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Factors affecting activities of daily living among patients with Wilson disease

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Abstract

Wilson disease (WD) is a congenital copper metabolism disorder with various manifestations and can be treated with oral medication. This study examined the factors related to decline in activities of daily living (ADL) in patients with WD as research in this area remains limited. We enrolled 308 patients with WD, including patients who participated in a national survey and those who sought cares at the Department of Pediatrics, Toho University Ohashi Medical Center, from 2016 to 2017. We analyzed the association between ADL decline and factors including age at diagnosis, period from diagnosis to survey, hepatic symptoms, neurological signs, and psychiatric presentation at diagnosis. The relative risks (RRs) for ADL decline were estimated for each factor using multivariate modified Poisson regression analysis. Overall, 97 out of 308 (31.5%) patients experienced ADL decline. After adjusting for explanatory variables, regression analysis revealed that factors significantly associated with ADL decline were a period of ≥20 years from diagnosis to survey (adjusted RR = 2.34, 95% confidence interval [CI]: 1.47–3.74), hepatic symptoms with splenomegaly (adjusted RR = 2.57, 95% CI: 1.26–5.24), mild neurological signs (adjusted RR = 3.20, 95% CI: 1.96–5.23), and severe neurological signs (adjusted RR = 3.63, 95% CI: 2.28–5.77). Neurological signs, hepatic symptoms with splenomegaly, and a period of 20 years from diagnosis to survey are associated with ADL decline. Thus, careful assessment of patients for these factors is necessary, and these findings may guide future efforts to improve patient prognosis.

KEYWORDS

activities of daily living, hepatic symptom, national survey, neurological sign, Wilson disease

1 | INTRODUCTION

Wilson disease (WD) is an autosomal recessive inherited disorder caused by an abnormality in the *ATP7B* gene. This causes impaired excretion of copper from the liver into the bile and the secretion of cellular plasmin into the blood.[1] It is characterized by excessive deposition of copper in hepatocytes, the brain, kidneys, corneas, and other tissues. Thus, WD presents with a variety of symptoms.[2,3] The incidence of WD is estimated to be one in 30 000–34 000 live births, based on a 1990–1991 national survey in Japan.[4]

WD is one of the genetic disorders that can be treated with oral medication,[5] and thus early diagnosis and

appropriate treatment are essential to save patient's lives. Currently, the main pharmacological treatments for WD are chelating drugs (D-penicillamine and trientine) and zinc preparations.[6–9] Moreover, the recommended initial therapy for patients with hepatic failure is a combination of trientine and zinc.[10]

There have been several studies on the mortality related to WD, the necessity of liver transplantation, and the prognosis of WD outside Japan.[11–16] However, few studies have reported the living conditions, such as the activities of daily living (ADL) in patients with WD.[17–19] Furthermore, limited studies have evaluated the relationship between the factors present at diagnosis and their effect on ADL.

The Department of Pediatrics of Toho University Ohashi Medical Center conducted two national surveys on WD in 1990–1991 and 2005–2009,[20] where the clinical features of WD were examined; however, factors related to ADL have not yet been fully elucidated. Additionally, while there are WD guidelines in the United States, Europe, and Japan,[21,22] none discuss ADL thoroughly.

Thus, this study aimed to examine factors related to ADL in patients with WD using data from a third national survey conducted in 2015–2016 and data from our institution. Our findings may help guide research to improve the prognosis of WD.

2 | MATERIALS AND METHODS

2.1 | Study population

The study population included patients with WD identified by the results of a 2016 national survey, in addition to patients with WD who attended the Department of Pediatrics, Toho University Ohashi Medical Center in 2016 and 2017.

We conducted a national survey in 2016 that included 207 institutions that treat patients with WD. These institutions were previously identified in the initial 2015 national survey. The data of 284 (60.7%) patients were collected and included in this study (Figure 1).The national survey in 2015 and included institutions with >200 beds had pediatrics, gastroenterology, neurology, psychiatry, and transplant surgery departments. An initial survey to determine the annual number of patients with WD was distributed to 4133 institutions, of which 1739 (42.1%) responded with whether or not they treated patients with WD. Results from the initial survey showed that 207 institutions reported the management of a total of 468 patients with WD in 2015. In 2016, a secondary questionnaire was distributed to 207 institutions, and the data of 284 (60.7%) patients were collected (Figure 1).

The Department of Pediatrics, Toho University Ohashi Medical Center is one of the hospitals that

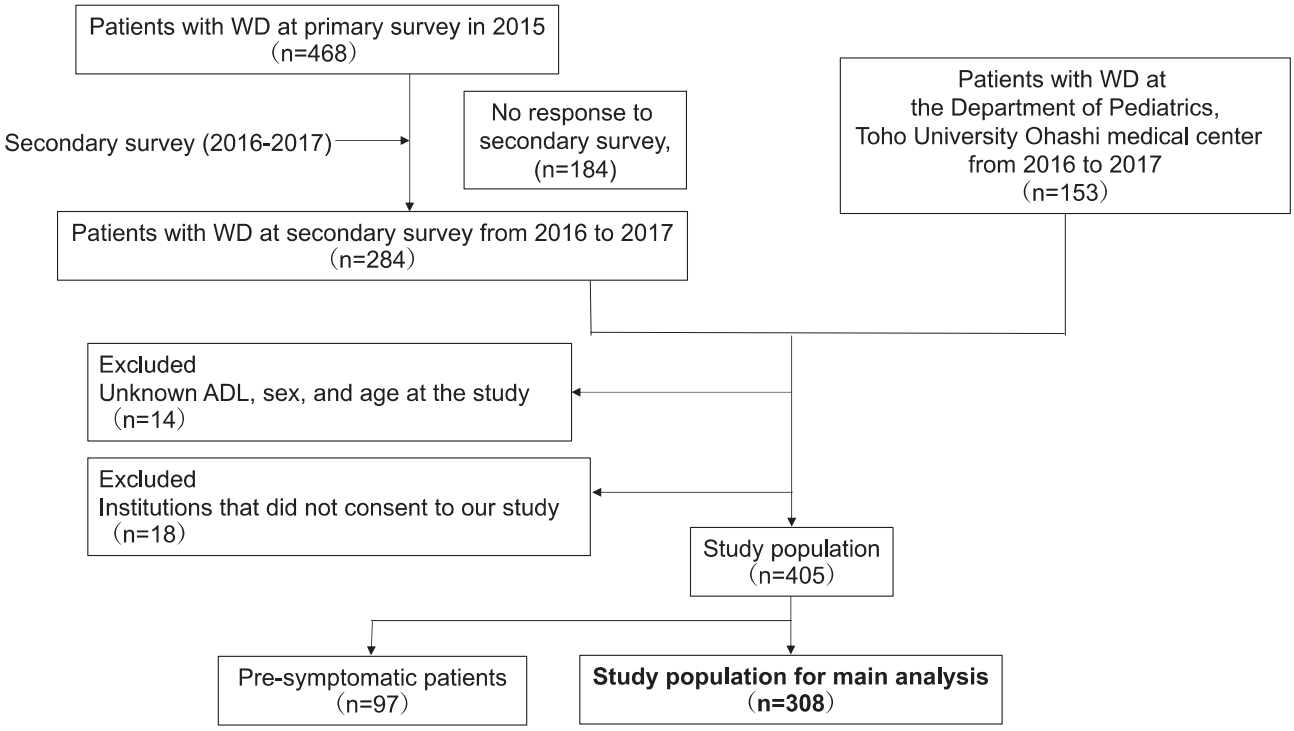

FIGURE 1 Study population. ADL, activities of daily living; WD, Wilson disease.

specialize in treating patients with WD in Japan and receives referrals for diagnosis and treatment of WD from other hospitals. A total of 153 patients who visited this department between 2016 and 2017 were included in the survey population; there was no overlap between the cases in the national survey and the patients from this institution. Cases with missing information on ADL, sex, and age (14 cases); those who did not consent to participate (18 cases); and those who were presymptomatic (97 cases) were excluded. Presymptomatic patients were those who were diagnosed in the absence of symptoms. Presymptomatic patients were determined based on intrafamilial searches (49 cases), during testing for other liver dysfunctions (40 cases), through pilot studies on mass screening for WD (4 cases), by identification of Kayser–Fleischer ring (3 cases) or positive of occult blood in urine (1 case). After checking the patient background in the study population, which included patients who were presymptomatic, the main analysis included 308 patients, excluding those who were presymptomatic (Figure 1).

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (No. A20054). The protocols of the study were disclosed on the institutions' websites or other places, such as bulletin boards, and provisions to opt out were presented.

2.2 | Outcome measurement

The attending physician scored the survey using a 5-point scale: point 1 was scored when there was no decline in ADL; point 2 when patients with WD had impaired function and ADL decline; point 3 when the patient received partial caregiving; point 4 when the patient received full-caregiving; and point 5 when the patient was under medical treatment (i.e., admitted to a hospital). For this study, outcome classifications were created following past national surveys. Points 2–5 were classified as ADL decline, while point 1 was classified as no ADL decline. The rationale for this classification was that the number of cases with points 3–5 was small making analysis difficult. This may be attributed to the development of therapeutic agents that halt disease progression.

2.3 | Explanatory variable measurement

The following items were investigated in this study: gender, age (age at diagnosis and age at time of survey), hepatic symptoms at diagnosis (jaundice, hepatomegaly, ascites, splenomegaly, esophageal varices, abnormal liver function, and others), neurological symptoms at diagnosis (dysarthria, gait disorder, hygrostomia, flapping tremor, dystonia, cerebellar ataxia, consciousness disorder, and others), and psychiatric signs at diagnosis (intellectual disability, depression, hallucinations, and others) (Appendix A).

In addition to sex and the period from diagnosis to survey, the following information at diagnosis was used as explanatory variables: age, hepatic symptoms, neurological signs, and psychiatric signs.

The ages at the time of diagnosis were categorized as follows: 0–9, 10–19, and ≥20 years. The period from diagnosis to survey was calculated by subtracting the age at diagnosis from the age at the survey or from the review of medical records. Thus, the period from diagnosis to survey was categorized as follows: 0–9, 10–19, and ≥20 years.

Ascites, esophageal varices, and splenomegaly are thought to be caused by liver cirrhosis. However, in our study, the number of cases presenting with ascites and esophageal varices was small (Appendix A). Therefore, hepatic symptoms at diagnosis were classified as follows: no hepatic symptoms, hepatic symptoms without splenomegaly, and hepatic symptoms with splenomegaly.

Neurological signs at diagnosis were classified as follows: no neurological signs, mild (absence of dystonia, disturbance in gait, cerebellar ataxia, and consciousness disorder), and severe (presence of dystonia, and/or disturbance in gait, and/or cerebellar ataxia, and/or disorder in consciousness). Mild symptoms included dysarthria, hygrostomia, and others (Appendix A). Symptoms, including dysarthria and hygrostomia, were classified as mild since the patients were able to speak, eat, and continue with their lives despite the inconvenience.

Only a few patients presented with psychiatric signs at diagnosis; thus, they were classified into two groups according to the presence or absence of psychiatric signs at diagnosis.

No specific definitions were used for the classification of explanatory variables, such as hepatic symptoms with splenomegaly, neurological signs, and psychiatric signs at diagnosis. Assessment of patients for the presence of these variables was left to the discretion of the attending physicians.

2.4 | Statistical analysis

A descriptive analysis was performed on the explanatory variables. The relationship between the explanatory variables and ADL decline was assessed using modified Poisson regression. Poisson regression with a robust error variance was developed to rectify variance overestimation.[23] In addition to crude analysis, we applied a multivariable-adjusted model, which included sex, age at

diagnosis, period from diagnosis to survey, hepatic symptoms, neurological signs, and psychiatric signs at diagnosis. The strength of the association was expressed as the relative risks (RRs) and related 95% confidence intervals (CIs). The reference for age at diagnosis and period from diagnosis to survey was set at 0–9 years. For hepatic symptoms without splenomegaly at diagnosis, indicating the lowest risk of ADL decline at the time of the preliminary analysis, was used as a reference. Meanwhile, the reference for neurological and psychiatric signs at diagnosis was no neurological and psychiatric signs, respectively.

We confirmed the validity of the model by checking for collinearity and model outliers. However, statistical power was not calculated before starting this study because the analysis was based on the collection of as many cases as possible.

Statistical significance was set at $p < 0.05$. All analyses were performed using STATA version 15.0 (STATA Corporation).

3 | RESULTS

Table 1 shows the characteristics of the study population. The median age at diagnosis of patients with WD and without ADL decline who were not presymptomatic was 10 (range: 0–46) years. In contrast, the median age at diagnosis of patients with WD and ADL decline who were not presymptomatic was 15 (range: 4–45) years. In addition, the median period from diagnosis to survey was 11 (range: 0–45) years for patients with WD and without ADL decline and

TABLE 1 Characteristics of the study participants.

Explanatory variables		All patients, $n = 405$, n (%)	Presymptomatic type, $n = 97$, n (%)	Not presymptomatic type, $n = 308$	
				ADL decline "No," $n = 211$, n (%)	ADL decline "Yes," n = 97, n (%)
Sex	Male	187 (46.2)	41 (42.3)	99 (46.9)	47 (48.5)
	Female	218 (53.8)	56 (57.7)	112 (53.1)	50 (51.6)
Age at diagnosis (years)	0–9	169 (41.7)	67 (69.1)	91 (43.1)	11 (11.3)
	10–19	150 (37.0)	21 (21.6)	76 (36.0)	53 (54.6)
	≥20	68 (16.8)	6 (6.2)	35 (16.6)	27 (27.8)
	Unknown	18 (4.4)	3 (3.1)	9 (4.3)	6 (6.2)
Period from diagnosis to survey (years)	0–9	145 (35.8)	34 (35.1)	90 (42.7)	21 (21.6)
	10–19	133 (32.8)	36 (37.1)	72 (34.1)	25 (25.8)
	≥20	109 (26.9)	24 (24.7)	40 (19.0)	45 (46.4)
	Unknown	18 (4.4)	3 (3.1)	9 (4.3)	6 (6.2)
Hepatic symptoms at diagnosis	Hepatic symptoms without splenomegaly	267 (65.9)	59 (60.8)	153 (72.5)	55 (56.7)
	Hepatic symptoms with splenomegaly	22 (5.4)	0 (0.0)	14 (6.6)	8 (8.2)
	No hepatic symptoms	93 (23.0)	38 (39.2)	27 (12.8)	28 (28.9)
	Unknown	23 (5.7)	0 (0.0)	17 (8.1)	6 (6.2)
Neurological signs at diagnosis	No neurological signs	296 (73.1)	97 (100.0)	168 (79.6)	31 (32.0)
	Mild[a]	51 (12.6)	0 (0.0)	19 (9.0)	32 (33.0)
	Severe[b]	34 (8.4)	0 (0.0)	7 (3.3)	27 (27.8)
	Unknown	24 (5.9)	0 (0.0)	17 (8.1)	7 (7.2)
Psychiatric signs at diagnosis	No	370 (91.4)	97 (100.0)	198 (93.8)	75 (77.3)
	Yes	23 (5.7)	0 (0.0)	5 (2.4)	18 (18.6)
	Unknown	12 (3.0)	0 (0.0)	8 (3.8)	4 (4.1)

Abbreviation: ADL, activities of daily living.

[a]Mild (absence of dystonia, disturbance in gait, cerebellar ataxia, and consciousness disorder).

[b]Severe (presence of dystonia, and/or disturbance in gait, and/or cerebellar ataxia, and/or consciousness disorder).

TABLE 2 Number of patients with ADL decline and the association between factors and ADL.

		Number of patients with ADL decline/all patients (%)		Crude RR (95% CI)		Adjusted RR (95% CI)[a]	
Sex	Male	47/146	(32.2)	Ref	–	Ref	–
	Female	50/162	(30.9)	0.96	(0.69–1.33)	1.14	(0.82–1.59)
Age at diagnosis (years)	0–9	11/102	(10.8)	Ref	–	Ref	–
	10–19	53/129	(41.1)	3.81	(2.10–6.92)	1.48	(0.75–2.93)
	≥20	27/62	(43.6)	4.04	(2.16–7.56)	1.68	(0.81–3.49)
Period from diagnosis to survey (years)	0–9	21/111	(18.9)	Ref	–	Ref	–
	10–19	25/97	(25.8)	1.36	(0.82–2.28)	1.36	(0.82–2.24)
	≥20	45/85	(52.9)	2.80	(1.81–4.32)	2.34	(1.47–3.74)
Hepatic symptoms at diagnosis	Hepatic symptoms without splenomegaly	55/208	(26.4)	Ref	–	Ref	–
	Hepatic symptoms with splenomegaly	8/22	(36.4)	1.38	(0.76–2.50)	2.57	(1.26–5.24)
	No hepatic symptoms	28/55	(50.9)	1.93	(1.36–2.72)	1.41	(0.97–2.05)
Neurological signs at diagnosis	No neurological signs	31/199	(15.6)	Ref	–	Ref	–
	Mild[b]	32/51	(62.8)	4.03	(2.73–5.93)	3.20	(1.96–5.23)
	Severe[c]	27/34	(79.3)	5.10	(3.53–7.35)	3.63	(2.28–5.77)
Psychiatric signs at diagnosis	No	75/273	(27.5)	Ref	–	Ref	–
	Yes	18/23	(78.3)	2.85	(2.13–3.81)	1.30	(0.91–1.86)

Abbreviations: ADL, activities of daily living; CI, confidence interval; RR, relative risk.

[a]All explanatory variables have been adjusted.

[b]Mild (absence of dystonia, disturbance in gait, cerebellar ataxia, and consciousness disorder).

[c]Severe (presence of dystonia, and/or disturbance in gait, and/or cerebellar ataxia, and/or consciousness disorder).

18 (range: 1–50) years for patients with WD and ADL decline.

Approximately 31.4% of patients with WD who were not presymptomatic had ADL decline. The proportion of patients with ADL decline and a period of ≥20 years from diagnosis to survey was high at 46.4%. Concerning hepatic symptoms at diagnosis, 12.8% of the patients without ADL decline did not have any hepatic symptoms. In contrast, 28.9% of patients with ADL decline showed no hepatic symptoms.

A total of 60.8% and 12.3% (mild: 9.0%; severe: 3.3%) of patients with and without ADL decline, respectively, had neurological signs (Table 1). Other mild symptoms described by the attending physicians included finger tremors, intention tremors, dysgraphia, clumsiness of the hand (i.e., awkwardness in using buttons and playing the piano), involuntary movements of the lower limbs, bradykinesia, dysphagia, convulsions, and tension of the upper limbs (Appendix A).

Among patients with and without ADL decline, 18.6% and 2.4%, respectively, presented with psychiatric signs (Table 1). Other mild psychiatric symptoms described by the attending physicians included anxiety, withdrawal, emotional instability such as frustration, conversion disorder, obsessive-compulsive disorder, behavioral disorders such as violence, and immature mental function.

Table 2 shows the association between the individual factors and ADL decline. Even after adjusting for all explanatory variables, the period ≥20 years from diagnosis to survey, hepatic symptoms with splenomegaly at diagnosis, and both mild and severe neurological signs at diagnosis were still associated with ADL decline (Table 2). Longer duration from diagnosis to survey was associated with ADL decline. The adjusted RR (95% CI) of the period ≥20 years from diagnosis to survey was 2.34 (1.47–3.74). Moreover, the presence of hepatic symptoms with splenomegaly at diagnosis was more likely to be associated with ADL decline (adjusted RR [95% CI] was 2.57 [1.26–5.24]) as compared to the reference category. Both mild and severe neurological signs at diagnosis showed an elevated risk of ADL decline (adjusted RR (95% CI) for severe and mild signs, was 3.20 [1.96–5.23] and 3.63 [2.28–5.77], respectively) even in the multivariable-adjusted model.

However, age at diagnosis, absence of hepatic symptoms, and psychiatric presentation at diagnosis were not associated with ADL decline (Table 2). The crude RR (95% CI) for age at diagnosis was 3.81 (2.01–6.92) for

those aged 10–19 years and 4.04 (2.16–7.56) for those aged ≥20 years old. However, after adjusting for all covariates, these associations were no longer statistically significant. Although the crude RR (95% CI) of no hepatic symptoms was 1.93 (1.36–2.72), the association became insignificant (adjusted RR = 1.4, 95% CI: 0.97–2.05) after adjusting for other factors. Similarly, psychiatric presentation at diagnosis was not associated with ADL decline.

4 | DISCUSSION

Neurological symptoms, the presence of splenomegaly at diagnosis, and a period of ≥20 years from diagnosis to survey were associated with a decline in ADL in patients with WD. Remarkably, the proportion of presymptomatic patients was as high as 24.0% (97/405), which is considerably higher than the 3.3% (14/425) reported from the first national survey from 1990 to 1991.[20] This could be attributed to the increase in intrafamilial searches and opportunities to collect blood samples from children for testing, such as allergy and preoperative testing.

A period of ≥20 years from diagnosis to survey was associated with ADL decline. A longer period from diagnosis may result in ADL decline due to the effects of aging itself and may indicate that complications associated with WD may have developed. These complications can be detected or managed through immediate follow-up consultation and may include decrease in white blood cell and platelet counts[24,25] and esophageal varices, which are a typical complication in patients with WD and splenomegaly. Meanwhile, aspiration pneumonia and scoliosis are possible complications in patients with neurological signs.[26,27] Other complications include osteoporosis, susceptibility to fractures, and osteoarthritis.[28–30] These complications may be related to copper accumulation without adequate treatment. We were unable to analyze information on medication compliance and drug neglect due to the presence of many missing values. This topic may be addressed in future studies.

Neurological signs at diagnosis had the highest adjusted RR. Masełbas et al. reported that neurological manifestations at diagnosis impair workability.[31] Additionally, they reported that patients with neurological manifestations at diagnosis declared low salaries as the primary income, and more often were on disability pensions.[31] Svetel et al. reported that lower scores on the SF-36 domains (a generic instrument that provides a profile assessment of the health-related quality of life in eight domains) were found in patients with neurological signs compared with those with a predominantly hepatic form of WD at the time of investigation.[18] Patients with neurologic signs at diagnosis may have had residual neurologic signs at the time of the investigation.

The crude RR of no hepatic symptoms was as high as 1.93 (95% CI: 1.36–2.72), which could be attributed to the fact that patients who lack hepatic symptoms inevitably have neurological signs and/or psychiatric presentations. In the multivariable adjustment model, this association diminished. However, hepatic symptoms with splenomegaly at diagnosis were associated with ADL decline even after adjusting for explanatory variables. This may be explained by the presence of hypersplenism associated with splenomegaly. Hypersplenism causes anemia and thrombocytopenia that can lead to fatigue and bleeding tendency, respectively, and contribute to a decline in ADL.[25] Svetel et al. reported that the liver domain of the Global Assessment Scale for WD has positive associations with the "role functioning physical" and "role functioning emotional" of SF-36.[18] Therefore, patients with splenomegaly at diagnosis may have had residual hepatic symptoms at the time of the investigation. Liver cirrhosis is generally considered irreversible; however, there are reports in which reversal of fibrosis/cirrhosis was possible in various clinical conditions, such as WD, hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis.[32]

Our study had several strengths. First, it was conducted across Japan. Second, we examined the association between ADL and patients' conditions at diagnosis, rather than the current symptoms and findings. Third, the data collected, such as the age at diagnosis and other findings, were objective as the questionnaire was answered by the attending physician, and not the patient.

Our study had several limitations. First, due to the nature of the questionnaire, we selected the words that could be interpreted as either "at diagnosis" or "at first onset." While it is expected that most physicians would describe the situation at the time of diagnosis, some physicians might describe findings at the time of the first onset if there was a delay between onset and diagnosis. Second, for assessing ADL, we used our own classification method, modified from previously used assessment indices. Moreover, there is no reference for the sources from which the outcome classification created for this study was based. Additionally, no questionnaire was available for standardization of the assessment. Third, no specific definitions were used for all explanatory variables listed in the questionnaire, and this process was left to the discretion of the attending physician, which could lead to misclassification. Fourth, the diagnosis of WD was left to the attending physician as the diagnostic criteria were not specified in the questionnaire. Fifth, although data on treatment and medication status between diagnosis and survey were collected in the questionnaire, we were unable to analyze the data owing to

variability in treatment patterns and the presence of many missing values making them difficult to use. Sixth, only surviving patients were included. Seventh, the patients were from hospitals with >200 beds; patients from small facilities, such as clinics were not included. However, WD is rare, and physicians usually treat WD only at advanced facilities. Finally, a longer follow-up period indicates longer survival of patients. Therefore, the RR for ADL decline might be underestimated in this analysis.

5 | CONCLUSIONS

Neurological signs, hepatic symptoms with splenomegaly at diagnosis, and a period of ≥20 years from diagnosis to survey are associated with ADL decline in patients with WD. It may be necessary to carefully assess patients with WD for neurological signs or hepatic symptoms with splenomegaly at initial diagnosis.

AUTHOR CONTRIBUTIONS

Ayumi Amemiya and Norikazu Shimizu conceived the study. Ayumi Amemiya, Keiko Asakura, and Yuji Nishiwaki developed the statistical analysis plan and conducted statistical analyses. All authors contributed to the interpretation of the results. Ayumi Amemiya drafted the original manuscript. Norikazu Shimizu supervised the implementation of the study. All authors reviewed the manuscript draft and revised it critically for intellectual content. All authors approved the final version of the manuscript to be published.

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CONFLICT OF INTEREST STATEMENT

Norikazu Shimizu received an honorarium from Alexion Pharmaceuticals, Inc.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (No. A20054). The protocols of the study were disclosed on the institutions' websites or other places, such as bulletin boards, and provisions to opt out were presented. Therefore, written consent was not obtained.

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REFERENCES

1. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. *Lancet*. 2007;369(9559):397-408. doi:10.1016/S0140-6736(07)60196-2
2. Stremmel W, Merle U, Weiskirchen R. Clinical features of Wilson disease. *Ann Transl Med*. 2019;7(Suppl 2):S61. doi:10.21037/atm.2019.01.20
3. Saito T. Presenting symptoms and natural history of Wilson disease. *Eur J Pediatr*. 1987;146(3):261-265. doi:10.1007/BF00716470
4. Aoki T, Suzuki M, Fujioka Y, et al. Nationwide survey of clinical features of Wilson's disease in Japan. In: Lam STS, Pang CCP, eds. *Neonatal and Perinatal Screening, the Asian Pacific Perspective*. The Chinese University Press; 1996:25-28.
5. Shimizu N, Yamaguchi Y, Aoki T. Treatment and management of Wilson's disease. *Pediatr Int*. 1999;41(4):419-422. doi:10.1046/j.1442-200x.1999.01093.x
6. Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med*. 1956;21(4):487-495. doi:10.1016/0002-9343(56)90066-3
7. Dixon HB, Gibbs K, Walshe JM. Preparation of triethylenetetramine dihydrochloride for the treatment of Wilson's disease. *Lancet*. 1972;1(7755):853. doi:10.1016/s0140-6736(72)90845-8
8. Eda K, Mizuochi T, Iwama I, et al. Zinc monotherapy for young children with presymptomatic Wilson disease: a multicenter study in Japan. *J Gastroenterol Hepatol*. 2018;33(1):264-269. doi:10.1111/jgh.13812
9. Walshe JM. Coper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. *Q J Med*. 1973;42(167):441-452.
10. Brewer GJ, Askari FK. Wilson's disease: clinical management and therapy. *J Hepatol*. 2005;42(Suppl 1):S13-S21. doi:10.1016/j.jhep.2004.11.013
11. Schilsky ML, Scheinberg IH, Sternlieb I. Prognosis of Wilsonian chronic active hepatitis. *Gastroenterology*. 1991;100(3):762-767. doi:10.1016/0016-5085(91)80023-3
12. Alam S, Lal BB, Stood V, Khanna R, Kumar G. AARC-ACLF score: best predictor of outcome in children and adolescents with decompensated Wilson disease. *Hepatol Int*. 2019;13(3):330-338. doi:10.1007/s12072-019-09938-3
13. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut*. 2007;56(1):115-120. doi:10.1136/gut.2005.087262
14. Beinhardt S, Leiss W, Stättermayer AF, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort. *Clin Gastroenterol Hepatol*. 2014;12(4):683-689. doi:10.1016/j.cgh.2013.09.025
15. Altraif I, Handoo FA, Ghamdi HA, Aljumah A, Al Jumah M, Afzal M. Presentation, diagnosis and outcome of predominantly hepatic Wilson's disease in adult Saudi patients: a single centre experience. *Saudi J Gastroentrerol*. 2012;18(5):334-338. doi:10.4103/1319-3767.101135
16. Członkowska A, Tarnacka B, Litwin T, Gajda J, Rodo M. Wilson's disease – cause of mortality in 164 patients during

1992-2003 observation period. *J Neurol*. 2005;252(6):698-703. doi:10.1007/s00415-005-0720-4
17. Prashanth LK, Taly AB, Shinha S, et al. Prognostic factors in patients presenting with severe neurological forms of Wilson's disease. *QJM*. 2005;98(8):557-563. doi:10.1093/qjmed/hci095
18. Svetel M, Pekmezović T, Tomić A, et al. Quality of life in patients with treated and clinically stable Wilson's disease. *Mov Disord*. 2011;26(8):1503-1508. doi:10.1002/mds.23608
19. Camarata MA, Ala A, Coskun AK, et al. The effect of mental health, neurological disease, and liver disease on quality of life in patients with Wilson disease. *J Acad Consult Liaison Psychiatry*. 2021;62(5):528-537. doi:10.1016/j.jaclp.2021.04.004
20. Shimizu N, Suzuki M, Yamaguchi Y, Aoki T, Matsuda I, Arima M. A nation-wide survey for neurologic and hepatoneurologic type of Wilson disease: clinical features and hepatic copper content. *No To Hattatsu*. 1996;28(5):391-397.
21. Roberts EA, Schilsky ML, American Association for Study of Liver Disease (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology*. 2008;47(6):2089-2111. doi:10.1002/hep.22261
22. European Association for Study of Liver. EASL clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-685. doi:10.1016/j.jhep.2011.11.007
23. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090
24. Sternlieb I, Scheinberg IH, Walshe JM. Bleeding oesophageal varices in patients with Wilson's disease. *Lancet*. 1970;1(7648):638-641. doi:10.1016/s0140-6736(70)90883-4
25. Zhong HJ, Xiao P, Lin D, Zhou HM, He XX. Cirrhosis in Wilson disease is characterized by impaired hepatic synthesis, leukopenia and thrombocytopenia. *Int J Med Sci*. 2020;17(10):1345-1350. doi:10.7150/ijms.44338
26. Li XW, Li LY. Efficacy of neuromuscular electrical stimulation on Wilson's disease patients with dysphagia. *J Phys Ther Sci*. 2019;31(12):971-974. doi:10.1589/jpts.31.971
27. Gulyas AE, Salazar-Grueso EF. Pharyngeal dysmotility in a patient with Wilson's disease. *Dysphagia*. 1988;2(4):230-234. doi:10.1007/BF02414433
28. Hegedus D, Ferencz V, Lakatos PL, et al. Decreased bone density, elevated serum osteoprotegerin, and β-cross-laps in Wilson disease. *J Bone Miner Res*. 2002;17(11):1961-1967. doi:10.1359/jbmr.2002.17.11.1961
29. Chu NS, Hung TP. Geographic variations in Wilson's disease. *J Neurol Sci*. 1993;117(1-2):1-7. doi:10.1016/0022-510x(93)90145-o
30. Golding DN, Walshe JM. Arthropathy of Wilson's disease. Study of clinical and radiological features in 32 patients. *Ann Rheum Dis*. 1977;36(2):99-111. doi:10.1136/ard.36.2.99
31. Masełbas W, Litwin T, Czlonkowska A. Social and demographic characteristics of a Polish cohort with Wilson disease and the impact of treatment persistence. *Orphanet J Rare Dis*. 2019;14(1):167. doi:10.1186/s13023-019-1133-2
32. Shah AM, Malhotra A, Kothari S, Baddoura W, Depasquale J, Spira R. Reversal of liver cirrhosis in autoimmune hepatitis. *Hepatogastroenterology*. 2011;58(112):2115-2117. doi:10.5754/hge09768

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APPENDIX A

Hepatic symptoms	Jaundice
	Hepatomegaly
	Ascites
	Splenomegaly
	Esophageal varices
	Abnormal liver function
	Others
Neurological signs	Dysarthria
	Gait disorder
	Hygrostomia
	Flapping tremor
	Dystonia
	Cerebellar ataxia
	Consciousness disorder
	Others
Psychiatric signs	Intellectual disability
	Depression
	Hallucination
	Others