1. TITLE PAGE

TITLE

Risk factors, treatment, and survival rates of late-onset acquired hemophilia A: a cohort study from the Shizuoka Kokuho Database

RUNNING TITLE

Risk factors of acquired hemophilia A

AUTHORS

Aya Shoji-Asahina, MD[*,†], Eiji Nakatani, PhD[*], Yutaro Imaichi, MD[*], Emi Ohata, PhD[*], Michiko Oshima, BS[*], Akinori Miyakoshi, MD, PhD[*], Hiromu Miyake, MD, PhD[*], Yoshikazu Ichikawa, MD[*], Hisashi Dote, MD[*], Nanako Ubukata, MS[*], Daito Funaki, MS[*], Tetsumei Urano, MD, PhD[*,‡]

Drs Shoji-Asahina and Nakatani were equally contributed.

AFFILIATIONS

*Graduate School of Public Health, Shizuoka Graduate University of Public Health, Aoi-ku, Shizuoka 420-8527, Japan.

†Department of Clinical Laboratory, Japanese Red Cross Shizuoka Hospital, Aoi-ku, Shizuoka 420-0853

‡Department of Medical Physiology, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu 431-3192

CORRESPONDENCE

Aya Shoji-Asahina

Department of Clinical Laboratory,

Japanese Red Cross Shizuoka Hospital

Ote-machi 8-2, Aoi-ku, Shizuoka 420-0853, Japan

Tel: +81-54-254-4311, Fax: +81-54-252-8816

E-mail: asahina@kfx.biglobe.ne.jp

KEYWORDS

acquired hemophilia A, autoimmune disease, Alzheimer's disease, population-based cohort,

risk factor

MANUSCRIPT INFORMATION

Abstract, 203 words; body, 3,387 words; tables, 4; supplementary tables, 5; figure, 4;

references, 31

2. ABSTRACT

Introduction: Acquired hemophilia A (AHA) is a rare disease. The risk factors have yet to be studied.

Aim: We aimed to identify risk factors for late-onset AHA in Japan.

Methods: A population-based cohort study was conducted using data from the Shizuoka Kokuho Database. The study population was defined as individuals aged ≥60 years old. Cause-specific Cox regression analysis was performed to calculate hazard ratios.

Results: Of 1,160,934 registrants, there were 34 patients with newly diagnosed AHA. The mean follow-up period was 5.6 years, and the incidence of AHA was 5.21 per million person-years. Myocardial infarction, diabetes mellitus, solid tumors, antimicrobial agents, phenytoin, and anti-dementia drugs, which showed significant differences in the univariate analysis, were excluded from the multivariable analysis because of the small number of cases. Multivariable regression analysis showed that the presence of Alzheimer's disease (hazard ratio [HR]:4.28, 95% confidence interval [CI]:1.67-10.97) and rheumatic disease (HR:4.65, 95% CI:1.79-12.12) increased the risk of AHA development.

Conclusion: We found that comorbid Alzheimer's disease is a risk factor of AHA incidence in the general population. Our findings provide insight into the etiology of AHA, and the proof of

the coexistence of Alzheimer's disease may support the recent notion that Alzheimer disease is an autoimmune disease.

3. MAIN BODY OF TEXT

INTRODUCTION

Acquired hemophilia A (AHA) is a rare disease caused by an autoantibody against factor VIII (FVIII), which results in the decrease in FVIII activity and bleeding symptoms [1-3]. The incidence of AHA has been reported to be 0.8 to 1.83 per million persons per year in Japan [4, 5] and 1.34 per million persons per year in the UK [6]. Oleshkok et al. reported that the incidence of AHA in Germany increased from 2.6 per million population-years to 6.0 per million population-years [7]. The fatality rate is reported to be 7.9-33% [1, 4-6, 8-12], and the prognosis is poor. The most common clinical complaints are subcutaneous and intramuscular hemorrhage, hematuria, and persistent bleeding after delivery or surgery [3]. Early diagnosis and therapeutic intervention are necessary because the risk of bleeding is usually severe and fatal unless the inhibitor disappears [13]. Therefore, identifying a population with high-risk factors for AHA will help advance the diagnosis.

It is well known that underlying diseases may be present during the development of AHA. Common underlying diseases include autoimmune diseases (11.8-31.7%), malignancies (6.7-20%), pregnancy, and delivery (0-11%) [1, 4-6, 9-13], however, approximately half of the cases are idiopathic (44.1-63%) [1, 4, 5, 9, 10, 12, 13]. In addition, AHA is known to occur

more frequently in the elderly [4-6, 9, 10, 13]. Dysfunction of the immune system caused by aging can contribute to the loss of self-tolerance and potentially increase the risk of developing AHA [14]. Since immune mechanisms are thought to be involved in its pathogenesis [2], it makes sense that background immune abnormalities are highly prevalent. However, if autoimmune abnormalities are the only triggers, as in systemic lupus erythematosus and Graves' disease, they would be more common in younger patients than in older patients. Thus, other triggers associated with aging may be necessary for the development of AHA.

AHA has been increasingly recognized in recent years and the number of diagnosed cases is increasing [4, 11, 15]. Therefore, case-only registry studies [1, 8-12, 16], case-only single-center studies [4], and prospective cohort studies [5, 6, 13] have been conducted as epidemiological studies. However, it is difficult to comprehensively examine the risk factors for the development of AHA using these research populations because research content needs to be defined before starting the survey.

The Shizuoka Kokuho Database (SKDB) is a large and comprehensive dataset that is helpful in calculating the incidence and examining risk factors, even for rare diseases such as AHA [17]. The SKDB included most of the aged population in the region, making it advantageous for investigating AHA, which has a high incidence among older people. This

study aimed to identify risk factors for late-onset AHA.

MATERIALS AND METHODS

Setting and data source

SKDB is a claims database with registration data for 2,398,393 individuals (men, n=1,094,726, 45.6%) living in Shizuoka Prefecture near the center of Japan (population of approximately 3.6 million) [17]. It includes data from the National Health Insurance Service and is suitable for real-world studies because it contains accurate information on deaths and loss to follow-up from Japan's Basic Resident Registration Network System. This database contains information collected for the last 8.5 years, from April 2012 to September 2020, and includes basic information from the subscriber list (sex, age, zip code, observation period, and reason for disenrollment, including death). In addition, claims data from public health insurance organizations were included (< 75 years old for national health insurance and ≥ 75 years old for late-stage elderly medical care systems). SKDB has been used as a data source in several studies [18, 19].

Study design and participant population

The analysis was designed as a population-based cohort study using the SKDB. The study period was defined as the period from the date of enrollment in the health insurance organization or April 1, 2012, whichever occurred later, to the date of withdrawal from insurance or September 30, 2020, whichever occurred earlier.

The study population was defined as individuals aged 60 years and older, and the starting date of follow-up was one year after cohort entry. We described one year as the baseline period before the start date, and patients who had already developed AHA during the baseline period were excluded.

Covariates

Patient information and comorbidities were also collected during the baseline period. The candidate risk factors were age, sex, and Charlson Comorbidity Index (Supplementary Table 1), which are widely used in many studies [20]. Information was collected using the ICD-10 for pemphigoid [1, 9, 10, 12, 13, 16], epidermolysis bullosa [21], erythema annulare centrifugum [1, 16], erythema multiforme [16], exfoliative dermatitis [1, 16], and psoriasis [1, 9, 16] (Supplementary Table 2), which have been previously reported as candidate risk factors for the onset of AHA. For Alzheimer's disease, information was extracted using F00 and G30

of the ICD-10. Similarly, approximately 40 drugs previously reported as risk factors for the onset of AHA [1, 4, 9-13, 22] were also collected using Japanese claim codes (Supplementary Table 3).

Exact review of AHA onset

The primary outcome of this study was new-onset AHA. Death or insurance withdrawal, such as changes in the insurance system or address changes, was treated as censoring. For the exact definition of AHA onset, in the receipt data, the AHA extracted by the Japanese receipt disease code 8845658, primary disease for admission, and treatment and follow-up examination for AHA (at least three new steroid prescriptions and/or at least three new FVIII inhibitor tests) were reviewed.

Statistical analysis

Continuous and categorical variables were summarized as mean ± standard deviation and number (percentage). To compare the two groups, the Wilcoxon rank-sum test for continuous variables and the chi-square test with Yates' continuity correction for categorical variables were used.

To identify the risk factors for developing AHA, cause-specific Cox regression analysis was performed to calculate hazard ratios, 95% confidence intervals (CI), and P-values based on the Wald test. Sex, age, comorbidities measured using the Charlson comorbidity index, and prescribed medications were included in univariate regression analysis. In a multivariable analysis of covariates that were significantly different in the univariate analysis, Spearman's rank correlation coefficient between each covariate was calculated to eliminate multicollinearity, and correlations were considered to exist if the absolute value was ≥ 0.4. If there was a correlation between the two covariates, we considered which covariate to use, considering the covariate's clinical importance. When the number of persons recorded for each variable was less than four, it was not included in the multivariable analysis to avoid errors in reporting incorrect risk factors. Variables with statistical significance in multivariable analysis were identified as risk factors for AHA onset, and cumulative onset curves were plotted for these factors using the Kaplan-Meier method. The log-rank test was used to compare cumulative incidence curves. Because there were no missing values among all variables, the imputation method for missing data was not performed. All P values were two-sided. Statistical significance was set at $P < 0.05$. SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R statistical software version 4.1.2 (R Foundation for Statistical Computing,

Vienna, Austria) were used for the statistical analysis.

RESULTS

Study population

Figure 1 shows the flow diagram of the process used to select the participants. The baseline characteristics were classified according to the onset of AHA (Table 1). Patients with newly diagnosed AHA were older and more likely than those without AHA to have Alzheimer's disease and comorbidities defined by the Charlson comorbidity index, including dementia, myocardial infarction, congestive heart failure, peripheral vascular disease, rheumatic disease, diabetes mellitus without chronic complications, and metastatic solid tumors. Patients with AHA onset tended to be prescribed carbapenems and Alzheimer's medications (Supplementary Table 4).

Identification and incidence of AHA onset

The mean follow-up period was 5.6 ± 2.4 years. Figure 2 shows a flow diagram of the process used to define the AHA diagnosis. The 51 patients with new-onset acquired hemophilia A were extracted from this database. The patients with suspected coagulation abnormality and without

treatment were excluded (N=17). The following 34 patients were defined as having truly acquired hemophilia. Inpatients with AHA as the primary disease (N=28), inpatients with AHA and at least three steroid prescriptions and/or three FVIII inhibitor tests (N=4), and outpatients with AHA (at least three steroid prescriptions and three FVIII inhibitor tests (N=2). Compared to the number of AHA patients (51) in which the receipt disease code was used as the diagnosis code, the positive predictive value was 66.7%. The incidence of AHA was 5.21 per million person-years in the population aged 60 years and older.

Identification of risk factors for AHA onset

The results of univariate regression analysis are shown in Table 2. Variables with statistical significance in the univariate analysis were entered into a multivariable model. The combination of dementia and Alzheimer's disease had an absolute Spearman's correlation coefficient >0.4 (Supplementary Table 5). Therefore, only Alzheimer's was included in the multivariable analysis because all dementia comorbidities in patients who developed AHA were Alzheimer's disease. However, myocardial infarction, diabetes mellitus without chronic complications, metastatic solid tumors, antimicrobial agents, phenytoin, and anti-dementia drugs that showed significant differences in univariate analysis were excluded from the

multivariable analysis because the number of patients was less than four.

The results of multivariable regression analysis are presented in Table 3. The presence of Alzheimer's disease and rheumatic disease increases the risk of developing AHAs. According to the results of the univariate analysis, the cumulative incidence of AHA was significantly higher in the group with Alzheimer's disease or rheumatic disease (both $P < 0.001$, Figure 3).

Treatment in AHA onset subgroup

From the month of diagnosis, immunosuppressive therapy, bypassing agents, or blood transfusions were administered within 3 months in 32 of the 34 patients (94.1%) (Table 4). No significant difference was observed between the transfusion and bypassing agents. Both the bypassing agent and blood transfusions were performed a month before and after diagnosis. Two patients (6.3%) did not receive immunosuppressive or bypassing agents; their primary diagnosis on admission was AHA, and they were alive after discharge.

Survival curve in AHA onset subgroup

None of the newly diagnosed AHA patients died within seven days of registration for AHA disease, 19 (55.9%) died during the observation period; and one had a follow-up period of 12

days after disease onset. In summary, 4 of 33 patients (12.1%) died within 28 days and 10 of 33 (30.3%) died within 90 days. The overall survival rates of patients with AHA are shown in Figure 4.

DISCUSSION

This study explored the risk factors for late-onset AHA using a cohort study from SKDB. To our knowledge, there have been no previous attempts to use cohort data to identify the risk factors for AHA onset.

The new-onset AHA group was older than the non-onset AHA group, and there was no difference in sex; the incidence of AHA and total mortality rates were much higher than previously reported [1, 4-6, 8-13, 16]. The reason may be that the present study was limited to those aged 60 years or older, which is the age group most likely to develop AHA [9]. We suspect this is because we used receipt data to comprehensively extract the AHA [7].

In this study, age, Alzheimer's disease, myocardial infarction, congestive heart failure, peripheral vascular disease, rheumatic disease, diabetes mellitus without chronic complications, metastatic solid tumors, antimicrobial agents, phenytoin, and anti-dementia drugs were identified as candidate risk factors in the univariate analysis to identify risk factors for AHA

development. Among these, age [2-6, 10, 12, 15], rheumatic diseases [2-6, 9-11], solid tumors [2-6, 9, 10, 13, 15], antimicrobial agents [2, 9, 16, 22], and phenytoin [16] have been previously reported to be associated with the development of AHA. Myocardial infarction, diabetes mellitus, solid tumors, antimicrobial agents, phenytoin, and anti-dementia drugs were not included in the multivariable analysis because of their small numbers. A database with a larger number of patients than that in the present study would clarify the association between these factors and the development of AHA.

In addition to previously reported rheumatic diseases, the presence of Alzheimer's disease was associated with the development of AHA in this study: six patients with dementia comorbid with AHA, all with Alzheimer's disease (ICD-10 G30), or dementia of the Alzheimer type (ICD-10 F00). The association between Alzheimer's disease and AHA has not yet been reported. To our knowledge, the only epidemiological report indicated that rivastigmine, an Alzheimer's drug, was prescribed to 1/501 patients with AHA in the EACH2 registry [9]. Our report is based on a small number of patients with AHA; therefore, the association between Alzheimer's disease and AHA development should be interpreted with caution. However, we believe that Alzheimer's disease and AHA may share a pathogenic autoimmune mechanism. Alzheimer's disease is hypothesized to have an autoimmune etiology [23-25], and several

reports have supported this hypothesis. Patients with Alzheimer's disease have significantly higher rates of autoantibody detection than controls [26]. Alzheimer's disease is epidemiologically associated with autoimmune diseases such as rheumatoid arthritis [27], bullous pemphigoid [28], pyogenic hidradenitis [28], and systemic lupus erythematosus [29]. The genetic loci associated with Alzheimer's disease include genes related to the immune system [30]. Nevertheless, the small number of patients with Alzheimer's disease comorbid with AHA and the effects of aging may not be entirely excluded. Epidemiological studies, including biological studies and causal effect estimation designs, are needed to examine the relationship between Alzheimer's disease and AHA. In addition, it is likely that patients with Alzheimer's are more likely to receive advanced medical care, have better medical observation, and are more likely to receive a diagnosis if they develop AHA.

Approximately half of the patients in the new-onset AHA group died during the observational period. This is due to the elderly population and long observation period. The mortality rate 90 days after onset was 30%, which is comparable to the SACHA registry [11] and a 2-year national surveillance study in the United Kingdom [13]. Causes of death in AHA are related to infections, comorbidities, and hemorrhage, which are side effects of immunosuppressive therapy [4, 5, 9] Data on causes of death are not available in the SKDB, so

it was not possible to examine them. There were no deaths within seven days of diagnosis, but the high rate of deaths in the acute to subacute phases indicates that the control of bleeding and infection during this period is critical.

In the current study, more than 90% of the patients with AHA were treated with immunosuppressive therapy, which is consistent with previous reports [4-6, 9-11, 13]. There was no difference in the number of age group-specific users between the steroid-alone and cyclophosphamide combination groups. Bleeding complications in the acute period seemed to be properly controlled in this study because bypassing agents and transfusion of red blood cells were performed within a month before and after the date of diagnosis. In the present study, 29% of patients with AHA received bypass agents, with variation in previously published studies (29.7-70.5%) [4-6, 9-11, 13]. In the registry study EACH2 [9], 70.1% received bypass treatment compared to 46% in the prospective cohort study SACHA [11]. Although other studies and our study differ in data sources and AHA definitions, the detailed reasons for the low rate of bypass therapy are unclear. It is possible that there was less bypass therapy in our study because we collected cases treated by general internists as well as hematologists and that their bleeding (symptoms) was less severe.

Patients with Alzheimer's disease may require screening with a blood coagulation test

when bleeding symptoms appear. In general, patients with Alzheimer's disease have difficulty adequately describing bleeding symptoms, such as hematomas. Therefore, when bleeding symptoms, such as unexplained subcutaneous, intramuscular, or gingival hemorrhage, appear in patients with Alzheimer's disease, blood coagulation disorders, including AHA, can occur. This is because patients with AHA generally require immediate inpatient management. Awareness of AHA among the elderly should continue to be promoted, as bleeding can be judged erroneously to be due to anticoagulants, antiplatelet medications, trauma, or skin fragility [10, 11].

This population-based study had several limitations. First, the study included individuals aged 60 years or older, and data related to pregnant women were not included because the SKDB does not record pregnancy and delivery data. Therefore, the present study could not examine pregnancy and delivery, which are important risk factors for AHA that have been identified in previous reports. Second, the diagnosis of AHA is based on ICD-10 codes, which do not allow us to confirm accurate information, including specific medical findings, such as the presence or absence of bleeding symptoms, severity of bleeding symptoms, laboratory data, and cause of death. Therefore, lupus anticoagulant cases may not have been excluded, and guidelines recommend the exclusion of lupus anticoagulant cases for the

diagnosis of AHA [31, 32]. Because lupus anticoagulant cases have an apparent decrease in FVIII activity and may also have false-positive inhibitors [32-34], it is difficult to differentiate them based on FVIII and inhibitor test results alone. The pathophysiology of negative lupus anticoagulant specifically decreased FVIII activity, and cross-mixing test patterns could also not be ascertained because clinical laboratory values were unavailable. The diagnosis of AHA in this study was based not only on the disease code, but also on the primary disease, hospitalization, clinical examination, and drug codes. Of the 51 patients with disease codes for AHA, 17 (33%, Figure 2) were not tested for factor VIII inhibitors and only underwent screening coagulation tests, such as prothrombin time and activated partial thromboplastin time. However, whether a patient has AHA cannot be determined solely based on the presence or absence of a screening coagulation test. Therefore, we defined the onset of AHA by considering patients with AHA as the primary disease at hospitalization, and if not, also with factor VIII inhibitor testing and steroid prescriptions. The specificity for the determination of AHA onset in this study was high, and the reliability of the outcome was thus high. AHA is a sporadic disease with an incidence of 5.21 per million persons per year over 60 years of age. Even in this population base, 34 patients with AHA could be extracted. Although univariate analysis showed significant differences in candidate risk factors, such as solid tumors, the number of cases was

small, and multivariable analysis was not performed conservatively. Fourth, bleeding symptoms such as location and severity are unknown. Instead, the frequency of red blood cell transfusions was investigated. Fifth, only the previously reported drugs were examined. However, this is the first report to investigate the involvement of drugs in patients with and without AHA. Sixth, as candidate risk factors, we examined the association of autoimmune diseases, such as rheumatic diseases in the Charlson comorbidity index and autoimmune skin diseases, with the development of AHA, but not organ-specific autoimmune diseases, such as autoimmune hepatitis and Hashimoto's disease.

CONCLUSION

In addition to the previously reported coexistence of old age and rheumatic diseases, we identified a new risk factor for the development of AHA in the general population and the coexistence of Alzheimer's disease. Our findings provide insight into the etiology of AHA, and the proof of the coexistence of Alzheimer's disease may support the recent notion that Alzheimer’s disease is an autoimmune disease.

AUTHOR CONTRIBUTIONS

AA: drafted the manuscript. AA, YI, and EM performed statistical analyses. AA and EN interpreted data. EN, YI, EM, MO, TU, AM, HM, YI, HD, NU, and DF contributed to critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

4. ACKNOWLEDGMENT

ACKNOWLEDGMENT

A database from the Japan Pharmaceutical Information Center was used for drug code search.

We thank Editage (https://www.editage.jp/) for editing the manuscript draft.

CONFLICT OF INTEREST

Nanako Ubukata is an employee of Sato Pharmaceutical Co. The other authors have no conflicts of interest to declare.

FINANCIAL DISCLOSURE

The Shizuoka Graduate University of Public Health conducts research projects on public health under contracts with the Shizuoka Prefecture, including this study.

DATA AVAILABILITY STATEMENT

According to Shizuoka Prefecture's data use agreement with local insurers, readers cannot access the analyzed data. Researchers interested in accessing this data set may submit an application to Shizuoka Prefecture to request access. Please contact the staff of Shizuoka Graduate University of Public Health (Email: info@s-sph.ac.jp).

ETHICS STATEMENT

All patient data were anonymized [17]. This study was approved by the Ethics Committee of the Shizuoka University Graduate School of Social and Health Medicine (# SGUPH_2021_001).

5. REFERENCE LIST

1. Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. *Thromb Haemost.* 1981;45(3):200-203.

2. Collins PW. Management of acquired haemophilia A. *J Thromb Haemost.* 2011;9 Suppl 1:226-235.

3. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol.* 2003;121(1):21-35.

4. Ogawa Y, Yanagisawa K, Uchiumi H, et al. Clinical characteristics and outcomes of acquired hemophilia A: experience at a single center in Japan. *Int J Hematol.* 2017;106(1):82-89.

5. Ogawa Y, Amano K, Matsuo-Tezuka Y, et al. ORIHIME study: real-world treatment patterns and clinical outcomes of 338 patients with acquired hemophilia A from a Japanese administrative database. *Int J Hematol.* 2022.

6. Collins P, Macartney N, Davies R, et al. A population based, unselected, consecutive cohort of patients with acquired haemophilia A. *Br J Haematol.* 2004;124(1):86-90.

7. Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A:

limitations, consequences, and challenges. *Semin Thromb Hemost.* 2014;40(7):803-811.

8. Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost.* 1997;78(6):1463-1467.

9. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost.* 2012;10(4):622-631.

10. Mingot-Castellano ME, Pardos-Gea J, Haya S, et al. Management of acquired hemophilia A: results from the Spanish registry. *Blood Adv.* 2021;5(19):3821-3829.

11. Borg JY, Guillet B, Le Cam-Duchez V, Goudemand J, Lévesque H. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise) registry. *Haemophilia.* 2013;19(4):564-570.

12. Morrison AE, Ludlam CA, Kessler C. Use of porcine factor VIII in the treatment of patients with acquired hemophilia. *Blood.* 1993;81(6):1513-1520.

13. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre

Doctors' Organisation. *Blood.* 2007;109(5):1870-1877.

14. Oleshko O, Werwitzke S, Klingberg A, et al. Targets of autoantibodies in acquired hemophilia A are not restricted to factor VIII: data from the GTH-AH 01/2010 study. *Blood Adv.* 2023;7(1):122-130.

15. Napolitano M, Siragusa S, Mancuso S, Kessler CM. Acquired haemophilia in cancer: A systematic and critical literature review. *Haemophilia.* 2018;24(1):43-56.

16. Bossi P, Cabane J, Ninet J, et al. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med.* 1998;105(5):400-408.

17. Nakatani E, Tabara Y, Sato Y, Tsuchiya A, Miyachi Y. Data resource profile of Shizuoka Kokuho Database (SKDB) using integrated health- and care-insurance claims and health checkups: the Shizuoka Study. *J Epidemiol.* 2021.

18. Goto H, Nakatani E, Yagi H, et al. Late-onset development of psoriasis in Japan: a population-based cohort study. *JAAD Int.* 2021;2:51-61.

19. Nishimura S, Kumamaru H, Shoji S, et al. Assessment of coding-based frailty algorithms for long-term outcome prediction among older people in community settings: a cohort study from the Shizuoka Kokuho Database. *Age Ageing.* 2022;51(3).

20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities

in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.

21. Yan TM, He CX, Hua BL, et al. Coexistence of acquired hemophilia A and epidermolysis bullosa acquisita: Two case reports and published work review. *J Dermatol.* 2017;44(1):76-79.

22. Franchini M, Capra F, Nicolini N, et al. Drug-induced anti-factor VIII antibodies: a systematic review. *Med Sci Monit.* 2007;13(4):Ra55-61.

23. Arshavsky YI. Alzheimer's Disease: From Amyloid to Autoimmune Hypothesis. *Neuroscientist.* 2020;26(5-6):455-470.

24. Wu KM, Zhang YR, Huang YY, et al. The role of the immune system in Alzheimer's disease. *Ageing Res Rev.* 2021;70:101409.

25. Bettcher BM, Tansey MG, Dorothée G, Heneka MT. Peripheral and central immune system crosstalk in Alzheimer disease - a research prospectus. *Nat Rev Neurol.* 2021;17(11):689-701.

26. Shim SM, Koh YH, Kim JH, Jeon JP. A combination of multiple autoantibodies is associated with the risk of Alzheimer's disease and cognitive impairment. *Sci Rep.* 2022;12(1):1312.

27. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-

articular manifestations and comorbidities. *Autoimmun Rev.* 2021;20(4):102776.

28. Zhang H, Zhang D, Tang K, Sun Q. The Relationship Between Alzheimer's Disease and Skin Diseases: A Review. *Clin Cosmet Investig Dermatol.* 2021;14:1551-1560.

29. Park H, Yim DH, Ochirpurev B, et al. Association between dementia and systemic rheumatic disease: A nationwide population-based study. *PLoS One.* 2021;16(3):e0248395.

30. Bettens K, Sleegers K, Van Broeckhoven C. Genetic insights in Alzheimer's disease. *Lancet Neurol.* 2013;12(1):92-104.

31. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. *Am J Hematol.* 2017;92(7):695-705.

32. P W C, Chalmers E, Hart D, et al. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol.* 2013;162(6):758-773.

33. Kazmi MA, Pickering W, Smith MP, Holland LJ, Savidge GF. Acquired haemophilia A: errors in the diagnosis. *Blood Coagul Fibrinolysis.* 1998;9(7):623-628.

34. Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost.* 2014;40(7):803-811.

6. TABLE AND FIGURE CAPTION LIST

Table 1. Participants' characteristics with and without acquired hemophilia A for the baseline period.

AHA, acquired hemophilia A; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus. The bold type indicates statistical significance. *Skin diseases include pemphigus, epidermolysis bullosa, erythema annulare centrifugum, erythema multiforme, exfoliative dermatitis and psoriasis.

Table 2. Univariate Cox Regression Hazards Analysis for incidence of acquired hemophilia A.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; DRI, direct renin inhibitor; HR, hazard ratio; NE, not estimated. The bold type indicates statistical significance. *Skin diseases include pemphigus, epidermolysis bullosa, erythema annulare centrifugum, erythema multiforme, exfoliative dermatitis and psoriasis.

Table 3. Multivariable Cox regression analysis for incidence of acquired hemophilia A.

The HR is for presence of the risk factor and for one year of age.

CI, confidence interval; HR, hazard ratio. The bold type indicates statistical significance. Alzheimer's disease and rheumatic disease were identified as risk factors for acquired hemophilia A.

Table 4. Treatment among patients with acquired hemophilia A.

AHA, acquired hemophilia A.

Figure 1. Flowchart for inclusion of participants in the study.

AHA, acquired hemophilia.

Figure 2. The procedure of diagnosis for AHA in this study.

AHA, acquired hemophilia; SKDB, Shizuoka Kokuho Database.

Figure 3. Cumulative incidence for AHA in participants with or without Alzheimer's disease (**A**) and rheumatic disease (**B**).

AHA, acquired hemophilia.

Figure 4. Survival probability in newly diagnosed AHA patients.

AHA, acquired hemophilia.

Figure 1.

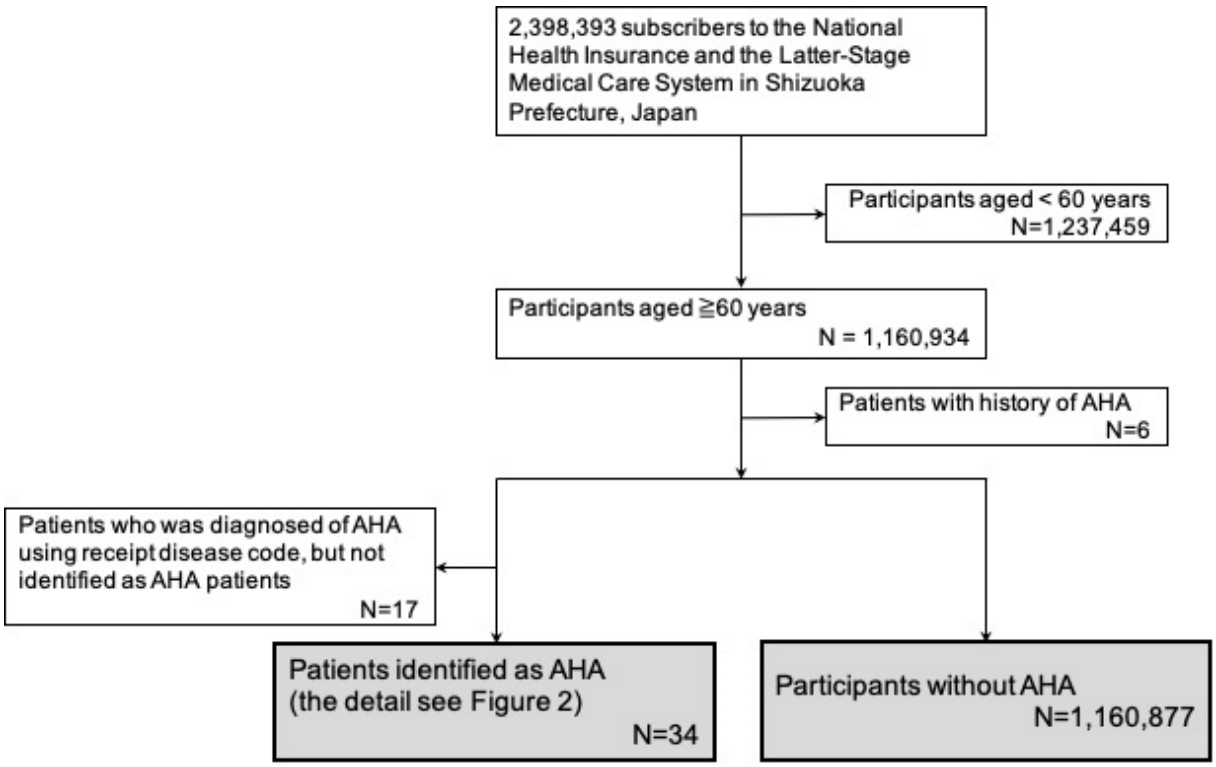

2,398,393 subscribers to the National Health Insurance and the Latter-Stage Medical Care System in Shizuoka Prefecture, Japan
Participants aged < 60 years N=1,237,459
Participants aged ≧60 years N = 1,160,934
Patients with history of AHA N=6
Patients who was diagnosed of AHA using receipt disease code, but not identified as AHA patients N=17
Patients identified as AHA (the detail see Figure 2) N=34
Participants without AHA N=1,160,877

Figure 2.

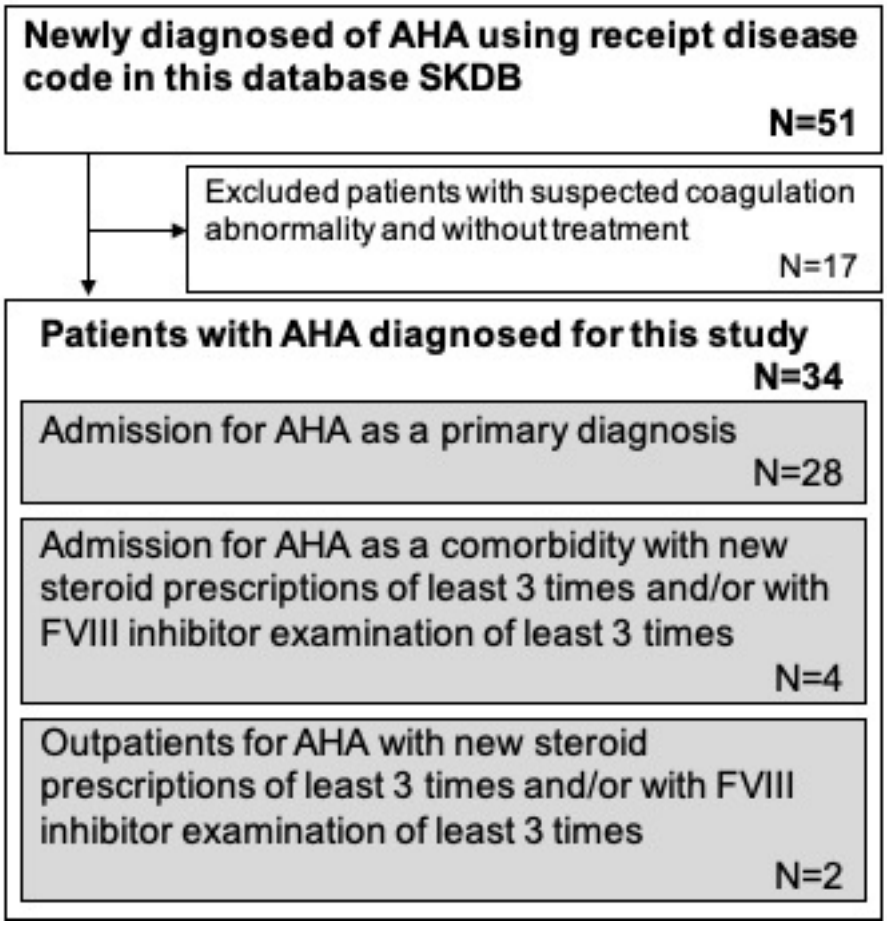

Newly diagnosed of AHA using receipt disease code in this database SKDB
N=51
Excluded patients with suspected coagulation abnormality and without treatment
N=17
Patients with AHA diagnosed for this study
N=34
Admission for AHA as a primary diagnosis
N=28
Admission for AHA as a comorbidity with new steroid prescriptions of least 3 times and/or with FVIII inhibitor examination of least 3 times
N=4
Outpatients for AHA with new steroid prescriptions of least 3 times and/or with FVIII inhibitor examination of least 3 times
N=2

Figure 3.

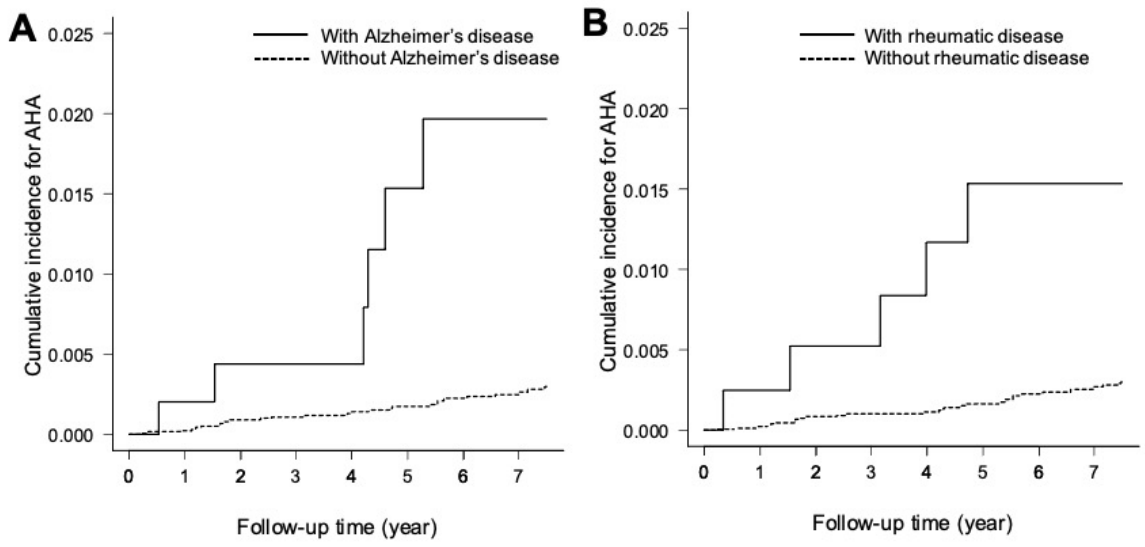
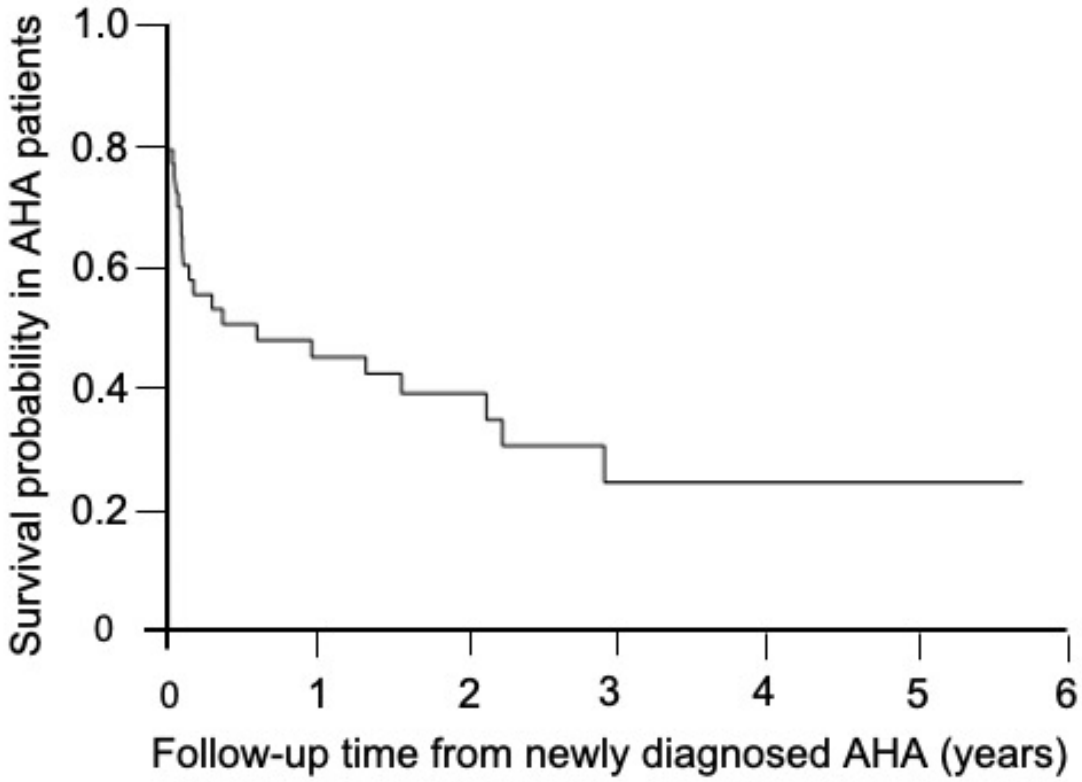

A
B
With Alzheimer's disease
Without Alzheimer's disease
With rheumatic disease
Without rheumatic disease
Cumulative incidence for AHA
0.025
0.020
0.015
0.010
0.005
0.000
0
1
2
3
4
5
6
7
Follow-up time (year)

Figure 4.


Survival probability in AHA patients
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
Follow-up time from newly diagnosed AHA (years)