepatocellular carcinoma (HCC), which is one of the most common causes of cancer related deaths worldwide [3]. It is thus no wonder that NAFLD and NASH have been recognized as a growing public health problem. The disease burden of NAFLD is influenced by diabetes mellitus type 2, obesity, metabolic syndrome and hypothyroidism which have all been recognized as risk factors in its development as

these conditions either directly or indirectly, promote fat accumulation in the liver[4-7]. Unfortunately, these conditions are not expected to decrease in the forthcoming decades. NAFLD and its related liver complications (NASH, cirrhosis and HCC) are the leading cause of chronic liver disease and the major cause of liver transplantation in the United States[8,9]. NAFLD is not only associated with liver related morbidity and mortality, clinical evidence also suggests its associations with other important extra-hepatic diseases such as cardiovascular diseases ranging from cardiomyopathy, coronary heart disease, cardiac arrhythmias to hypertension and kidney diseases such as chronic kidney disease[10-12]. These cardiovascular manifestations are recognized to be the leading cause of death in patients with NAFLD [13,14]. No wonder a tailored multistep approach involving lifestyle changes, anti-diabetic drugs and lipid lowering medications are have in been put in place for the management of NAFLD to reduce incidence of cardiovascular complication and also concomitantly treat existing comorbid conditions.

Nephrotic syndrome (NS) is a kidney disorder characterized by excessive proteinuria (urinary loss of ≥ 3 g of proteins per 24 h or, on a single spot urine sample, the presence of ≥ 2 g of protein per gram of urinary creatinine) resulting in hypoalbuminemia, dyslipidemia and oedema[15]. Dyslipidemia is known to cause premature atherosclerosis increasing the risk for acute coronary syndrome and stroke. Furthermore, there is increased risk of thrombosis in patients with nephrotic syndrome, not only from increased urinary loss of antithrombotic factors but also atherosclerosis induced platelet hyperreactivity [16]. Nutritional optimization as well as pharmacological interventions involving use of, Ace inhibitors, albumin, corticosteroid, antibiotic, anticoagulation therapy have all been proposed as measures to reduce mortality from NS.

Given their association with dyslipidemia, NAFLD and NS might have similarities in their pathophysiology. Both disease processes are associated with elevated levels of circulating free fatty acid [17-20]. In NAFLD, patients have underlying insulin resistance causing decreased inhibitory effect of insulin on peripheral lipolysis leading to increased pool of circulating free fatty acid and glycerol. As fat and triglycerides in the form of VLDL accumulates in the liver, it eventually leads to excessive production of ROS by Kupffer cells and alteration in mitochondrial DNA occurs. This demonstrates the slowed progression of hepatic steatosis to NASH, hepatocellular necroinflammation and fibrosis and lastly carcinoma[21-24]. Interestingly, patients with NS also exhibit dysregulated fatty acid metabolism with or without the presence of chronic kidney disease. In these patients, injury to podocytes stems from elevated plasma concentrations of major lipoproteins. This alteration in lipid metabolism stems from downregulation of lipoprotein lipase in peripheral tissues, suppression of hepatic lipase and increased activity of acetyl-CoA carboxylase and fatty acid synthase[17-20].

Our hypothesis is that the excess synthesized and circulating lipids in patients with NS affect fat metabolism in the liver, increasing the risk of NAFLD. It has been proven that NS might lead to chronic kidney disease (CKD), and there have been studies suggesting increased prevalence of NAFLD in patients with CKD[4,25-27]. However, there have been few studies, if any, correlating prevalence of NAFLD in patients with NS. Given the increasing prevalence of NAFLD and associated morbidity and mortality, identification of at-risk patients is essential for targeted monitoring and treatment. Since NAFLD and NASH often do not cause any symptoms, surveillance strategies for at-risk patients might aid in early diagnosis and help prevent adverse outcomes. Since both NAFLD and NS are associated with elevated circulating lipids, patients with NS might be at risk for NAFLD, especially if they have other risk factors for NAFLD such as diabetes mellitus, obesity, or steroid use. It is essential to know if NS itself can be a risk factor for NAFLD, since only then can cost-effectiveness and usefulness of any surveillance and preemptive strategies be commented on. Furthermore, if patients with NS are at increased risk of NAFLD, more aggressive approach towards controlling other NAFLD risk factors and reducing use of certain medications such as steroids might be warranted. Therefore, we conducted a study with the aim of assessing the prevalence as well as risk factors of NAFLD in patients with NS.

MATERIALS AND METHODS

Our cohort's data were obtained using a validated, multicenter and daily-updated database called Explorys (Explorys Inc, Cleveland, OH, United States) developed by IBM Corporation, Watson Health [IBM corporation]. Explorys consists of electronic health records of 26 different healthcare systems with a total of about 360 hospitals and more than 70 million patients across the United States. Explorys utilizes Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) for the definition of the diseases. The diagnosis is made by individual health care providers and the collected data is then uploaded into the database in the form of SNOMED-CT codes. The database pools large outpatient as well as inpatient deidentified data that can be formulated into numerous cohorts according to the clinical element being studied. Explorys does not record individual patient data such as laboratory or imaging results. Since the data is pooled from multiple organizations, different organizations, and by extension health care providers, may differ in method of diagnoses of various medical conditions. The way the database is established, assessment of the method of diagnoses is not feasible, and thus the database is largely dependent on individual organizations providing accurate data. The approval of Institutional Review Board is not required since Explorys is a Health Insurance Portability and Account-

ability Act (HIPAA)-compliant platform. Use of this database has been validated in multiple fields including cardiology, hematology and gastroenterology.

Patient selection

A cohort of patients with a SNOMED-CT diagnosis of "Non-Alcoholic Fatty Liver Disease" and "Nephrotic syndrome" between 1999 and May 2022 was identified. Inclusion criteria were age ≥ 18 years, presence of NAFLD, presence of NS. There were no specific exclusion criteria.

Covariates

We collected age > 65 years, gender and Caucasian race as variables. Confounding factors associated with NAFLD and NS were also identified and collected if SNOMED-CT diagnoses were available. These were obesity, diabetes mellitus type 2, metabolic syndrome, dyslipidemia, chronic kidney disease and hypothyroidism.

Statistical analysis

To account for confounding from the covariates listed above, we conducted 1024 searches to explore every probability, with NS as one of the variables. A univariate analysis was conducted initially for all the variables, followed by multivariate analysis. Statistical analysis was performed using R and RStudio (version 1.4.1717), and for all analyses, a 2-sided *P* value of < 0.05 was considered statistically significant. Multivariate analysis was performed to adjust for multiple factors including age ≥ 65 years, gender, caucasian race, obesity, diabetes mellitus type 2, metabolic syndrome, dyslipidemia, chronic kidney disease and hypothyroidism. The study was reviewed by our expert biostatistician Antoine Boustany, MD, MPH, MEM.

RESULTS

Among the 78734750 individuals screened in this database, there were a total of 49700 subjects with NAFLD. Most subjects with NAFLD were between the age of 18-65 years, with female affected more than males. Interestingly, while majority of subjects were Caucasians, 5% were African Americans. About half the patients with NAFLD had BMI ≥ 30, with the prevalence of NAFLD rising with the increase in BMI (Table 1). In univariate analysis, the odds of having NAFLD with age ≥ 65 years was 2.18 [95% confidence interval (95%CI) 2.15-2.22], while it was also high in females [odds ratio (OR) 1.18, 95%CI 1.16-1.20], Caucasians (OR 3.62, 95%CI 3.55–3.69), subjects with NS (OR 14.84, 95%CI 13.67-16.10), type 2 diabetes mellitus (OR 17.05, 95%CI 16.78-17.32), hypothyroidism (OR 6.99, 95%CI 6.87-7.11), dyslipidemia (OR 13.61, 95%CI 13.38-13.84), obesity (OR 19.19, 95%CI 18.89-7.11), metabolic syndrome (OR 29.09, 95%CI 28.26-29.95) and CKD (OR 9.05, 95%CI 8.88-9.22). In multivariate analysis, the odds of having NAFLD amongst patients with nephrotic syndrome was 1.85 (95% CI 1.70-2.02), while the odds also remained high in patients that have type 2 diabetes mellitus (OR 3.84), hypothyroidism (OR 1.57), obesity (OR 5.10), hyperlipidemia (OR 3.09), metabolic syndrome (OR 3.42) and CKD (OR 1.33) (Figure 1).

DISCUSSION

With the high prevalence of NAFLD and its associated complications, there is worldwide interest in learning more about the disease and its associations with other systemic illnesses. To date despite extensive research, we were unable to find another study reporting the prevalence of NAFLD in patients with NS. Two prospective studies conducted by Targher *et al*[28,29], one in patients with type 1 diabetes mellitus (T1DM) and the other in T2DM, to assess the development of CKD in patients with NAFLD did not report development of NS in any patient over a follow-up period of 5.2 years and 6.5 years, respectively. In our study, patients with NS were frequently found to have NAFLD. One explanation is that impairment in lipid metabolism in NS promotes development of NAFLD. However, further studies are needed to explore this possibility.

In contrast, there have been several studies assessing renal impairment in patients with NAFLD. The results of these studies have been contradictory. Musso *et al*[10] conducted a systematic review and meta-analysis of articles published through 1980 -2014 and showed that NAFLD was associated with increase in prevalence as well as incidence of CKD [odds ratio (OR) 2.12, 95%CI 1.69-2.66; and hazard ratio (HR) 1.79, 95%CI 1.65-1.95, respectively]. Furthermore, NASH was associated with a higher prevalence and incidence of CKD (OR 2.53, 95%CI 1.58-4.05; and HR 2.12, 95%CI 1.42-3.17, respectively) than simple steatosis[10]. Our study had similar results, with increased odds of having CKD in patients with NAFLD, which remained significant on multivariate analysis.

In comparison, two studies by Targher *et al*[29], one conducted in patients with type 2 diabetes mellitus and the other in type 1 diabetes mellitus, showed that patients with NAFLD had lower

Table 1 Baseline characteristics of patients with non-alcoholic fatty liver disease

Parameters	NAFLD, *n* (%)	No NAFLD, *n* (%)	*P* value
Age, yr			< 0.00001
Adults 18-65	30980 (62.33)	56486180 (71.79)	
Seniors > 65	18720 (37.67)	22198870 (28.21)	
Gender			< 0.00001
Male	20640 (41.53)	35921730 (45.65)	
Female	29060 (58.47)	42763320 (54.35)	
Race			< 0.00001
Caucasian	39420 (79.32)	40569460 (51.56)	
African American	2550 (5.13)	7765730 (9.87)	
Hispanic/Latino	790 (1.59)	1037520 (1.32)	
Other	6940 (13.96)	29312340 (37.25)	
BMI			< 0.00001
< 18.5	1180 (2.38)	3610880 (4.59)	
18.5-24.9	7860 (15.81)	13727720 (17.45)	
25.0-29.9	16810 (33.82)	13117450 (16.67)	
> 30.0	23850 (47.99)	48229000 (61.29)	
Type 2 diabetes mellitus	24830 (49.95)	4526510 (5.75)	< 0.00001
Metabolic syndrome	3640 (7.32)	205830 (0.26)	< 0.00001
Hyperlipidemia	33130 (66.65)	10,152,960 (12.90)	< 0.00001
Nephrotic syndrome	100 (0.14)	17300 (0.02)	< 0.00001
Hypothyroidism	11930 (24.00)	3472880 (4.41)	< 0.00001
Chronic kidney disease	13485 (27.13)	2347230 (2.98)	< 0.00001
Total	49700	78685050	

NAFLD: Non-alcoholic fatty liver disease.

estimated glomerular filtration rate and increased incidence of CKD as compared to patients without NAFLD In contrast, a study by Sirota *et al*[30] conducted on the National Health And Nutrition Examination Survey III (NHANES III) data showed increased prevalence of NAFLD in patients with CKD, which was not significant after adjusting for certain risk factors. One possible explanation for these discrepancies is that the prevalence of NAFLD in CKD may be driven by race, which was adjusted for in the latter study but not the former one. In our study, the prevalence of NAFLD remained significant in patients with CKD, even on multivariate analysis and adjusting for Caucasian race. The reason for this discrepancy is unclear, although a larger sample size in our cohort might have played a role.

With regards to factors associated with NAFLD, our study concluded that patients with type 2 DM, obesity, hypothyroidism, metabolic syndrome and hyperlipidemia have higher prevalence of NAFLD, even on multivariate analysis, which is similar to studies done elsewhere[6,28,29,31]. One interesting finding was that 5% of patients with NAFLD in our cohort identified as African American, which is consistent with low prevalence of NAFLD in this population as reported in the literature[32]. In our study, the prevalence of NAFLD increased as BMI rose, with a prevalence of 48% in subjects with BMI ≥ 30 as compared to 33.82%, 15.81%, and 2.38% in patients with BMI 25.0-29.9, 18.5-24.9, and < 18.5, respectively. Similar results have been observed in literature, with one study by Loomis *et al*[6], demonstrating a strong and striking near-linear relationship between BMI and future risk of recorded NAFLD.

Our study has several strengths. To the best of our knowledge, this is the first study to assess the prevalence of NAFLD in patients with NS. Being a multicenter study with a large sample size derived from the United States population, our results are reliable and generalizable. We assessed several common risk factors, and our study showed that these factors were independently associated with increased prevalence of NAFLD, which have been well documented in the literature.

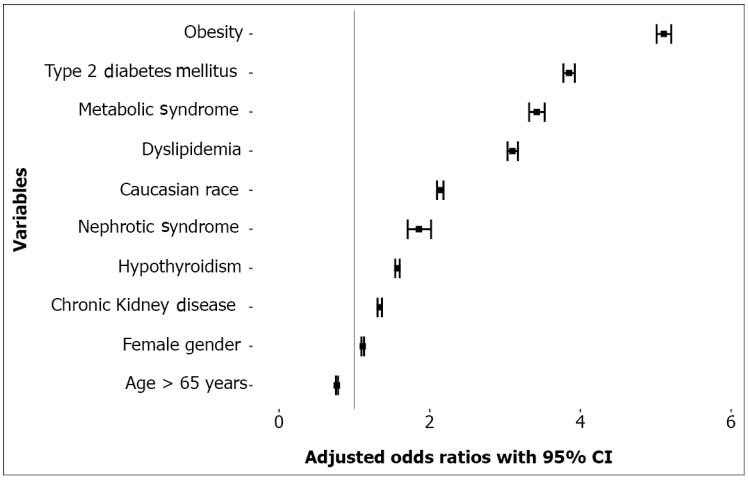

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Figure 1 Multivariate analysis assessing the risk of non-alcoholic fatty liver disease. 95%CI: 95% confidence interval.

LIMITS OF THE STUDY

Limitation to our study includes its retrospective nature and inability to establish causality. Being a database study, there is always a concern regarding selection bias. Furthermore, given that this database is HIPAA-compliant and anonymous, it is not possible to verify the accuracy of the diagnoses made. Hence, further in-depth analysis is not feasible. Also, certain NAFLD risk factors such as presence of elevated uric acid levels and pharmacological interventions such as corticosteroid use, hormonal therapy, certain chemotherapeutic agents, *etc.* could not be assessed.

CONCLUSION

Our study demonstrates that patients with NS are frequently found to have NAFLD, even when adjusting for common risk factors including CKD. Females and subjects with age 18-65 years were most commonly affected with NAFLD, with most subjects being Caucasians and only 5% were African American. The American Association for the Study of Liver Disease still recommends against routine screening for NAFLD in any population[1]. Further studies are needed to assess the relationship between NS and NAFLD. While lipid metabolism is abnormal in both these diseases, whether these diseases develop independently of each other or through a common pathway needs to be further explored. Clinicians should be aware of the increased prevalence of NAFLD in this patient population.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide, with hyperlipidemia as one of its risk factors. Nephrotic syndrome (NS) is known to cause hyperlipidemia. Since both NAFLD and NS patients are known to have abnormalities in lipid metabolism, patients with NS might be at increased risk of developing NAFLD.

Research motivation

Given the increasing prevalence of NAFLD and associated morbidity and mortality, assessment of risk factors for targeted surveillance is warranted. This might help in early diagnosis of NAFLD and improve outcomes. We hypothesized that the excess synthesized and circulating lipids in patients with NS affect fat metabolism in the liver, increasing the risk of NAFLD.

Research objectives

To conduct a cross-sectional population-based study to assess the prevalence of NAFLD in patients with NS while adjusting for common risk factors.

Research methods

A large multicenter database (Explorys Inc., Cleveland, OH, United States) was utilized for this study. A cohort of patients with a diagnosis of "Non-Alcoholic fatty liver disease" was identified. Inclusion criteria were age ≥ 18 years, presence of NAFLD, presence of NS. There were no specific exclusion criteria. Univariate and multivariate analyses were performed to adjust for multiple risk factors including age, gender, Caucasian race, nephrotic syndrome, type II diabetes mellitus, hypothyroidism, dyslipidemia, obesity, metabolic syndrome and chronic kidney disease. Statistical analysis was conducted using R, and for all analyses, a 2-sided *P* value of < 0.05 was considered statistically significant.

Research results

In multivariate analysis, the odds of having NAFLD amongst patients with NS was 1.85 (95%Cl 1.70-2.02), while the odds also remained high in patients that have type 2 diabetes mellitus (OR 3.84), hypothyroidism (OR 1.57), obesity (OR 5.10), hyperlipidemia (OR 3.09), metabolic syndrome (OR 3.42) and chronic kidney disease (CKD) (OR 1.33).

Research conclusions

Our study demonstrates that patients with NS are frequently found to have NAFLD, even when adjusting for common risk factors including CKD. Further studies are required to confirm these findings, investigate causality and assess the utility of surveillance strategies for NAFLD in patients with NS.

Research perspectives

Studies assessing associations of NAFLD with other diseases can help identify at-risk populations that may benefit from routine screening. While patients with NS seem to have higher prevalence of NAFLD, further research is required to assess if routine surveillance of patients with NS is cost-effective and improves outcomes.

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FOOTNOTES

Author contributions: Onwuzo S designed the research study; Hitawala A and Boustany A performed the biostatistical analysis; Boustany A and Kumar P carried out the data collection; Onwuzo S, Hitawala A, Onwuzo C, Almomani A, Monteiro J, and Asaad I contributed to the manuscript writing, editing and scientific review; All authors have read and agree to the submitted version of the manuscript.

Institutional review board statement: Our cohort's data were obtained using a validated, multicentered and daily-updated database called Explorys (Explorys Inc, Cleveland, OH, United States). Explorys does not record individual patient data such as name, laboratory or imaging results. Patient's informed consent and approval of Institutional Review Board are not required since Explorys is a Health Insurance Portability and Accountability Act (HIPAA)-compliant platform.

Informed consent statement: Consent was not obtained but the presented data are anonymized without any risk of identification.

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