의학석사 학위논문

한국 윌슨병 환자 354 명의 장기 예후에 대한 단일 기관 분석

Long-term Outcome Of Wilson's Disease: A Single Center Analysis Of 354 Korean Patients

울산대학교 대학원

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남 효 진

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이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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남효진의 의학석사 학위 논문을 인준함

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국문요약

연구배경: 아시아 윌슨병 환자들의 장기 예후와 생존에 대해서 보고된 바가 많지 않다. 이에 본 연구에서는 한국 윌슨병 환자들을 대상으로 임상적 장기 예후를 분석하고자 하였다.

연구 방법: 서울아산병원에서 2000 년부터 2022 년 사이 윌슨병으로 진단된 354 명의 환자들을 후향적으로 분석하였다. 윌슨병의 진단은 전형적인 증상과, 임상양상, 생화학적, 유전적 소견을 기반으로 하였다. 무이식 생존율(transplant-free survival)과 전체 환자에서 간세포암 발생률을 분석하였으며, 진단 시 간경변증이 없었던 환자 중 추적 관찰 중 간경변증으로 이행한 비율을 또한 분석하였다.

연구결과: 진단 시 연령의 중앙값은 14.2 세였고, 전체 환자 중 205 명(57.9%)이 남성이었다. 처음 진단 시 146 명(41.2%)이 간경변증이 있었으며, 그 중 31 명(8.8%)은 비대상성 간경변증을 보였다. 5, 10, 15, 20 년째의 무이식 생존율은 각각 99.7%, 98.0%, 97.5%, 97.5% 였다. 5, 10, 15, 20 년 간 간세포암의 누적 발생률은 각각 0.0%, 1.2%, 2.9%, 5.2% 였다. 진단 시 간경변증이 없었던 208 명의 환자 중 12 명(5.8%)이 추적 기간 동안 간경변증으로 진행하였으며, 5, 10, 15, 20 년째 간경변증 진행의 누적 위험도는 각각 3.5%, 5.3%, 6.3%, 11.9% 였다. 진단 시 간경변증이 없었던 환자 중 사망하거나 간세포암이 발생한 환자는 없었다. 진단 시 간경변증이 있었거나, 나이가 많은 환자일수록 생존율이 유의하게 낮았다($P < 0.05$).

연구결론: 한국의 윌슨병 환자들은 좋은 장기 예후를 보였다. 그러나 진단 시 나이가 많거나, 간경변증이 있는 경우 사망 및 간세포암 발생의 위험이 증가한다.

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INTRODUCTION

Wilson's disease (WD) is a rare disease that disrupts copper homeostasis of body. It is an autosomal recessive disease that occurs in about one in 30,000 to 100,000 patients in United States. It is caused by the mutation of ATP7B gene, which is coding a copper-transporting ATPase of hepatocytes. Hepatocytes normally incorporate copper into ceruloplasmin, and transport excess copper into bile, then removes it through feces. However, impairment of ATPase disrupts copper excretion, and incorporation of ceruloplasmin, therefore causing copper accumulation in liver and other internal organs such as liver, brain, and cornea (1).

WD can be classified into two main types based on its phenotype: hepatic type and neurologic type (2). Patients can first present with neurologic symptoms such as dysarthria, tremor, and gait abnormality (3). Others may present hepatic manifestations ranging from acute hepatitis that requires liver transplantation, to asymptomatic hepatomegaly or mild elevation of liver enzymes. It is known that most of the neurologic WD patients have underlying liver disease and are diagnosed at an older age than hepatic WD patients (4). Some asymptomatic patients are also diagnosed by family screening of the patients' siblings.

Patients who are diagnosed with WD require lifelong treatment, regardless of the presence of symptoms. The most important treatment is the oral chelating agent, such as D-penicillamine and trientine. These chelators promote urinary excretion of copper. Another effective treatment is zinc, which is known to impede the intestinal copper absorption (1). Appropriate treatment of WD is essential, and if not treated properly, it can result in development of liver cirrhosis or liver failure, and hepatocellular carcinoma (HCC). On the other hand, previous studies showed promising outcomes and even comparable survival rates of the patients of WD to the general population, when treated adequately (5, 6). However, these studies have been limited to European cohorts, and the long-term survival and probability of developing hepatocellular carcinoma and liver cirrhosis is not well known, especially in Asian patients.

Therefore, the purpose of this study was to analyze the long-term outcome of large Korean WD cohort, and to identify the risk factors of developing liver cirrhosis and HCC.

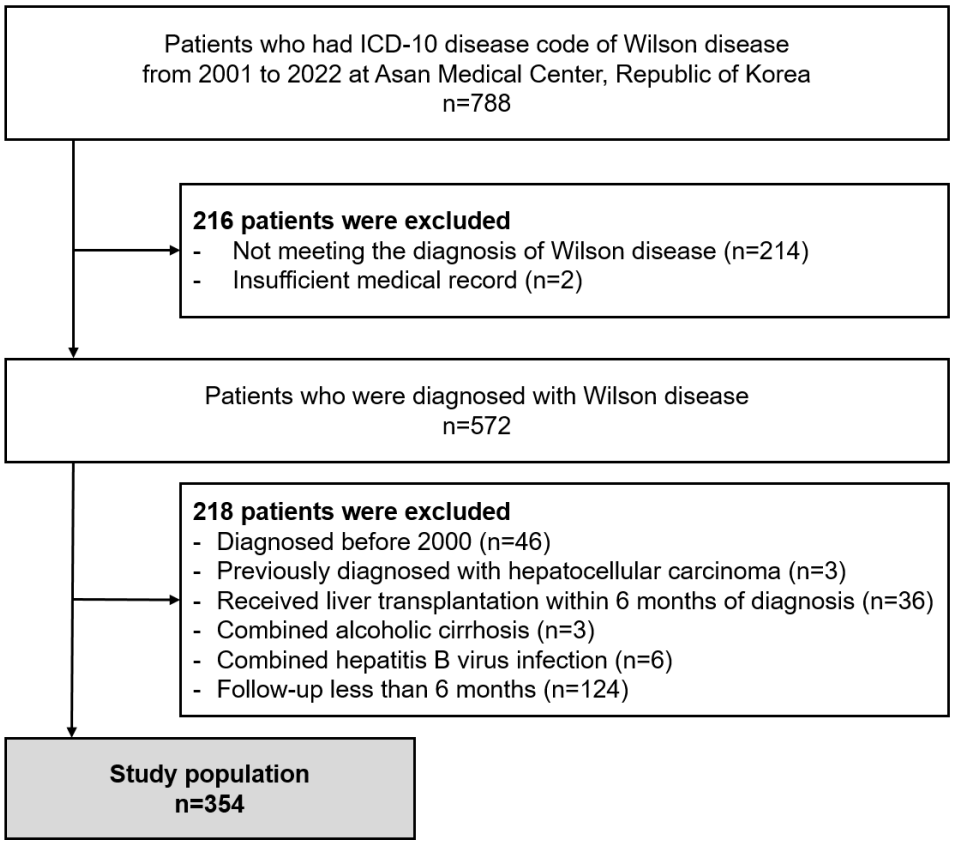
METHODS

Study population

A total of 788 patients who have the disease code of either 'Wilson's disease', 'Disorders of copper metabolism', or the International classification of disease-10 code of E830, from 2000 to 2022 at Asan Medical Center, Seoul, Republic of Korea were retrospectively analyzed. Among them, 214 patients not meeting the disease criteria of WD were excluded, and 2 patients with insufficient medical record were also excluded. The other exclusion criteria for this study were as follows: 1) previously diagnosed with HCC before the diagnosis of WD, 2) received liver transplantation within 6 months after diagnosis, 3) combined alcoholic cirrhosis, 4) combined hepatitis B virus infection, and 5) follow-up period less than 6 months. Finally, 354 patients were included in the present study.

The institutional Review Board of Asan Medical Center (IRB No. 2021-0419) approved this study and the need for informed consent was waived by the IRB due to the retrospective nature of this study.

Figure 1. Flowchart of screening and selection of study population



Data collection, definitions

All data was extracted from the electronic medical records of the Asan Medical center. Clinical and radiologic data including age, sex, the presence of Kayser-Fleischer ring by slit lamp examination, computed tomographic (CT) image, Magnetic resonance (MR) image, and abdominal ultrasound sonography were also obtained. The laboratory data at the time of diagnosis was only available in 304 patients, and the following data were obtained: alanine aminotransferase (AST), aspartate aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin, international normalized ratio (INR), platelet count, serum ceruloplasmin, serum copper, 24-hour urine copper, 24-hour urine creatinine. Finally, liver biopsy and ATP7B gene test results were also collected. Based on these data, liver cirrhosis is identified if any of the following are confirmed: image findings consistent with liver cirrhosis, presence of varices, thrombocytopenia with no other apparent cause, or liver biopsy results corresponding to liver cirrhosis. Decompensated cirrhosis is identified by either a patient's history of variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis. It can also be defined by the presence of ascites or the use of diuretics to control ascites, or when one's total bilirubin level exceeds 3mg/dl.

Molecular genetic analysis

Genomic DNA was obtained by PCR sequencing from peripheral blood leucocytes. Details of methodology of PCR sequencing were previously described elsewhere (7).

Phenotypic classification

The entire 354 patients were categorized into four types based on their clinical presentation, according to the criteria previously suggested by Ferenci et al. (2). If there is no neurologic symptom or sign, patients were classified as hepatic type. H1 (hepatic-acute) is the phenotype with acute hepatitis or jaundice due to coombs negative hemolysis and H2 (hepatic-chronic) is any type of chronic liver disease. If there is any neurologic symptom or sign, patients were classified as neurologic type, and N1 stands for the neurologic type with any type of liver disease, and N2 without any evidence of liver disease.

Treatment

We also analyzed the initial treatment at diagnosis of whole study population. Treatment included D-penicillamine, trientine, and zinc. Dosing of these medications was decided according to the general practice guideline (1). It is indicated that D-penicillamine and trientine should be initiated at 15-20mg/kg/day (with a maximum of 2000mg/day) and subsequently tapered to 10-15mg/kg/day for maintenance. The dosing interval was determined by the discretion of physicians. In patients who received D-penicillamine, pyridoxine was routinely taken together, because D-penicillamine increases the excretion of vitamin B6 and reduces its activity.

Primary outcome and Secondary outcome

The primary outcome was the liver transplant-free survival, defined as the time to first occurrence of death or liver transplantation. Additionally, the occurrence of HCC was analyzed. As a secondary outcome, the development of liver cirrhosis was analyzed in patients who did not have it at the time of their initial diagnosis.

Statistical analysis

Liver transplant-free survival was analyzed using the Kaplan-Meier method. The Cox proportional hazards model was used to identify factors affecting the risk of death or liver transplantation using univariate and multivariate analyses. All statistical analyses were performed using R software (http://www.r-project.org). All reported P-values are two-sided, and P-values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population

Among the total 354 patients with WD, 149 (42.1%) patients were female. The median age at diagnosis was 14.17 years old. Diagnosis age ranged from 1 to 56 years old. At the time of diagnosis, 146 (41.2%) patients had liver cirrhosis, and out of them, 31 (8.8%) patients showed decompensated liver cirrhosis. Among the patients who showed decompensation, 11 patients had ascites, 13 patients presented

jaundice, and 3, 2, 1 patients had a history of variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis, respectively. KF ring was observed in 131 (37.5%) patients (Table 1).

Based on the phenotypic classification, among the total 354 study population, H1 type accounted for 15.3%, and H2 type accounted for 63.8%. For those who presented neurological symptoms at the time of diagnosis, 15.5% were N1 type patients, while 5.4% were N2 types. Laboratory data at diagnosis was available in 294 patients and it is described on Table 2. AST, ALT, and ALP were higher in hepatic type patients than neurologic type patients, and ceruloplasmin level was below 5mg/dL in all 4 phenotypes. The mean age at diagnosis was 8.7 years in H1 patients, 18.0 years in H2 patients, and neurologic type patients were diagnosed at older ages. KF ring was observed in 12.0% and 33.3% of H1 and H2 patients, respectively. On the other hand, it was present in 79.2% and 75.0% of N1 and N2 patients.

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At the time of diagnosis, 10 out of 52 H1 patients and 70 out of 182 H2 patients already head liver cirrhosis. Also, among the 61 neurologic type patients, 47 patients had liver cirrhosis at baseline. N type patients tended to have cirrhosis more frequently than H type patients._ Detailed clinical data with respect to the H1, H2, N1 and N2 presentations are given in Table 2.

Table 1. Baseline characteristics of whole 354 study population

Variables	All patients (n=354)
Gender, n (%)	
Female	149 (42.1%)
Male	205 (57.9%)
Age at diagnosis (y, median)	
Cirrhosis	
Cirrhosis, n (%)	146 (41.2%)
Decompensated cirrhosis, n (%)	31 (8.8%)
Type	
H1	54 (15.3%)
H2	226 (63.8%)
N1	55 (15.5%)
N2	19 (5.4%)
Kayser-Fleicher ring	
Present	131 (37.5%)
Absent	150 (43.0%)
Treatment at diagnosis	
D-penicillamine	176 (48.0%)
Trientine	102 (28.3%)
Zinc	37 (10.2%)
D-penicillamine + Trientine	1 (0.3%)
D-penicillamine + Zinc	15 (4.2%)
Trientine + Zinc	30 (8.3%)

Abbreviations: H, hepatic; N, neurologic;

Treatment

All 354 patients started either one of the chelating agent or zinc right after diagnosis, or even before the diagnosis was thoroughly confirmed. 176 (48.0%) patients received D-penicillamine alone as a first treatment, and 102 (28.3%) received trientine. Thirty seven (10.2%) patients received zinc, and 12.8% of patients received combination therapy at the time of diagnosis (Table 1). According to the phenotype, 27 and 98 of H1 and H2 patients, which is about half of hepatic type patients used D-penicillamine. However, only 38% of N1 type and 26% of N2 type patients received D-penicillamine as their first treatment.

Genetic mutation of ATP7B gene

We obtained the result of ATP7B genetic test of 310 patients. Over 30 mutations of ATP7B gene were detected. Among them, 59 (19%) patients were homozygote for ATP7B gene, 181 (58.4%) were compound heterozygote, 58 (18.7%) were heterozygote, and 12 (3.9%) had normal ATP7B gene. R778L was the most common mutation, which accounted for 66.2% (237) of total mutated alleles. The next most commonly detected mutations were A874V, N1270S and L1083F, accounting for 18.7%, 12.6%, 9.5% of the total mutated alleles, respectively (Table 3). Other missence mutations (G1035V, T1029I, R919G, V1106I…), deletion mutation (2513del), and insertion mutation (Met769HisfsX25) were also observed.

Transplant-free survival and Development of HCC

The median duration of follow-up was 12.5 years. The transplant-free survival rates for entire patients were 99.7% at 5 years, 98.0% at 10 years, 97.5% at 15 years, and 97.5% at 20 years (Figure 1). From 2000 to 2022, 6 patients died among the study population. One patient died due to HCC, one due to septic shock resulting from pneumoperitoneum, and one due to seizure and hepatic encephalopathy. Because we used the international health care data for survival analysis, the cause of death of other 3 patients who died outside of our hospital were unknown. Three patients died at their thirties, which was 4, 9, 9 years after diagnosis, respectively. Two patients died at their forties, and another 1 patient died at 62 years old. The mean age at the time of death was 44.1 years. Among the 6 patients, four patients were H2 type, other two patients were N1 type.

Twelve patients received liver transplantation during follow up period. The cause of liver

transplantation was fulminant hepatitis in underlying cirrhosis in 6 patients, decompensated but stable cirrhosis in 2 patients, and compensated liver cirrhosis in 4 patients. Among these patients, one patient had HCC. No one received liver transplantation for their neurological deterioration. At the time of diagnosis of WD, 8 patients were H2 type, 4 patients were N1 type. The mean interval from diagnosis to liver transplantation was 10.5 years.

Eight patients developed HCC during follow up period. The cumulative incidence of HCC at 5, 10, 15, and 20 years were 0.0%, 0.4 %, 2.0%, and 6.6%, respectively. The youngest patient developed HCC at 38 years old and the median age of diagnosis was 51 years old. Mean interval from diagnosis of WD to development of HCC was 11 years. All the 8 patients who developed HCC had liver cirrhosis at baseline, and no patients without baseline cirrhosis developed HCC during the observational period.

Development of liver cirrhosis and multivariable analysis

Of the 208 patients without LC at diagnosis, 12 (5.8%) patients showed progression to LC, with cumulative risk of 0.0%, 3.0%, 6.1% and 14.1% at 5, 10, 15, and 20 years, respectively (Figure 4). Among them, 5 patients were H2 type, 5 patients were N2 type, and another 2 were N1 type at baseline. The mean interval of progression to LC was 5.9 years. According to the multivariable analysis of transplant-free survival, older age at diagnosis and cirrhosis showed significant correlation with a worse survival rate. With increasing age, the risk of death or transplantation was significantly increased with an adjusted hazard ratio (AHR) of 1.05 (95% confidence interval [CI]: 1.01~1.09). Among the 208 patients without LC at diagnosis, not a single patient died or underwent liver transplantation throughout follow-up period. Decompensated cirrhosis was significantly related to worse outcome on univariate analysis, but it showed no significant correlation in multivariable analysis.

Table 2. Baseline characteristics of 304 patients with laboratory data at diagnosis, according to the presenting phenotype at the time of diagnosis

Variables	All patients (n=304)	Presenting phenotype				
		H1 (n=52)	H2 (n=182)	N1 (n=49)	N2 (n=12)	P-value
AST (IU/L)	90.2 ± 98.0	226.7 ± 154.2	70.4 ± 46.2	37.0 ± 24.6	26.8 ± 6.8	<0.001
ALT (IU/L)	122.4 ± 147.7	357.1 ± 199.2	88.3 ± 67.2	29.8 ± 21.6	19.5 ± 7.7	<0.001
ALP (IU/L)	233.9 ± 174.5	366.5 ± 237.7	226.8 ± 153.4	145.9 ± 90.2	136.2 ± 60.9	<0.001
Total bilirubin (mg/dL)	1.3 ± 4.0	1.5 ± 3.5	1.4 ± 4.8	1.0 ± 0.6	0.6 ± 0.2	0.819
Albumin (g/dL)	3.9 ± 0.7	4.0 ± 0.7	3.8 ± 0.7	3.8± 0.6	4.2 ± 0.3	0.128
Platelet (X10^3/uL)	223.9 ± 118.4	299.7 ± 122.1	228.8 ± 116.4	123.6 ± 59.8	237.8 ± 75.9	<0.001
INR	1.2 ± 0.5	1.3 ± 0.6	1.2 ± 0.5	1.2 ± 0.2	1.1 ± 0.1	0.717
Ceruloplasmin	4.1 ± 4.8	4.4 ± 7.5	4.5 ± 4.5	2.7 ± 1.8	4.0 ± 2.7	0.132
KF ring present (%)	39	12	33.3	79.2	75	<0.001
Age at diagnosis	17.6 ± 12.4	8.7 ± 6.0	18.0 ± 13.0	24.8 ± 9.0	18.6 ± 12.7	<0.001
Treatment at diagnosis D-penicillamine / Trientine / Zinc (No. of patients)†		27 / 22 / 10	98 / 69 / 39	22 / 20 / 15	3 / 8 / 5	
Cirrhosis / Decompensated cirrhosis (No. of patients)		10 / 7	70 / 15	47 / 3	0 / 0	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; INR, international normalized ratio; KF, Kayser-Fleischer ; H, hepatic; N, neurologic;

†Including patients with combination therapy

Figure 2. Liver transplant-free survival of whole 354 study population

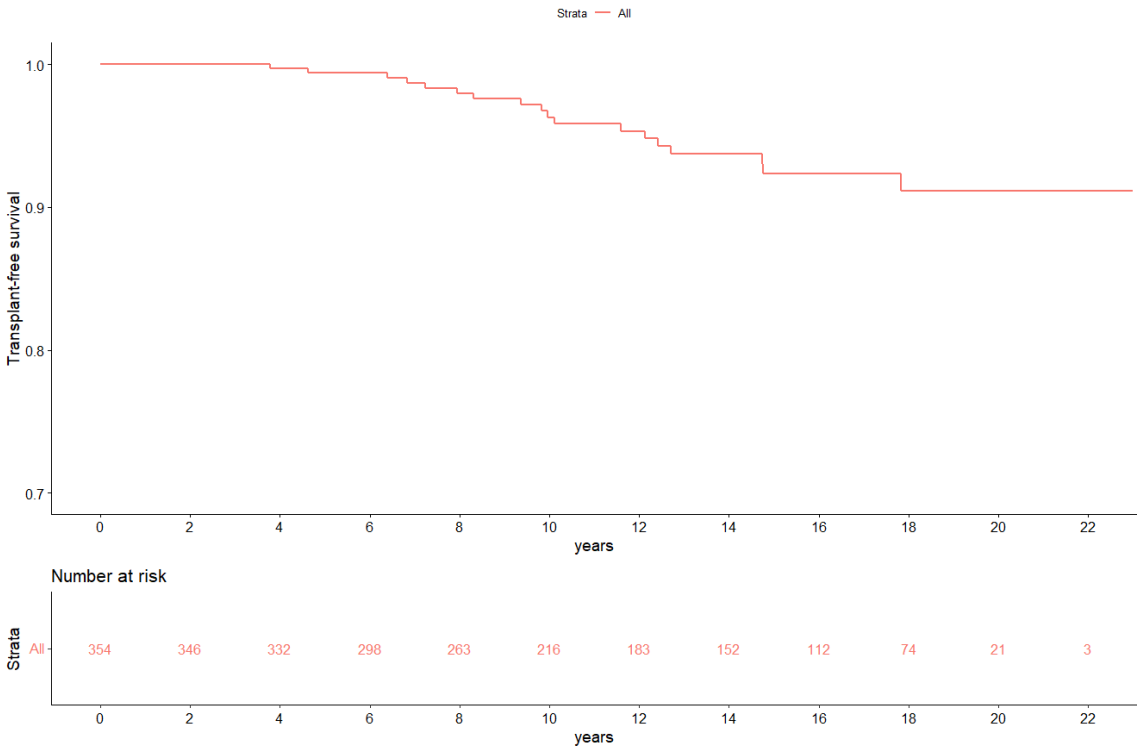

Figure 3. Cumulative incidence of HCC

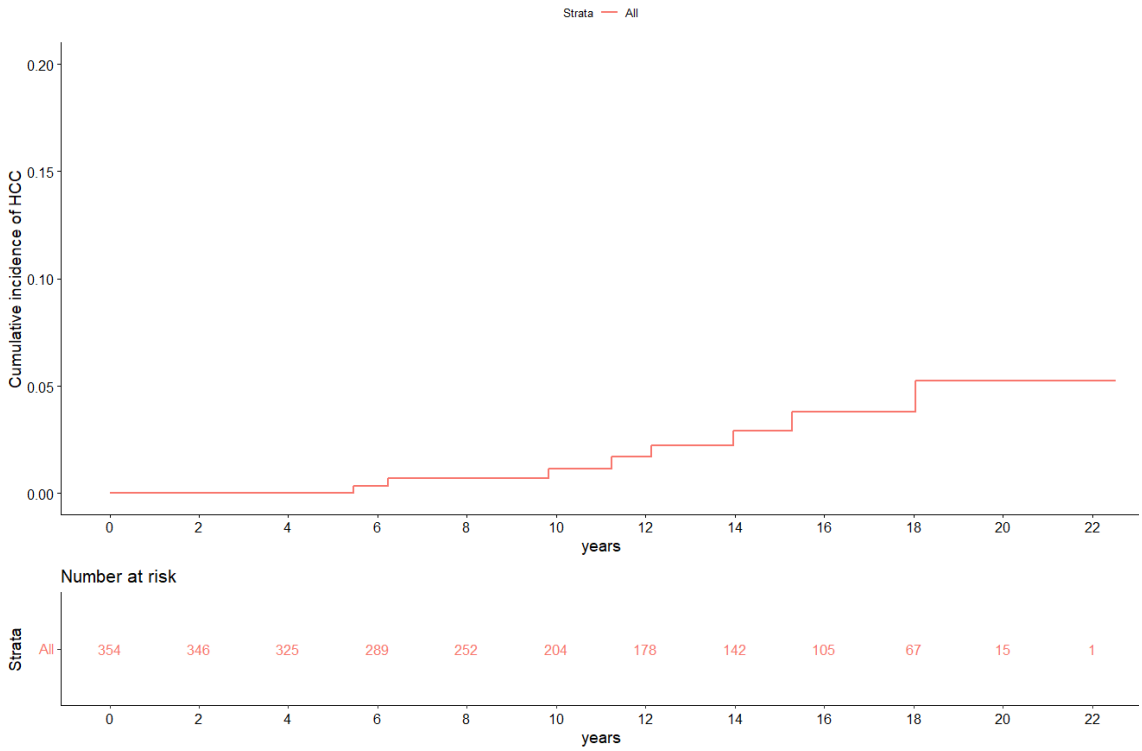

Figure 4. Cumulative incidence of LC in 208 patients who were not diagnosed with LC at baseline

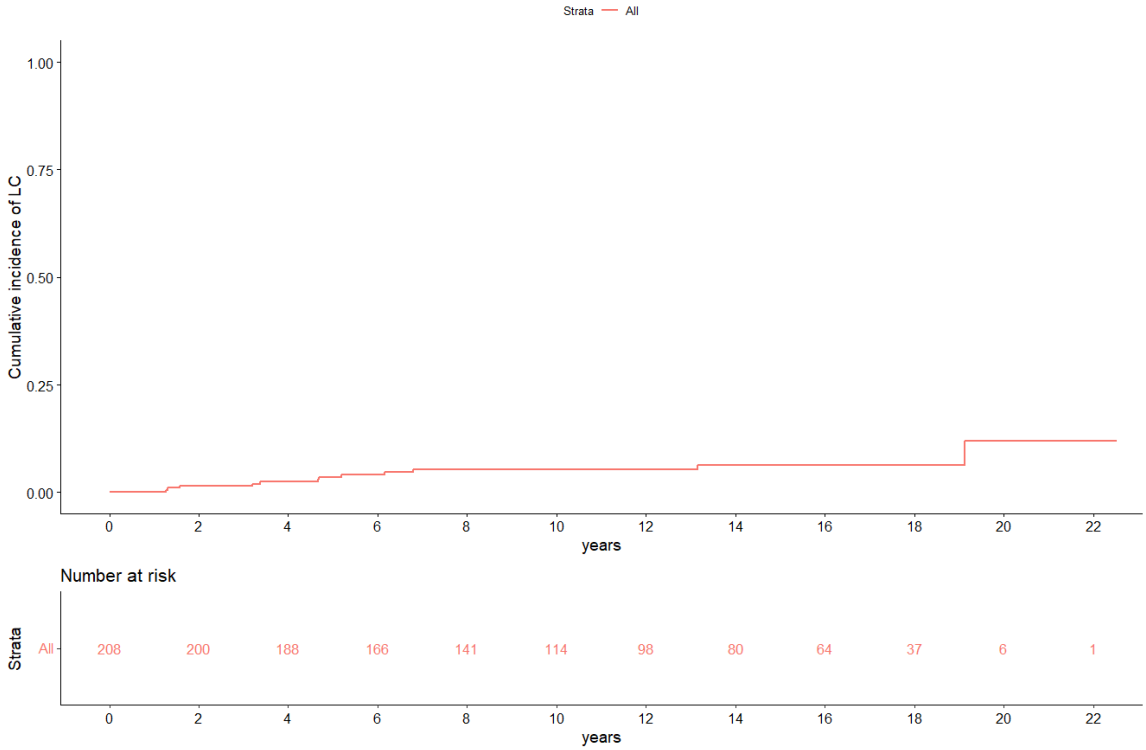

Table 3. ATP7B gene mutation of patients

Mutation	No. of patients	No. of alleles	Allele frequency (%)
R778L	191	237	66.2
A874V	62	67	18.7
N1270S	39	45	12.6
L1083F	33	34	9.5
del2513	22	23	6.4
G1035V	18	19	5.3
T1029I	12	12	3.4
R919G	12	12	3.4
Met769HisfsX25	7	7	2
V1106I	5	5	1.4

Table 4. Univariate and multivariate analysis of transplantation and death, whole study population

	Univariate analysis				Multivariable analysis			
Characteristics	**N**	**HR**	**95% CI**	**p-value**	**N**	**HR**	**95% CI**	**p-value**
Sex	354				354			
Female								
Male		0.28	0.10, 0.78	0.015				
Age at diagnosis, per 1 year increase	354	1.09	1.05, 1.13	<0.001	354	1.05	1.01, 1.09	0.012
Decompensated LC at diagnosis	354	5.4	2.02, 14.4	<0.001	354	1.76	0.65, 4.77	0.3

Abbreviations: LC, liver cirrhosis; HR, hazard ratio; CI, confidence interval;

DISCUSSION

Wilson disease is a rare genetic disease that results in abnormal accumulation of copper in various organs. ATP7B mutation is the known for the cause of this disease. At early stage of WD, hepatic inflammation occurs and patients can present as asymptomatic liver enzyme elevation or mild symptoms of hepatitis. As inflammation continues, patients progress to chronic liver disease, sometimes even leading to liver cirrhosis. During this course, various neurologic symptoms or other organ involvement such as KF ring, fanconi syndrome, or hemolytic anemia can occur. Some patients even progress to acute liver failure that requires liver transplantation. Patients die due to acute liver failure or complications of decompensated liver cirrhosis or HCC.

In this study, a total of 354 patients who were diagnosed as WD were retrospective analyzed for the long term outcome, and showed favorable transplant-free survival rate. The transplant-free survival was around 98% at 20 years from diagnosis and only 6 patients died during follow up period. Also, with multivariable analysis, we revealed that older age and cirrhosis at diagnosis were significantly associated with worse survival rate.

Previous studies from western countries already showed similar outcomes in terms of long term outcomes of WD. One study analyzing 228 Austrian patients of WD showed a 92% of transplant-free survival, and also revealed that cirrhosis at diagnosis was an important factor for death and transplantation (5). Patients who received adequate treatment such as D-penicillamine, trientine, or zinc, showed favorable outcome. A study in Czech also revealed that long-term survival of patients with WD did not differ from that of general Czech population (6). Our study showed comparable outcomes to these previous studies for more than 300 patients, especially in Asian cohort.

In our study, cumulative incidence of HCC and LC were also analyzed. The 20-year incidence of HCC was 5.2%, and no patients without LC at diagnosis developed HCC during study period. There are previous studies supporting relatively low incidence of HCC in patients with WD, because of the protective effect of copper in the hepatocytes from oncogenic sequence (8, 9). More studies are needed for further evaluation. In our study, the mean age at diagnosis of HCC was 52.3 years old, which is much younger than that of other underlying liver disease. As we excluded patients who already diagnosed with HCC at the time of diagnosis of WD, the age of HCC can be even younger than we observed.

There are few studies analyzing the incidence of liver cirrhosis in WD patients. In our study, 41.2% patients had liver cirrhosis at the time of diagnosis, and among the patients without cirrhosis at baseline,

5.3% and 11.9% progressed to cirrhosis at 10 year and 20 year, respectively. Previous studies showed around 40 to 60% incidence of cirrhosis at baseline (5, 6, 10). In our study, only 64 out of 354 patients performed liver biopsy and other noninvasive tests for evaluation of cirrhosis was rarely done at the time of diagnosis, so the incidence of cirrhosis might be underestimated.

According to our study, N type patients showed higher rate of cirrhosis at baseline and higher rate of progression to cirrhosis. At baseline, 47 out of 51 patients with neuropsychiatric manifestation already had liver cirrhosis. Also, among the 12 patients who finally progressed to liver cirrhosis, 5 patients were N2 type, and 2 patients were N1 type at baseline. One reason for this is that neurologic symptoms tend to occur at older ages than hepatic symptoms, and usually symptoms are nonspecific and difficult to distinguish from other neuropsychiatric disease. As a results, N type patients were usually diagnosed at older age and there is more likelihood that hepatic inflammation has already progressed at the time of diagnosis.

The treatment decision of WD depends on the symptoms or organ involvement. Patient should receive at least one treatment among D-penicillamine, trientine, and zinc, which should be administered lifelong unless there are some significant side effects severe enough to stop the treatment. One of the chelating agent, D-penicillamine or trientine, is recommended as the first-line treatment for symptomatic WD, and zinc has been used mainly for asymptomatic patients or in combination with chelators in more severe disease. D-penicillamine was known for the severe paradoxical worsening of neurologic symptoms and sensitivity reactions, and trientine can be used in patients who are intolerant to D-penicillamine. In our study, over 50% of H1 and H2 patients used D-penicillamine as the first treatment, and 10 of them used it as combination with zinc. Trientine was also used in about 40% of hepatic type patients, also sometimes in combination with zinc. On the other hand, neurologic type patients used trientine and zinc relatively more than hepatic type. None of our study population stopped treatment during follow up period.

The strength of our study is that this study revealed long-term outcome of Korean patients of WD, from the largest single center cohort. We analyzed not only the transplant-free survival, but also the incidence of HCC and LC, which is the first study in Asian countries. Also, we classified patients into 4 phenotypes, and analyzed the baseline clinical data and treatment of this rare disease.

In our study we could not evaluate the compliance and effect of each treatment, so it needs s further study. Also, genotype-phenotype correlation and prognostic significance of ATP7B gene mutation was not evaluated in this study.

In conclusion, Korean patients of WD have favorable long-term outcome, showing 5.3% transplant-

free survival for 10 year. However, older age and LC at the time of diagnosis increased the risk of death and transplantation. Therefore, we suggests that early detection and treatment are important to prevent poor long-term outcome in patients with WD.

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ABSTRACT

Background & Aims: There are few data regarding long-term outcomes and survival of patients with Wilson disease (WD) from large Asian cohorts. We aimed to analyze the clinical long-term data in a large Korean cohort of WD.

Methods: Between 2000 and 2022, 354 patients with WD were retrospectively analyzed at Asan Medical Center, Seoul, Republic of Korea. Diagnosis of WD were made on typical symptoms, clinical, biochemical and genetic findings. Primary outcome was liver transplant-free survival. Development of hepatocellular carcinoma (HCC) in the entire patients and progression to liver cirrhosis (LC) in patients without LC at diagnosis were also analyzed. Patients who met the following criteria were excluded: 1) received liver transplantation within 6 months of diagnosis; 2) follow-up period less than 6 months; 3) co-infection with hepatitis B virus; 4) combined alcoholic liver disease. Median follow-up period was 12.5 years.

Results: The median age at diagnosis was 14.2 years, and 205 (57.9%) of the patients were male. At diagnosis, 146 (41.2%) patients had LC, of which 31 (8.8%) patients showed decompensation. Transplant-free survival rates at 5-, 10-, 15-, and 20-years were 99.7%, 98.0%, 97.5%, and 97.5%, respectively. Cumulative probabilities of HCC development at 5-, 10-, 15-, and 20-years were 0.0%, 1.2%, 2.9%, and 5.2%, respectively. Of the 208 patients without LC at diagnosis, 12 (5.8%) patients showed progression to LC with cumulative risks of 3.5%, 5.3%, 6.3% and 11.9% at 5, 10, 15, and 20 years, respectively. No patients without LC at diagnosis died or developed HCC during the follow-up period. Older age and LC at diagnosis were significantly associated with a worse survival rate (P<0.05 for all).

Conclusions: Korean patients with WD had a favorable long-term prognosis However, older age and LC at the time of diagnosis increase the risk of death and HCC development.