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Azathioprine on Risk of Extrahepatic Malignancy in Patients with Autoimmune Hepatitis : A Nationwide Claims Study in South Korea

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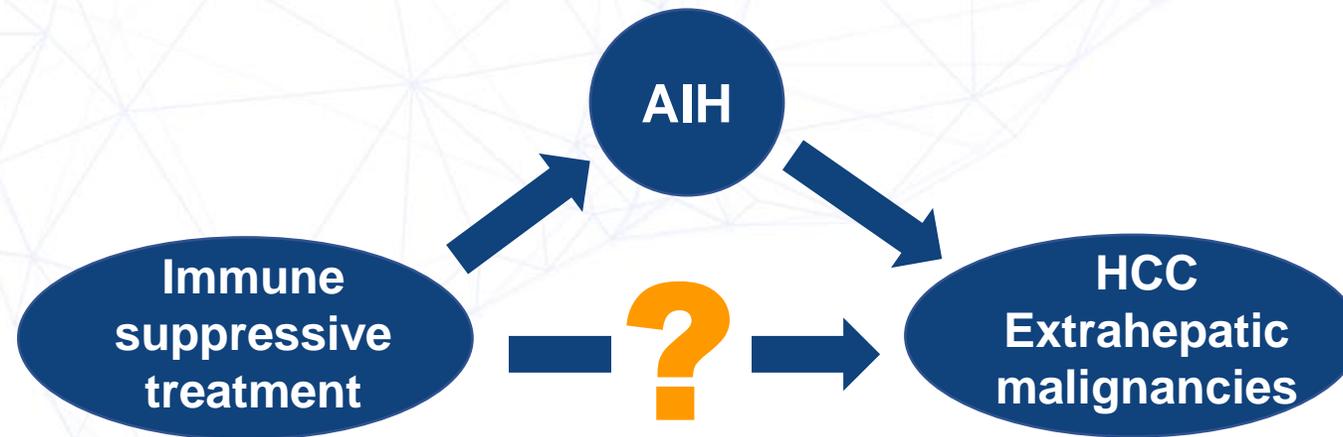
Backgrounds

Autoimmune hepatitis (AIH)

: chronic inflammation of liver parenchymal

→ Long term immune suppressive therapy

→ Liver cirrhosis, hepatocellular carcinoma, death



Is *immunosuppressive therapy* a **risk factor** of *HCC and extrahepatic cancers*?

Backgrounds

Is *immunosuppressive therapy* a **risk factor** of *any cancers*?

YES

- Immunosuppressive therapy is a risk factor of HCC
- Patients with AIH has increased risk of HCC and extracellular cancer, associated with duration of azathioprine and non steroid immunosuppressive treatments
- Incidence of non melanoma skin cancer are increased in patients with azathioprine treatments for AIH

NO

- There is no association between azathioprine treatment and HCC development
- Prednisolone and immunosuppressive therapy is not a risk factor of HCC

Aims

Small researches of the association between AIH patients with immunosuppressive therapy and any cancer risks

The risk of **extrahepatic malignancy** is unknown in **Korean AIH patients**

The impact of azathioprine (AZT) treatment on extrahepatic malignancy risks in Korean AIH patients

Methods

DATA : national claims data of the Health Insurance Review and Assessment Service (HIRA)

Index date : 180days after AIH diagnosed

Azathioprine treatment : patient's treated AZT continuously

Continuous : re-treated within 30 days

Discontinuous : stopped more than 30 days

Follow up period

Start : index date

End : cancer(HCC and extrahepatic malignancy), death, 2020/12/31,

controls who treated of AZT, patients who discontinue AZT more than 30 days

Methods

Patients with AIH (K75.4 and V175) 2008~2020 : 8,280

- Excluded any cancer, death before index date, AIH diagnosed before research period
- Excluded patients who didn't matched patients or controls (ex, patient who didn't have azathioprine at index date)

Patients who have AIH with azathioprine(AZT)

- Have treated with AZT at index date within 180days after AIH diagnosis : 3,059

Controls who AIH without AZT

- Have not treated with AZT within 180 days after AIH diagnosis : 5,221

Methods

Confounder

- DM : At least 2 visits within 1 year from the start of observation
- Cirrhosis : At least 2 visits within 1 year from the start of observation
- Steroid : Treatments more than 90 days within 1 year from the start of observation

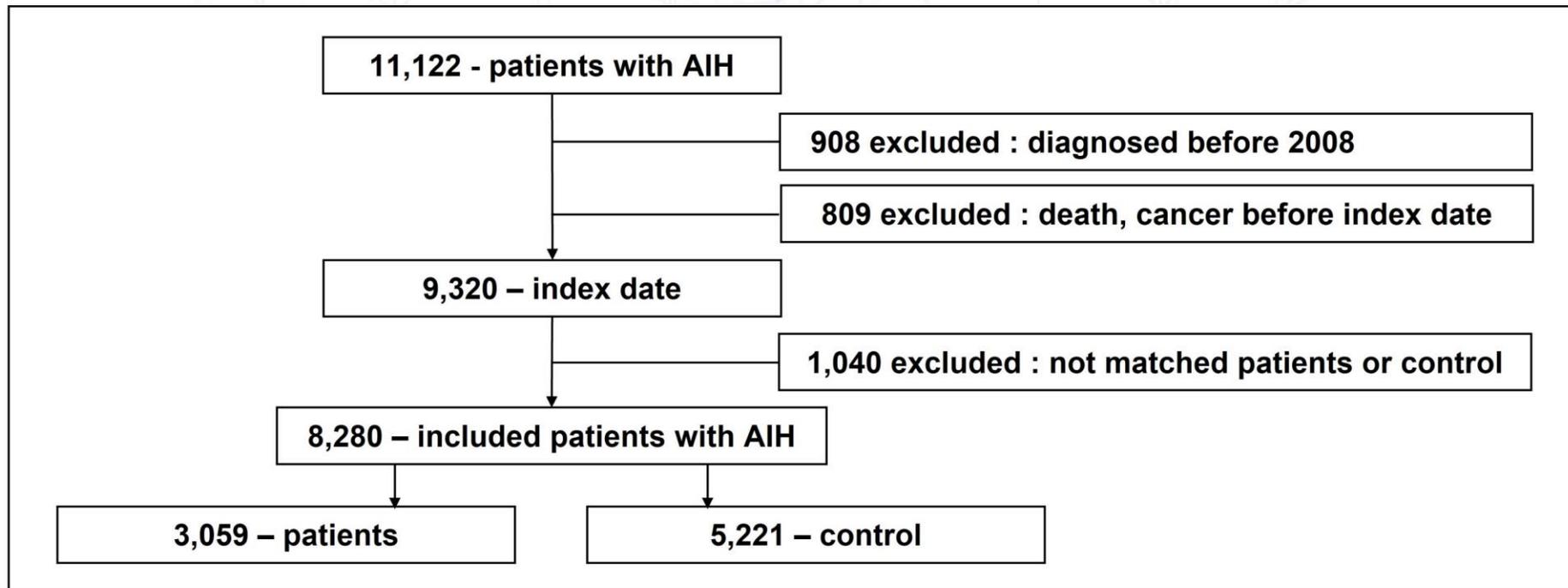


Figure 1. AIH patients flowchart

Results

Table 1. Characteristics of patients and controls

		Total N = 8,280		Patient N = 3,059		Control N = 5,221		P-value
Age		56.7+13.5		57.2+12.6		56.5+14.0		0.011
	18-64	5,811	70.2%	2,150	70.3%	3,661	70.1%	0.881
	65-90	2,469	29.8%	909	29.7%	1,560	29.9%	
Sex	male	1,299	15.7%	483	15.8%	816	15.6%	0.851
	female	6,981	84.3%	2,576	84.2%	4,405	84.4%	
Comorbidity	DM	2,418	29.2%	957	31.3%	1,461	28.0%	0.001
	LC	3,131	37.8%	1,102	36.0%	2,029	38.9%	0.010
Steroid		4,180	50.5%	2,614	85.5%	1,566	30.0%	<0.001
Follow-up	(month)	49.8+43.1		28.8+27.6		62.1+45.8		<0.001

Table 1. Characteristics of patients and controls

Among 8,280 patients, the mean age was 56.7 ± 13.5 years, 84.3% were women, and the follow-up period was 49.8 ± 43.1 months. The mean age and sex are not different between patients treated with and without AZT. However, the number of patients with diabetes was higher in patients treated with AZT (31.3% vs. 28.0%). The number of patients with liver cirrhosis was higher in patients treated without AZT (36.0% vs. 38.9%). At the time of diagnosis, 85.5% of patients with AZT and 30.0% of patients without AZT were treated with steroids for more than 90 days ($P < 0.001$)

Results

Table 2. Cancer risks for patients with AZT and without AZT in AIH

		Total N = 8,280	Patient N = 3,059	Control N = 5,221	P-value
All cancer	cancer	433	100	333	
	person-year	34,381	7,349	27,032	
	Incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.08(0.86-1.36)	ref	0.530
	adj HR		1.14(0.87-1.49)	ref	0.347
HCC	cancer	139	33	106	
	incidence(/100 py)	0.40(0.34-0.48)	0.45(0.31-0.63)	0.39(0.32-0.47)	
	crude HR		1.11(0.74-1.66)	ref	0.603
	adj HR		1.25(0.78-2.01)	ref	0.351
Non-HCC	cancer	294	67	227	
	incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.06(0.80-1.40)	ref	0.685
	adj HR		1.09(0.79-1.51)	ref	0.600

Table 2. Cancer risks for patients with azathioprine and without azathioprine in AIH

The incidence of extrahepatic malignancy was 1.36 and 1.23 per 100 person-years in the patients treated with AZT and without AZT, respectively (P=0.685). After we adjusted for confounding by age, sex, diabetes, and liver cirrhosis, the HR(Hazard ratio) was 1.09 (95% confidence interval 0.79–1.51, P=0.600).

Conclusion

The national claims data of HIRA **not show** that **AZT significantly increases the risk of extrahepatic malignancy among AIH patients.**

There are few studies of the association between immunosuppressive treatment for AIH patients with extrahepatic cancer. Especially, the risk of **extrahepatic malignancy** is unknown in **Korean AIH patients**. The strength of our study is that perspective and **large cohort study** using the national claims data of HIRA.