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Association of Autoimmune Hepatitis and Cardiovascular Disease

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ABSTRACT

Background: Autoimmune Hepatitis is a chronic liver disease while Cardiovascular Disease is seen in inflammatory states. This study sought to determine if Cardiovascular Disease was associated with Autoimmune Hepatitis.
Methods: The National Inpatient Sample selected patients with a primary diagnosis of Autoimmune Hepatitis and secondary diagnosis of Cardiovascular Disease in 2014. The primary outcome was the association of Autoimmune Hepatitis with Cardiovascular Disease. Secondary outcomes evaluated the hospital burden with Cardiovascular Disease.
Results: 16,375 patients with Autoimmune Hepatitis were included in the study. There was a decreased association between Autoimmune Hepatitis and Cardiovascular Disease (aOR 0.77, 95% CI 0.69–0.85, p < 0.00), Coronary Artery Disease, (aOR 0.75, 95% CI 0.67–0.85, p < 0.00), and Peripheral Vascular Disease (aOR 0.75, 95% CI 0.60–0.93, p = 0.01). Moreover, Coronary Artery Disease comprises 84% of the overall Cardiovascular Disease cohort and did not demonstrate significantly increased length of stay (aOR −0.53, 95% CI −1.16 to 0.12, p = 0.11) or hospitalization cost (aOR −6711, 95% CI −14336 to 912, p = 0.08).
Discussion: The decreased association between Autoimmune Hepatitis and Cardiovascular Disease is likely multifactorial in etiology. Consequently, this observation requires further examination with prospective trials.

1. Introduction

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver which leads to increased morbidity and mortality. Based on European studies, the incidence of AIH can reach up to 2 per 100,000 persons per year [1,2]. The disease is known to affect females more often than males, with a 4:1 predominance in type 1 AIH and a 10:1 predominance in type 2 AIH [1–4]. While there appears to be a gender preference, AIH can develop at any age without a known ethnic predilection [4,5]. Moreover, patients also have a variable presentation, ranging from asymptomatic to acute liver failure or cirrhosis [5,6].

Autoimmune Hepatitis is a T cell-mediated disease, with linkage to Human Leukocyte Antigen (HLA) II genes [7], specifically HLA-DR3, HLA-DR4, and *DRB1*1501* [8,9]. Studies have shown both a quantitative and qualitative failure of T regulatory cells (Treg) to adequately control intrahepatic inflammation [10]. Unfortunately, most T cell antigens and triggering environmental events are not known. However, AIH is associated with several antibodies, with targets including ribonucleoprotein, filamentous actin, and cytochrome P450 2D6 [11].

A few additional theories of AIH inflammation includes increased activation of the T-helper cell 17 pathway (Th17), with higher levels of Interleukin-17, Interleukin-23, and Th17 measured in the liver and serum [12,13]. A prevalent hypothesis is that molecular mimicry is involved via similar amino acid sequences [14], which elicit a greater T cell reaction than true identity [15]. It is further asserted that auto-reactive immune cells are stimulated by molecular mimicry and "bystander activation" [16]. Lastly, multiple viruses have also been associated with this immune process, including Cytomegalovirus, Epstein Barr Virus, Varicella Zoster Virus, Hepatitis A Virus, and Hepatitis B Virus [6,17].

An equally integral component of this work involves Cardiovascular disease (CVD), which is highly prevalent and is the leading cause of death in most of the developed world [18]. In the INTERHEART study, potentially modifiable risk factors including smoking, hypertension, obesity, diabetes mellitus type 2, and regular alcohol consumption accounted for more than 90% of the population's

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risk for myocardial infarction [19]. Moreover, it has been well studied that the pathogenesis of atherosclerosis involves endothelial dysfunction which leads to smooth muscle proliferation, lipid accumulation, inflammation, and subsequent plaque formation [19–24].

As inflammation is a key component in the development of CVD and atherosclerosis, many studies have demonstrated an increased incidence of CVD in patients with autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [25,26]. The greater amounts of cytokines such as Tumor Necrosis Factor alpha, Interleukin-1, and Interleukin-8 are released in autoimmune conditions which contributes to an excessive inflammatory response [27]. This initially results in endothelial dysfunction, impaired nitric oxide production, and decreased smooth muscle relaxation, later leading to intimal thickening and arterial stiffening [28]. Furthermore, biologic therapy has decreased inflammation and the ensuing arterial wall stiffness [29], thus bolstering the pivotal role of the inflammatory process in CVD.

Notably, a systematic review revealed that patients with SLE had two times the risk of developing CVD, as compared to the general population [30]. In fact, after adjusting for classic risk factors, RA is considered by some to be an independent cardiovascular risk factor [31]. Although other rheumatologic diseases have been linked with CVD, a thorough review of the literature (Cochrane Review, Pubmed Central, ResearchGate, WorldWideScience, Science.gov., Rutgers University Library, Google Scholar) reveals that this topic has not been previously investigated with regard to Autoimmune Hepatitis. This nationwide study was conducted to determine if there is an association between Autoimmune Hepatitis and the manifestations of Cardiovascular Disease.

2. Methods

2.1. Data source

The National Inpatient Sample (NIS) represents 20% of all non-federal hospitals in the United States. This large database was queried for demographic information in the Autoimmune Hepatitis population using the International Classification of Diseases-Ninth Edition Revision- Clinical Modification (ICD-9 CM). The NIS is a product of the Agency for Healthcare Research and Quality and contains patient information which has been de-identified. This is a nationally representative subset acquired through hospital discharge records and the largest in-patient database currently available in the United States. While a proportion of the national population has been sampled, yearly sampling weights are applied which then provide national estimates [32]. A multitude of works have verified the value of this sampling tool and thus it has been utilized for this study.

2.2. Study design and inclusion criteria

This is a Cross-Sectional Study and includes all patients ≥18 years old with a primary diagnosis of Autoimmune Hepatitis in 2014. The ICD-9 CM code used was 571.42. The database was then queried to include all patients with a secondary diagnosis of Coronary Artery Disease (41400, 41401, 41402, 41403, 41404, 41405, 41406, 41407, 412, V4582, V4581, 22731, 4109), Cerebrovascular Accident (43491), and Peripheral Vascular Disease (4330, 4431, 4432, 4438, 4439). Patients included in the study were required to have a primary diagnosis of AIH with a secondary diagnosis of any of the above mentioned forms of Cardiovascular Disease. Primary outcomes were the associations between AIH and Cardiovascular Disease, Coronary Artery Disease, Peripheral Vascular Disease, and Cerebrovascular Accident. Secondary outcome measures included mortality, cost of hospitalization, and length of stay. Various patient demographics (age, race, sex, income, and insurance status), comorbidities, and hospital characteristics (region and size) were obtained. The severity of the co-morbidities was analyzed via the Deyo modification of the Charlson Comorbidity Index. This index measures 17 common medical conditions and assigns different weights to compile a score from 0 to 33 which correlates with overall severity of illness.

2.3. Statistical analysis

Stata IC version 13 (StataCorp. LP, College Station, Texas) was used for all statistical analyses. Specifically, the svy suite of commands was the extension package that was utilized. Categorical variables were analyzed with the X^2 test, while continuous variables were analyzed with the adjusted Wald's Test. Hypothesis testing was 2-sided. A multivariate logistic regression model was designed to investigate the association between AIH and CVD, Coronary Artery Disease, Cerebrovascular Disease, and Peripheral Vascular Disease. The hierarchal model included both hospital level characteristics (hospital teaching status, bed size, region) as well as patient level characteristics (age, race, sex, comorbidities), and the Charlson Comorbidity Index. To eliminate the effect of confounders, this was the primary means by which adjustments were made in the data for patient and hospital-level characteristics. Univariate analysis was first conducted on all of the above factors and co-morbidities that could affect Autoimmune Hepatitis hospitalization. Age, sex, race, Charlson Co-Morbidity Index, Congestive Heart Failure, End-Stage Renal Disease, Liver Disease, Complicated Diabetes Mellitus, and Hypertension were included in the multivariate logistic regression model as $p < 0.05$, indicating statistical significance on univariate analysis.

2.4. Ethical considerations

The data in the National Inpatient Sample is publicly available, and as a retrospective study, no patients were actively involved in the data collection process. Thus, it was not subject to Institutional Review Board approval and informed consent was not needed [33].

3. Results

In this study, we investigated the association between AIH and various forms of cardiovascular disease. There were a total of 16,375 patients, 15.5% of which had Cardiovascular Disease, as shown in Table 1. Those with CVD were older in age (68.9 ± 0.67 years vs. 55.3 ± 0.42 years, $p < 0.000$), predominantly male (89% vs. 31%, $p < 0.00$), with a Caucasian prevalence (76.6% vs. 63.2%, $p < 0.00$). Most co-morbidities were seen to a greater extent in the CVD population and include Chronic Liver Disease (91% vs. 83%, $p < 0.00$), Hypertension (70% vs. 44%, $p < 0.00$), Chronic Obstructive Pulmonary Disease (28% vs. 15%, $p < 0.00$), End Stage Renal Disease (22% vs. 12%, $p < 0.00$), Congestive Heart Failure, and Diabetes Mellitus type 2. Moreover, roughly 75% of the CVD cohort possesses a Charlson Index score of 3, while 25% of the non-CVD cohort had a Charlson Index score of 3. Hospital characteristics (region, size), insurance status, and income were not markedly different among the populations. Of note, Chronic Liver Disease includes Chronic Hepatitis B, Chronic Hepatitis C, Alcoholic Fatty Liver Disease, Alcoholic Cirrhosis, Cirrhosis (without mention of alcohol), and Chronic Non-Alcoholic Liver Disease.

For the measures of hospital admission, there was a similar mortality rate between the CVD cohort and those without CVD (3.34% vs. 3.90%). Moreover, there was no statistically significant difference in hospitalization burden observed with CVD as compared to those without CVD in terms of length of stay (6.29 ± 0.27 days vs.

Table 1
Baseline characteristics of patients with autoimmune hepatitis.

Variable	AIH with CVD	AIH without CVD	P value
	n = 2,530	n = 13, 845	
Age (SEM)	68.9 ± 0.67	55.3 ± 0.42	<0.000
Female	279 (11)	9553 (69)	<0.000
Race			<0.000
Caucasian	(76.6)	8754 (63.2)	
Black	286 (11.3)	(16.4)	
Hispanic	217 (8.56)	(14.1)	
Asian	53 (2.09)	311 (2.25)	
Native American	6 (0.21)	116 (0.84)	
Other	30 (1.25)	443 (3.2)	
COPD	709 (28)	2077 (15)	<0.000
ESRD	557 (22)	1661 (12)	<0.000
CHF	582 (23)	831 (6)	<0.000
Liver disease[a]	2,303 (91)	(83)	<0.000
HTN	1,771 (70)	6092 (44)	<0.000
DM2	304 (12)	692 (5)	<0.000
CCI			<0.000
1	200 (7.91)	3337 (24.1)	
2	430 (17)	2561 (18.5)	
3	1900 (75.1)	7947 (57.4)	
Hospital Region			0.13
Northeast	395 (15.6)	2680 (19.4)	
Midwest	785 (31)	3141 (22.7)	
South	919 (36.3)	5405 (39)	
West	431 (17)	2619(19)	

Values are No. (%) except for age (mean + standard error mean); COPD-chronic obstructive pulmonary disease; ESRD = End stage renal disease; CHF = Congestive heart failure; HTN = Hypertension; DMcx = Complicated diabetes mellitus type 2; CCI = Charlson Co-Morbidity Index.

[a] Includes: Chronic Viral Hepatitis B With Hepatitis Delta, Chronic Viral Hepatitis B Without Hepatitis Delta, Chronic Hepatitis C, Alcoholic Fatty Liver Disease, Alcoholic Cirrhosis, Alcoholic Liver Damage Unspecified, Chronic Hepatitis, Chronic Persistent Hepatitis, Cirrhosis Without Mention Of Alcohol, Biliary Cirrhosis, Other Chronic Non-Alcoholic Liver Disease, Unspecified Chronic Liver Disease Without Mention Of Alcohol.

Table 2
Hospital admission measures.

Outcome	AIH with CVD	AIH without CVD	P value
Died (%)	85 (3.34)	540 (3.9)	
Mean LOS (SEM)	6.29 ± 0.27	5.76 ± 0.13	0.08
Cost of admission (SEM)	$58,786 ± $3482	$55,523 ± $1970	0.39

Variables are n (%) and mean ± SE; AIH = Autoimmune Hepatitis; CVD = Cardiovascular Disease; LOS = of stay.

5.76 ± 0.13 days, p = 0.077) and cost of hospitalization ($58,786 ± $ 3482 vs. $55,523 ± $1970, p = 0.39) (Table 2).

Logistic regression was later utilized to measure association between the populations. Univariate analysis revealed age, sex, race, Charlson Co-Morbidity Index, Congestive Heart Failure, End-Stage Renal Disease, Liver Disease, Complicated Diabetes Mellitus, and Hypertension to have a significance <0.05, so these variables were included in the multivariate logistic regression model to account for confounding. The association that exists between AIH and the various forms of Cardiovascular Disease was then analyzed. There was a decreased association noted in CVD (OR 0.82, 95% CI 0.74–0.91, p < 0.00; aOR 0.77, 95% CI 0.69–0.85, p < 0.00), Coronary Artery Disease (OR 0.76, 95% CI 0.68–0.85, p < 0.00; aOR 0.75, 95% CI 0.67–0.85, p < 0.00), and Peripheral Vascular Disease (OR 1.00, 95% CI 0.81–1.23, p = 0.98; aOR 0.75, 95% CI 0.60–0.93, p < 0.01), as seen in Table 3.

A sub- analysis was conducted with the aforementioned types of Cardiovascular Disease to examine the impact on AIH hospitalization. As Coronary Artery Disease comprises 84% of the CVD cohort, these figures were the most meaningful. Both hospitalization cost (OR −1438, 95% CI −8411 to 5534, p = 0.69; aOR −6711, 95% CI −14336 to 912) and length of stay (OR 0.19, 95% CI −0.36 to 0.75, p = 0.49; aOR −0.53, 95% CI −1.16 to 0.12, p = 0.11) demonstrated no significant difference, compared to those without Coronary Artery Disease. There was also a decreased association between AIH and death in this cohort (OR 0.77, 95% CI 0.43– 1.40 p = 0.40; aOR 0.43, 95% CI 0.24–0.80, p = 0.01) (Table 4). Moreover, while there was an increased association between hospitalization cost and Cerebrovascular Accident (OR 68731, 95% CI 8294–129169, p = 0.03; aOR 64116, 95% CI 3369–12,4862, p = 0.04), this group constitutes only 6% of the CVD population.

Lastly, baseline co-morbidities in this AIH population were assessed for association with CVD. The majority of risk factors had a positive association with CVD including Complicated Diabetes Mellitus Type 2, Hypertension, and Liver Disease. The largest influence was Congestive Heart Failure (OR 4.85, 95% CI 3.72–6.32, p < 0.00; aOR 2.83, 95% CI 2.13–3.76, p < 0.00), Hyperlipidemia (OR 3.80, 95% CI 3.09–4.68, p < 0.00; aOR 2.66, 95% CI 2.12–3.33, p <), and Smoking (OR 1.95, 95% CI 1.59–2.40, p < 0.00; aOR 2.22, 95% CI 1.77–2.77 p < 0.00). Interestingly, there was no significant association between AIH and End Stage Renal Disease (Table 5). Lastly, although Congestive Heart Failure (CHF) is a risk factor for CVD, Coronary Artery Disease itself has been studied as an important cause of CHF in recent years [34]. Prevalence of Coronary Artery Disease leading to CHF is estimated as high as 40% by some sources [34,35] and a National Health and Nutrition Examination Survey (NHANES) analysis recently found it to be a risk factor in 62% of patients with CHF [36].

4. Discussion

Using the National Inpatient Sample, this study examined Autoimmune Hepatitis to identify the association with various forms of Cardiovascular Disease. The major findings include a decreased association of AIH with both CVD and Peripheral Vascular Disease and a non-significant association with Cerebrovascular Accident.

Our analyses revealed a decreased association between AIH and Cardiovascular Disease (aOR 0.77, 95% CI 0.69–0.85, p < 0.00), Coronary Artery Disease (aOR 0.75, 95% CI 0.67–0.85, p < 0.00), and Peripheral Vascular Disease (aOR 0.75, 95% CI 0.60–0.93, p = 0.01) after adjusting for co-morbidities (Table 3). A possible explanation for this recent trend is the American Association for the Study of Liver Disease's alteration of their guideline in 2010 for the management of AIH. There was a transition towards more aggressive management with combined immunosuppressive regimens. Over the last few years, mycophenolate mofetil, tacrolimus, infliximab, and 6-mercaptopurine have been utilized with subsequent normalization of transaminases and decrease in IgG levels in several

Table 3
Association between Autoimmune Hepatitis and Cardiovascular Disease.

Condition	Proportion of AIH	Unadjusted Odds Ratio	95% CI	P value	Adjusted Odds Ratio	95% CI	P value
CVD	15.45%	0.82	0.74– 0.91	<0.00	0.77	0.69 to 0.85	<0.00
CAD	12.95%	0.76	0.68– 0.85	<0.00	0.75	0.67– 0.85	<0.00
CVA	0.94%	0.86	0.61– 1.22	0.41	0.72	0.50 to 1.03	0.08
PVD	3.02%	1.00	0.81– 1.23	0.98	0.75	0.60 to 0.93	0.01

CVD = Cardiovascular Disease; CAD = Coronary Artery Disease; CVA = Cerebrovascular Accident; PVD = Peripheral Vascular Disease; CI = Confidence Interval.

Table 4
Effect of various forms of Cardiovascular Disease on autoimmune hepatitis hospitalization.

Outcome	Unadjusted Odds Ratio	95% CI	P value	Adjusted Odds Ratio	95% CI	P value
Died[a]	0.77	0.43–1.40	0.40	0.43	0.24 to 0.80	0.01
LOS (days)[a]	0.19	−0.36 to 0.75	0.49	−0.53	−1.16 to 0.12	0.11
Hospitalization cost[a]		−8411 to 5534	0.69	−6711	− to 912	0.08
Died[b]	0.51	0.13 to 2.07	0.35	0.37	0.09– 1.49	0.16
LOS (days)[b]	0.92	−0.18 to 2.03	0.10	0.38	−0.81 to 1.56	0.53
Hospitalization Cost[b]	4330	−8743 to 17403	0.52	−395	− to 13337	0.96
Died[c]	2.74	0.81 to 9.31	0.11	1.89	0.52– 6.88	0.33
LOS (days)[c]	2.89	−0.60 to 6.39	0.11	2.60	−0.95 to 6.15	0.15
Hospitalization Cost[c]	68731	8294 to	0.03	64116	3369–	0.04

[a] Coronary artery disease.
[b] PVD = Peripheral vascular disease.
[c] CVA = Cerebrovascular accident; LOS =of Stay; CI = Confidence interval.

Table 5
Risk factors for Cardiovascular Disease in the autoimmune hepatitis population.

Variable	Unadjusted Odds Ratio	95% CI	P value	Adjusted Odds Ratio	95% CI	P value
ESRD	2.12	1.64– 2.76	<0.000	1.22	0.92– 1.60	0.17
Liver Disease	2.10	1.49– 2.95	<0.000	1.98	1.37– 2.84	<0.000
CHF	4.85	3.72– 6.32	<0.000	2.83	2.13– 3.76	<0.000
Obesity	1.25	0.96– 1.64	0.10	1.36	1.02– 1.82	0.04
HTN	3.00	2.42– 3.73	<0.000	1.99	1.58 to 2.51	<0.000
DMcx	2.67	1.89– 3.78	<0.000	2.15	1.48– 3.11	<0.000
Smoking	1.95	1.59– 2.40	<0.000	2.22	1.77– 2.77	<0.000
HLD	3.80	3.09– 4.68	<0.000	2.66	2.12– 3.33	<0.000
Age	1.05	1.04 to 1.06	<0.000	1.05	1.04– 1.05	<0.000
Female sex	0.55	0.44– 0.69	<0.000	0.43	0.33– 0.55	<0.000

ESRD = End Stage Renal Disease; CHF = Congestive Heart Failure; HTN= Hypertension; DMcx = Complicated Diabetes Mellitus; HLD= Hyperlipidemia; CI = Confidence Interval.

studies [37–42]. This may have altered the inflammatory milieu in AIH, but the argument that it has decreased subsequent atherosclerosis is a concept for which further examination is necessary.

Although there was a decreased association between AIH and CVD in this study, some individuals did possess Coronary Artery Disease or Peripheral Vascular Disease. This likely occurred as a result of harboring the associated cardiac risk factors, as they are common co-morbidities in the United States. Indeed, patients in this study with CVD had a greater prevalence of cardiovascular-related co-morbidities as well as greater overall morbidity (75% Charlson Index score 3 with CVD vs 25% Charlson Index score 3 without CVD), as seen in Table 1. Moreover, on multivariate logistic regression, Diabetes Mellitus Type 2, Hypertension, Obesity, Smoking, Liver Disease, and Congestive Heart Failure were all found to be independent risk factors for Cardiovascular Disease, shown in Table 5. The demographic most affected by CVD was the older Caucasian male, which supports the notion that in this population, CVD is likely due to an accumulation of cardiac risk factors.

Interestingly, mortality was similar between those with and without Cardiovascular Disease (3.34% vs. 3.9%, Table 2) and there was a decreased risk of mortality on multivariate analysis (aOR 0.43, 95% CI 0.24–0.80, p = 0.01), shown in Table 4. This unusual observation has also been documented in previous studies [43,44]. Moreover, length of stay (6.29 ± 0.27 days in CVD vs. 5.76 ± 0.13 days without CVD, p = 0.08) and cost of hospitalization ($58,786 ± $ 3482 in CVD vs. $55,523 ± $1970, p = 0.39) were also comparable between the AIH cohorts (Table 2). A plausible explanation for the above findings is that while those who have Cardiovascular Disease carry a high burden of illness, it is of a chronic nature and does not acutely increase risk of mortality or decompensation.

The patients included in this particular cohort exhibit decreased rates of Cardiovascular Disease. Moreover, the patients included in this cohort were all ≥18 years old, with mean age between 55–68 years old. These are characteristics more consistent with Type 1 AIH, which has a global presence and is known to be more responsive to therapeutic agents. Type 2 AIH typically occurs at a younger age and is more prevalent in Europe than the United States [45]. Type 2 AIH been linked to HLA DR7 (subtype DRB10701) which represents a more progressive form of disease, conferring a poorer prognosis [7,30]. Furthermore, the second subtype of AIH historically has a diminished response to immunomodulators, thus the propensity towards Cardiovascular Disease may differ from AIH type 1. If the cohort used for this work was primarily Type 1 AIH who derived more of a benefit from medications, this may also partially explain why there is a decreased association with Cardiovascular Disease.

Lastly, after review of this work, it appears that a clinical entity is similar to the scenario described above. Cirrhotic cardiomyopathy is characterized by cardiac dysfunction [46–49] due to systemic and splanchnic vasodilatation in advancing cirrhosis [50]. Analyses showed a correlation between severity of liver decompensation and cardiac disease [51], with increased inflammation thought to be involved in the latter process [50]. Indeed, cytokine release affects myocyte contractility, extracellular matrix, and myocardial remodeling [52,53]. If an AIH patient with cirrhosis were to develop cirrhotic cardiomyopathy, it would illustrate how this NIS study may manifest in a real-world setting. Our work is broad in scope and revealed an interesting finding, however, additional trials should be conducted to determine more practical applications of this study and how hospital measures differ under the varied conditions.

The National Inpatient Sample has several strengths and limitations that warrant consideration. With health-related information from 20% of non-federal hospitals, NIS has amassed a database that enables the study of uncommon conditions (including AIH). These sample sizes are typically larger than hospital funded studies, thus the trends observed are difficult to dispute and provide a national overview of disease. However, NIS is an administrative database which is susceptible to coding inaccuracies [32]. As laboratory values and imaging are not available, verification of the aforementioned conditions is not possible with this database. So while AIH type 1 cannot be verified by serology or genotype studies, epidemiology and clinical characteristics suggest that this is predominant

subtype in this AIH cohort. Furthermore, while multivariate logistic regression did account for a multitude of confounders (listed in the methods), there is a possibility that residual confounding still exists. Finally, as the NIS does not allow for prospective studies, determination of risk factors is not possible with this database. While decreased association between AIH and CVD identified by NIS is a meaningful outcome, the explanations offered in this work are theoretical ideas and will require controlled, prospective studies.

In this large, cross-sectional work, AIH was examined in the adult population to determine the association with Cardiovascular Disease. Those with CVD possessed more comorbidities and greater Charlson Co-Morbidity Index, which contributes to the atherosclerotic disease. CVD in this population is of a stable, chronic nature, explaining the comparable mortality and hospitalization burden between those with and without CVD. Moreover, the decreased association between Coronary Artery Disease, Peripheral Vascular Disease, Cardiovascular Disease, and AIH is likely multifactorial in etiology. As a result, future investigation will assist in gaining a greater understanding of the cause and clinical application of these findings.

Conflict of interest

The authors have no conflicts of interest to disclose.

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support required.

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