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Females with Autoimmune Liver Diseases are at Increased Risk of Major Adverse Cardiovascular Outcomes: A Nationwide Matched Cohort Study

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Abstract

Introduction: Cardiovascular disease (CVD) remains a leading cause of death in women. Atherosclerotic Cardiovascular Disease score does not encompass inflammatory diseases, which is associated with increased CVD risk. This score may underestimate risk in women with autoimmune liver diseases (AILD) such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). We investigated if women with AILD had increased CVD risk compared to female and male controls.

Methods: Using TriNetX, we conducted a multi-center, retrospective cohort study of patients with AIH, PBC, and PSC. Study cohorts were females with respective AILD who had diabetes mellitus (DM), hypertension (HTN), and lipidemia. Control cohorts were female or male with DM, HTN, and lipidemia with AILD, biologics, immune modulators, and steroids explicitly excluded. Female study versus female control were matched for age, race, ethnicity, ASCVD risk factors, and tobacco use. Female study versus male control were matched for age, race, ethnicity, and tobacco use. Primary outcome was summative cardiovascular (CV) risk including unstable angina, acute myocardial infarction, and presence of coronary angioplasty implant, coronary artery bypass, percutaneous coronary intervention, and cerebral infarction.

Results: Females with AIH had greater CV risk compared to control females (24.7% vs. 18.9%, P-value<0.0001), which was seen with PBC (24.9% vs. 18.4%, P-value<0.0001). There was no difference for PSC (26.4% vs. 20.7%, P-value=0.26).

When comparing to male controls, females with AIH did not have significant CV risk (24.7% vs. 22.4%, P-value=0.10), also seen in PBC (24.9% vs. 23.9%, P-value=0.53), and PSC (26.2% vs. 17.7%, P-value=0.08).

Conclusion: Females with AIH and PBC lose CV protection conferred by female sex. There is no difference in CV risk in females with AILD compared to male controls. There is a potential oversight in our risk stratification approach to females with chronic AILD. Enhancing risk assessment is imperative for optimizing patient outcomes.

Keywords: Autoimmune, Cardiovascular disease, Cardiac risk, Liver disease, Sex difference

Introduction

Cardiovascular disease (CVD) remains a leading cause of death in women, causing about 1 in every 5 female deaths. Currently, it affects 44% of women in the United States (CDC). While the mortality rate for cardiovascular disease related mortality for men has been declining, the mortality rate for women has plateaued [1]. Additionally, the prevalence of cardiovascular disease in immune-mediated diseases is higher than the general population, and women are more likely to

be affected by immune-mediated diseases [2]. Furthermore, women are generally underrepresented in dyslipidemia and statin clinical trials, less likely to be prescribed guideline-recommended statin therapy, and are less likely to agree to and continue initial statin therapy [3].

Even with the greater risk in women, there are inadequate CVD primary prevention strategies despite use of the Atherosclerotic Cardiovascular Disease (ASCVD) 10-year risk score, which is recommended by the American College of Cardiology. The ASCVD risk score is a tool that uses sex, age, cholesterol, blood pressure, smoking and diabetes history to estimate a 10-year risk for coronary heart disease (CHD) event. The risk estimate is further broken down into low (<5%), borderline (5–7.5%), intermediate (7.5–20%), and high (>20%) CHD risk to further guide medical decision making and primary preventative care [4]. However, the ASCVD risk stratification may underestimate CVD risk in women, who often fall within the borderline and intermediate risk categories.

Furthermore, on top of uncertain ASCVD risk in women, the predictor does not currently incorporate chronic inflammatory diseases, which has been shown to increase CVD risk. Additionally, women are more likely to develop autoimmune diseases, differences which are theorized to be due to chromosomal and sex hormone differences in mediating the immune and inflammatory response when compared to males [5]. As a result, women with inflammatory diseases like autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) may be at increased CVD risk, which may go under-recognized with the current model. Therefore, this study will evaluate the relationship between autoimmune liver disease and CVD, a relationship that is nuanced given the liver's unique effects on the cardiovascular system.

In terms of general types of liver disease and CVD, metabolic dysfunction-associated steatotic liver disease (MASLD) and its relationship with CVD has been previously studied. Patients who are lean and have MASLD have significantly higher ASCVD risk than obese patients with or without MASLD [6]. Furthermore, MASLD was associated with increased risk of cardiovascular and cerebrovascular diseases [7,8]. When specifically studying women with MASLD, they had significantly greater odds of cardiovascular disease, atherosclerotic cardiovascular disease, or ASCVD over 7.5% compared to women without MASLD, demonstrating its strong effects on cardiovascular health.

Regarding autoimmune disease and its role in cardiovascular outcomes, so far in the literature, it has been associated with increased risk of CVD and may increase progressively with number of autoimmune diseases [9]. Specifically, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondylarthritis, vasculitis, and other connective-tissue autoimmune diseases have been linked with increased risk of atherosclerosis [10,11]. SLE also has higher rates of atherosclerosis detected by computed tomography (CT) scan at all age groups [12].

The theorized reason as to why autoimmunity has a strong relationship with CVD is that it is a strong driver of atherogenesis. The inflammatory state is a catalyst for immune, lipid, and endothelial dysfunction, making patients more susceptible to atherosclerosis [11,13]. The pro-inflammatory state causes dysregulation of homeostasis, which can result in excessive inflammation or immune system activation. More specifically, proinflammatory cytokines like interleukin-1, IL-6, and tumor necrosis factor-alpha may promote cell death, endothelial permeability, and production of acute-phase proteins, all of which contribute to atherosclerosis [5].

Diving specifically into autoimmune liver disease (AILD) pathologies, Persaud *et al.* found a decreased association between AIH and CVD [14]. Surprisingly, patients with PBC were found to be less likely to develop coronary artery disease (CAD), stroke, or acute coronary syndromes (ACS) compared to patients without PBC [15], and another study found that cardiac involvement was a rare PBC complication in a 14-year longitudinal study [16]. Similarly, a few studies have described no increased risk of CVD in patients with PBC and hypercholesterolemia, unless they have concomitant metabolic syndromes [17]. But this has been challenged by meta-analysis that identified a pooled risk of 1.57 [17–21]. PSC has been shown to have positive association with various types of cancer and all-cause mortality, but not CVD [22]. In contrast, another study by Ludvigsson *et al.* found that PSC was associated with non-ischemic CVD [23]. With varied outcomes in this field, more research is required to parse through the relationship between autoimmune liver disease and CVD risk.

When put together, women are greatly affected by both autoimmune conditions while being underestimated in ASCVD risk prediction scores. Hence, the ASCVD risk score may still underestimate risk particularly in women with autoimmune liver diseases (AILD) such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Since there appears to be no substantial literature on the cardiovascular risk on women with AILD compared to control groups, we want to investigate if women with AILD are at increased CVD risk compared to female and male controls.

Methods

We used TriNetX, an online database with millions of de-identified patient information and over 120 healthcare organizations. TriNetX, LLC meets the Health Insurance Portability and Accountability Act (HIPAA) Security Rule since it is certified to the ISO 27001:2013 standard. Therefore, healthcare data used in this study is protected as it uses only de-

identified patient records and was exempt from Institutional Review Board approval, as determined by TriNetX experts. For more information regarding TriNetX, please explore this link: (https://trinetx.com/).

We conducted a multi-center, retrospective cohort study of patients with AIH, PBC, and PSC from January 1999 to January 2019 from the United States. We compared female study cohorts to female control cohort, and female study cohort to male control cohort. Cohorts were defined based on coding from the International Classification of Diseases, 10th Revision (ICD-10), Logical Observation Identifiers Names and Codes (LOINC), Current Procedural Terminology (CPT), and RxNorm.

Study cohorts were females with respective AILD (AIH, PBC, or PSC) who also had diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia (HLD). Control cohorts were either female or male with DM, HTN, and HLD. Each AILD was explicitly excluded from control cohorts. Additionally, control cohorts had biologics (Certolizumab Pegol, Vedolizumab, Adalimumab, Infliximab, Ustekinumab, Tofacitinib, Natalizumab, Upadacitinib, Ozanimod), Immune modulators (Mesalamine, Azathioprine, Sulfasalazine, Mycophenolate Mofetil, Mercaptopurine, Methotrexate), steroids (Methylprednisolone, Dexamethasone, Prednisone, Budesonide), and autoimmune conditions (Psoriasis, Rheumatoid arthritis, and Systemic Lupus Erythematosus (SLE)) explicitly excluded. This was to limit the possibility of the control cohort having immune modulation via disease or medication.

Female study versus female/male control cohort were 1:1 propensity-score matched (PSM) for age, race, ethnicity, and additional ASCVD risk factors, including total cholesterol, HDL cholesterol, systolic blood pressure, hypertension treatment, tobacco use, and hemoglobin A1c.

The primary outcome was summative cardiovascular (CV) risk including unstable angina, acute myocardial infarction, and presence of coronary angioplasty implant, coronary artery bypass, percutaneous coronary intervention, and cerebral infarction. The incidence of CV risk was calculated via pair-wise cohort comparison for risk difference and hazard ratios through TriNetX.

Results

In general, the female control group had 541,187 patients, with an average age of 72.5 years old. The male control group had 607,737 patients with an average age of 71 years old.

AIH

Prior to PSM, we identified 1,820 patients in the AIH female study group, with an average age of 70.1 years old. 9.6% of the AIH female study group had a significantly greater personal history of nicotine dependence, in comparison to 2.4% in the female control group (P-value<0.0001).

For the AIH female study group versus female control group, after PSM, there were 1,790 patients in this specific analysis. Female patients with AIH had significantly greater summative CV risk (24.7% vs. 18.9%, P-value<0.0001) than the female control group as seen in **Table 1**.

When comparing the AIH female study group to the male control group, 1,790 patients were analyzed after PSM in this comparison. There was significantly greater history of nicotine usage in the female study group (9.6% vs. 3.8%, P-value<0.0001). When looking at the composite outcome, there was no significant difference in CV risk (24.7% vs. 22.4%, P-value=0.10) between the two cohorts as seen in **Table 2**.

PBC

Before matching, the PBC Female study group had 1,647 patients with an average age of 71.7 years old. When comparing the PBC female study versus female control group, there were 1,599 patients after PSM. The female study group had

Table 1. Cardiovascular risk comparison for female study vs. female control groups.

Outcome of Interest	Female Study Group	Female Control Group	P-Value*
AIH			
Summative CV Risk	24.7%	18.9%	<0.0001
PBC			
Summative CV Risk	24.9%	18.4%	<0.0001
PSC			
Summative CV Risk	26.4%	20.7%	0.26

*P-value<0.05 considered significant

*AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis

Table 2. Cardiovascular risk comparison for female study vs. male control cohorts.

Outcome of Interest	Female Study Group	Male Control Group	P-Value*
AIH			
Summative CV Risk	24.7%	22.4%	0.10
PBC			
Summative CV Risk	24.9%	23.9%	0.53
PSC			
Summative CV Risk	26.2%	17.7%	0.08

*P-value<0.05 considered significant

*AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis

significantly greater history of nicotine usage (9.9% vs. 2.4%, P-value<0.0001). PBC patients had significantly greater CV risk (24.9% vs. 18.4%, P-value<0.0001) than the control group. For the PBC female study versus male control comparison, there were 1,601 patients in the analysis after matching. Regarding prior smoking history, the female study group had significantly greater smoking history (9.9% vs. 3.8%, P<0.0001). There was no difference in CV outcomes (24.9% vs. 23.9%, P-value=0.53).

PSC

The PSC female study group had 142 patients prior to PSM with an average age of 67.6 years old. In the PSC female study versus female control comparison, 140 patients remained in this specific analysis after matching. For smoking history, there was significantly greater history in the female study group (9.9% vs. 2.4%, P-value<0.0001). There was no significant difference in CV risk between cohorts (26.4% vs. 20.7%, P-value=0.26). In comparing the PSC female study versus the male control groups, 141 patients were analyzed after matching. There was significantly greater smoking history in the female study group (9.9% vs. 3.8%, P-value=0.0001). Regarding overall outcomes, there was no significant difference between these two cohorts in terms of CV risk (26.2% vs. 17.7%, P-value=0.08).

Discussion

Overall, there is some elevated risk of poor CV outcomes in female patients with AILD as reflected in elevated CV risk compared to female control cohorts and similar CV risk compared to male control cohorts. In this study, the female AIH cohort had significantly greater CV risk compared to female control groups and no difference in CV risk compared to the male control cohort. In PBC, there were similar results where female study group had significantly greater CV risk compared to the female control group and similar CV risk compared to the male control group. In PSC, there were no significant difference in CV risk in both comparisons with female control and male control cohorts, thought to be potentially from smaller cohort size. Overall, there was no difference in CV risk in females with AILD compared to male controls, which shows how females with inflammatory liver disease lose CV protection conferred by female sex.

Based on these results, clinicians may not be addressing a vulnerable patient population based on the traditional ASCVD risk calculator, which underestimates the CVD risk in these patients. These are relatively uncommon diseases, which make large-scale prospective studies difficult to coordinate. Additionally, inflammatory disease phenotypes are all varied in presentation and time of diagnosis. Furthermore, atherosclerotic plaque must be calcified to actually be detected on CT scan, for which some may be undetectable especially in the younger patient population with autoimmune disease. Other barriers to appropriate treatment also pertain to provider hesitancy in prescribing statin medications to women with chronic liver disease. Given the increased risk in the AIH and PBC population, it may be beneficial to consider coronary artery calcium or breast arterial calcification scoring even if patients have low risk based on the traditional ASCVD risk stratification.

Limitations of this study include coding inconsistencies between health care organizations, which could affect the size and accuracy of the study cohorts. Additionally, there was no controlling for other concomitant active diseases within unique patients, although we did control for major, common autoimmune diseases and contributing exposure history. Finally, there are inherent differences in coding for patient diagnoses and lab testing based on individual providers.

This project lays the foundation for future research projects in terms of tailoring unique patient ASCVD risk as an indicator for medical therapy or further screening with coronary artery calcium or breast arterial calcification scoring, if that is proven to be an effective screening method in this population. We hope that patients, specifically females, with autoimmune liver disease are better captured and monitored for cardiovascular

risk. However, this will require not only early recognition of increased CVD risk, but also interdisciplinary collaboration between primary care, hepatology, and cardiology for holistic care—including weight loss, lipid and blood pressure management, and lifestyle modifications.

Abbreviations

AILD: Autoimmune Liver Disease; ASCVD: Atherosclerotic Cardiovascular Disease; CVD: Cardiovascular Disease; CV: Cardiovascular; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis; AIH: Autoimmune Hepatitis; HTN: Hypertension; DM: Diabetes Mellitus; SLE: Systemic Lupus Erythematosus

Author Contributions

JZ: Data analysis, manuscript writing, and project conception.

RR: Data analysis, manuscript writing, and project conception.

TT: Data analysis and project conception.

DH: Manuscript writing and project conception.

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Disclosure statement

Authors have no disclosures. No funding was used for this study.

Conflicts of interest

None. No ethics approval or patient consent required for this study.

Data availability

TriNetX data is limited to use on the platform.

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