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Original Article

Incidence, Cause of Death, and Survival of Amyloidosis in Korea: A Retrospective Population-Based Study

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Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Jang SY, Jeon ES; Data curation: Jang SY; Formal analysis: Jang

ABSTRACT

Background and Objectives: We sought to assess incidence, cause of death, and survival for amyloidosis. We acquired amyloidosis data from the National Health Insurance Service in Korea from 2006 through 2017 (n=2,233; male 53.5%).
Methods: We calculated the age-standardized incidence rate, analyzed the survival rate (SR) using the Kaplan-Meier method, and analyzed the death risk using Cox proportional hazards methods.
Results: The mean age was 57.0±16.7 years in males and 56.8±15.6 years in females (p=0.795). The proportion of death was 34.7%. The causes of death were endocrine, nutritional, and metabolic diseases (33.9%), malignant neoplasm (20.8%), and diseases of the circulatory system (9.68%). The overall age-standardized incidence rate was 0.47 persons per 100,000 persons in 2017. Overall, the 10-year SR for amyloidosis was 57.7%. Adjusted hazard ratios were 9.16 among 40s′, 16.1 among 50s′, 30.3 among 60s′, 48.7 among 70s′, 80.1 among people 80 years or older, and 1.21 in the medium-level socioeconomic position group.
Conclusions: The age-standardized incidence rate of amyloidosis was about 0.5 persons per 100,000 persons in 2017. The 10-year SR of amyloidosis was about 58%. The most common cause of death was endocrine, nutritional, and metabolic diseases. The risk of death from amyloidosis increased with age and medium socioeconomic position.

Keywords: Incidence; Survival rates; Cause of death; Proportional hazards models; Amyloidosis

INTRODUCTION

Amyloidosis is a rare disease that involves multiple organs. Due to delayed diagnosis and involvement of vital organs, prognosis for amyloidosis patients is usually considered to be grave. Few studies have evaluated the incidence, survival rate (SR), cause of death, and risk factors for death of amyloidosis. We have previously reported the prevalence of amyloidosis in Korea.[1] In the current study, we analyzed the age-standardized incidence rate, cause of death, and SR for amyloidosis patients using Korean National Health Insurance Service (KNHIS) data from 2006 through 2017.

SY; Investigation: Kim D, Choi JO, Jeon ES; Methodology: Jang SY; Resources: Jang SY; Software: Jang SY; Supervision: Choi JO, Jeon ES; Validation: Kim D; Visualization: Jang SY; Writing - original draft: Jang SY; Writing - review & editing: Jang SY, Kim D, Choi JO, Jeon ES.

METHODS

Study population

We collected newly diagnosed amyloidosis data from Korean National Health Insurance benefit records from 2006 through 2017 (n=2,233; male:female = 1.15:1). The data contained primary diagnoses related to amyloidosis according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Due to the limitation of data, amyloidosis (ICD-10: E85) diagnoses were extracted from the records after consideration of the data given for the primary diagnoses regardless of amyloidosis subtypes such as AL which is associated with a light chain-producing plasma cell dyscrasia, AA which is associated with longstanding inflammation, wild-type ATTR which is associated with normal transthyretin and old age, or hereditary ATTR which is associated with a transthyretin mutation. Besides, amyloidosis is covered by the National Health Insurance expanded benefit coverage for a rare incurable disease in Korea.[1)]

KNHIS database

The universal coverage health insurance system in Korea for all citizens was initiated in 1963, based on the National Medical Insurance Act. And universal healthcare coverage was achieved in 1989.[2)] The KNHIS database for Health insurance subscribers and Medicare recipients excluding foreigners consists of the following four databases: 1) qualification database including age, sex, type of subscription, and income rank; 2) medical check-up database includes the health examination data and lifetime transition period medical check-ups at 40 year-old and 66 year old; 3) medical institution database; and 4) treatment database including the type of disease, disease code using the ICD-10, and prescription. Treatment database has four categories of medicine, dentist, oriental medicine, and pharmacy. Among those 4 categories of treatment database, we only used the medicine. And we used variables from the qualifications database in conjunction with the treatment database.[3)4)]

Definition of variables

The age was defined as the first amyloidosis diagnosed age. Ages were categorized as 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 years or older. Socioeconomic factors included percentile group of income level using the Korean National Health Insurance premium divided into 20 quartiles. Income levels were categorized as upper, medium, and lower.

Death data

In this study, we used the death data of Korean people from 2006 through 2018. Korean citizens must submit 1) a death declaration and 2) a death certificate or a corpse optometry report by medical doctor to the town office of the deceased's place of residence or an area prescribed by law within one month of death, and its submission must be done by a direct family member or a person prescribed by law. The death declaration must include the following information: 1) the deceased's name, gender, resident registration number, address, death date and time, place of death, cause of death, death type such as death due to disease or accident, if accident; type of accident, accident date, place of accident, nationality, and marriage status; 2) the reporter's name, identification number, relationship with the dead, and contact information; and 3) Submitter's name and identification number. Among all the aforementioned information, we received only the cause of death and the date of death from the Korea Statistics Promotion Institute in accordance with the official procedure.[4)]

Cause of death

7We evaluated primary cause of death: certain infections and parasitic diseases (ICD-10: A00-B99); malignant neoplasm (ICD-10: C00-C97); benign neoplasm (ICD-10: D00-D48) & diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10: D50-D89); endocrine, nutritional, and metabolic diseases (ICD-10: E00-E90); mental and behavioral disorders (ICD-10: F01-F99); diseases of the nervous system (ICD-10: G00-G98); diseases of the circulatory system (ICD-10: I00-I99); diseases of the respiratory system (ICD-10: J00-J98); diseases of the digestive system (ICD-10: K00-K92); diseases of the skin and subcutaneous tissue (ICD-10: L00-L99); diseases of the musculoskeletal system and connective tissue (ICD-10: M00-M99); diseases of the genitourinary system (ICD-10: N00-N99); symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (ICD-10: R00-R99); injury, poisoning, and certain other consequences of external causes (ICD-10: S00-T98); and not provided.

Statistical methods

The differences in age, socioeconomic position, and causes of death by sex were analyzed using the Student's *t*-test for continuous variables and the χ^2 test for categorical variables. We calculated the age-standardized incidence of amyloidosis with the direct method using the beneficiaries of health insurance from the Korean National Health Insurance Statistical Yearbook from 2006 through 2017 as the subjects and the estimated Korean population in 2015 as the reference.[1)5)] The Kaplan-Meier method was also used to compare survival among patients with amyloidosis by age group and sex using log-rank tests. Simple and multiple Cox proportional hazards analyses were carried out using the variables of age, sex, and socioeconomic position.

Ethics approval and consent to participate

This research protocol was reviewed by the Institutional Review Board (IRB) of Samsung Medical Center, exempted from the consent, and approved as a review exemption with the following contents (IRB file number 2017-02-032): This study does not exceed the minimum risk for the subject. The exemption of informed consent does not adversely affect the rights or well-being of the study subject. It is practically impossible to obtain the informed consent from the subjects during the timeframe of research process. There is no reason to presume the subject's refusal to informed consent. Even if we do not give informed consent, the risk level for the subjects is extremely low. Therefore, this study received the informed consent exemption from IRB of Samsung Medical Center. The retrospective study aims to show the incidence, SR, and cause of death for amyloidosis by receiving the data from the KNHIS in a form without personal identification information for amyloidosis patients registered with the KNHIS from 2006 to 2017. The protocol of this study satisfies the IRB of Samsung Medical Center review exemption requirements.

RESULTS

Table 1 shows the distribution of the patients with newly diagnosed amyloidosis by sex in Korea. The mean±standard deviation) age of amyloidosis patients was 57.0±16.7 years in males and 56.8±15.6 years in females (p=non-significant [NS]). The male proportion was 53.5%. The proportion of death in amyloidosis patients was 34.7%. The proportions of cause of death were 33.9% for endocrine, nutritional, and metabolic diseases, 20.8% for malignant neoplasm, 9.68% for diseases of the circulatory system, and 9.29% for diseases of

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Table 1. The distribution of general characteristics, socioeconomic position, and cause of death by sex in AM and death risk for AM (n=2,233)

Variables	Total (n=2,233)	Male (n=1,195)	Female (n=1,038)	p-value*	Crude HR and 95% CI	Adjusted HR and 95% CI§
Age (years)	56.9±16.2	57.0±16.7	56.8±15.6	0.795	-	-
0–9	19 (0.9)	13 (1.1)	6 (0.6)	0.052	0.00 (0.00–999)	0.00 (0.00–999)
10–19	31 (1.4)	17 (1.4)	14 (1.3)		0.00 (0.00–999)	0.00 (0.00–999)
20–29	88 (3.9)	45 (3.8)	43 (4.1)		1.0	1.0
30–39	192 (8.6)	116 (9.7)	67 (6.5)		4.01 (0.92–17.4)	4.06 (0.93–17.6)
40–49	323 (14.5)	160 (13.4)	166 (16.0)		8.95 (2.18–36.6)‡	9.16 (2.23–37.5)‡
50–59	511 (22.9)	256 (21.4)	255 (24.6)		15.9 (3.95–64.5)†	16.1 (4.00–65.3)†
60–69	536 (24.0)	297 (24.9)	239 (23.0)		29.5 (7.34–118.8)†	30.3 (7.53–122.0)†
70–79	419 (18.8)	219 (18.3)	200 (19.3)		46.2 (11.4–186.2)†	48.7 (12.1–196.3)†
80+	114 (5.1)	72 (6.0)	42 (4.0)		75.7 (18.6–308.3)†	80.1 (19.6–326.3)†
Sex, male	1,195 (53.5)	1,195 (100.0)	0 (0.0)		1.04 (0.90–1.20)	1.00 (0.86–1.15)
Socioeconomic position				0.248		
Upper	1,079 (48.3)	596 (49.9)	483 (46.5)		1.0	1.0
Medium	585 (26.2)	299 (25.0)	286 (27.6)		0.93 (0.78–1.11)	1.21 (1.02–1.44)‡
Lower	569 (25.5)	300 (25.1)	269 (25.9)		1.01 (0.85–1.20)	1.18 (0.99–1.40)
Death	775 (34.7)	421 (35.2)	354 (34.1)	0.577	-	-
Cause of death	(n=775)	(n=421)	(n=354)	0.016	-	-
Certain infections and parasitic diseases (A00-B99)	18 (2.3)	7 (1.7)	11 (3.1)			
Malignant neoplasm (C00-C97)	161 (20.8)	84 (20.0)	77 (21.8)			
Benign neoplasm (D00-D48) and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	11 (1.4)	7 (1.7)	4 (1.1)			
Endocrine, nutritional, and metabolic diseases (E00-E90)	263 (33.9)	140 (33.3)	123 (34.7)			
Mental and behavioral disorders (F01-F99)	1 (0.1)	1 (0.2)	0 (0.0)			
Diseases of the nervous system (G00-G98)	3 (0.4)	2 (0.5)	1 (0.3)			
Diseases of the circulatory system (I00-I99)	75 (9.7)	44 (10.5)	31 (8.8)			
Diseases of the respiratory system (J00-J98)	24 (3.1)	17 (4.0)	7 (2.0)			
Diseases of the digestive system (K00-K92)	13 (1.7)	10 (2.4)	3 (0.8)			
Diseases of the skin and subcutaneous tissue (L00-L99)	3 (0.4)	1 (0.2)	2 (0.6)			
Diseases of the musculoskeletal system and connective tissue (M00-M99)	10 (1.3)	6 (1.4)	4 (1.1)			
Diseases of the genitourinary system (N00-N99)	72 (9.3)	23 (5.5)	49 (13.8)			
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	12 (1.5)	6 (1.4)	6 (1.7)			
Injury, poisoning, and certain other consequences of external causes (S00-T98)	19 (2.5)	15 (3.6)	4 (1.1)			
Not provided	90 (11.6)	58 (13.8)	32 (9.0)			

Values are presented as mean±standard deviation or number (%).
AM = amyloidosis; CI = confidence interval; HR = hazard ratio
*Student's *t*-test or χ^2 test, †p<0.001, ‡p<0.005, §Estimated by Cox proportional hazard model analysis using the variables indicated in the table.

the genitourinary system (p<0.05). Adjusted hazard ratios (HR) of death from amyloidosis were 9.16 (95% confidence interval [CI], 2.23–37.5) in the 40- to 49-year age group, 16.1 (95% CI, 4.00–65.3) in the 50- to 59-year age group, 30.3 (95% CI, 7.53–122.0) in the 60- to 69-year age group, and 48.7 (95% CI, 12.1–196.3) in the 70- to 79-year age group, 80.1 (95% CI, 19.6–326.3) in the 80 years or older age group, and 1.21 (95% CI, 1.02–1.44) in medium-level socioeconomic position group (**Table 1**).

The overall age-standardized incidence of amyloidosis was 0.34 persons per 100,000 persons in 2006 and 0.47 persons per 100,000 persons in 2017. We also showed age-standardized incidence of amyloidosis by sex and by age group (**Figure 1** and **Supplementary Table 1**).

Overall, the 10-year SR for amyloidosis was 57.7% (55.9% in males and 59.2% in females, p=NS). The 10-year SRs for the 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79-year age groups were 100%, 100%, 97.7%, 89.1%, 77.4%, 64.8%, 43.2%, and 27.8%,

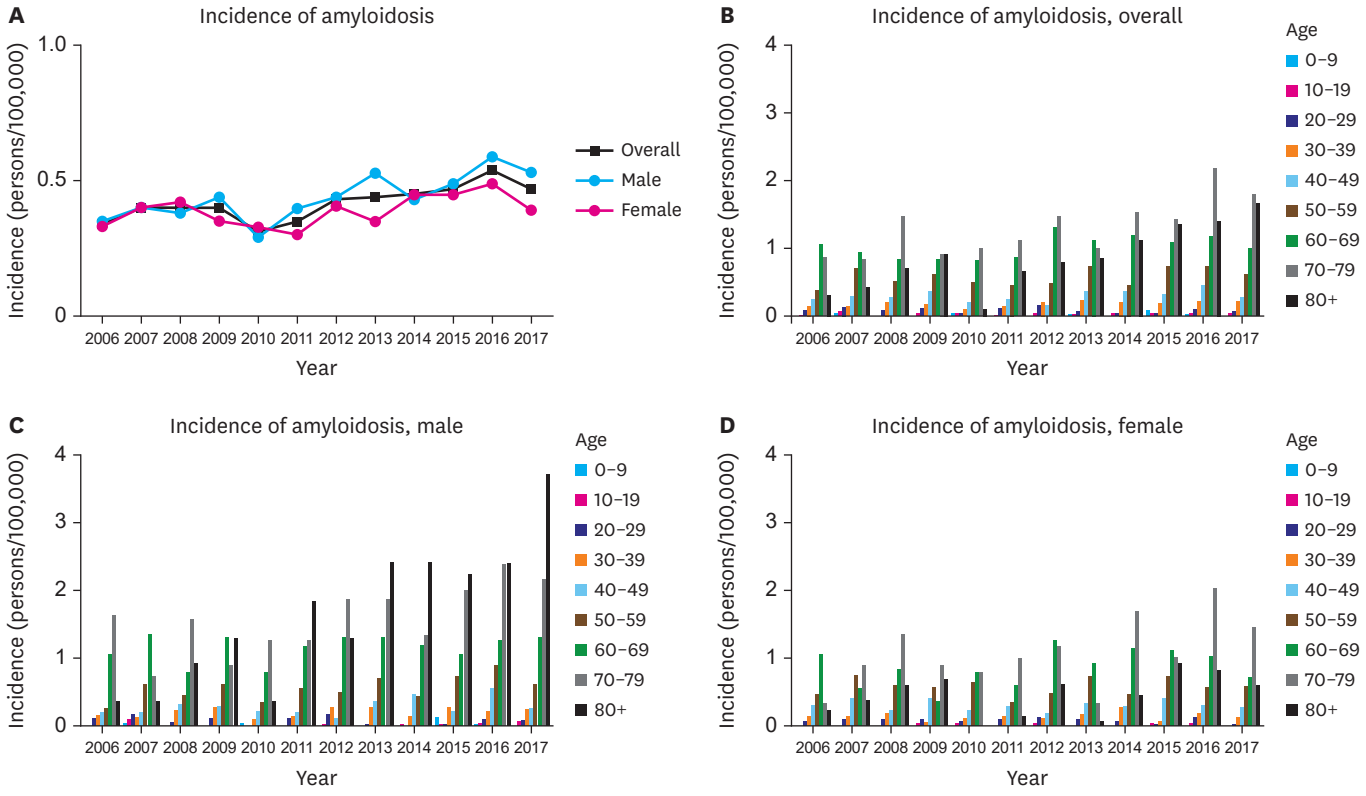

Figure 1. The age-standardized incidence of amyloidosis overall, by age group, sex, and year per 100, 000 persons between 2006 and 2017. (A) The age-standardized incidence of amyloidosis overall (middle), by sex (male: upper; female: lower), and by year per 100,000 persons between 2006 and 2017, (B) the age-standardized incidence of amyloidosis overall, (C) in males, and (D) in females by age group and by year per 100,000 persons between 2006 and 2017.

respectively. The 80 years or older group was censored at 9.47 years. Also, estimated survival time (mean±standard error) was 8.20±0.01 years in overall; 8.30± 0.17 years in female and 7.60±0.14 years in male (**Figure 2** and **Supplementary Table 2**).

DISCUSSION

We found that older amyloidosis patients showed a higher risk of death; adjusted HR values were higher in the age groups. A previous population-based study in Queensland, Australia from 1999 to 2013 showed higher HR with age.[6] The mean age in this study was 56.9±16.2 years; this is similar to the mean age of 129 amyloidosis patients from a tertiary hospital in Korea from 1999 to 2011.[7] On the other hand, 447 Australian amyloidosis patients showed a higher age of 66±64 years at the time of diagnosis. The 10-year SR by age group in this study showed lower SR with age. Few studies have found HR and SR by age group using population-based method; therefore, we could not compare SR by age group.

Adjusted HR for male sex was not significant in this study, similar to the Australian population-based study.[6] The 10-year SR in this study also did not differ much by sex. The proportion of males was 53.5% in this study, in close agreement with another study of 129 Korean amyloidosis patients that were 58.9%.[7] However, in the Australian study, the proportion of males was higher at 64%.

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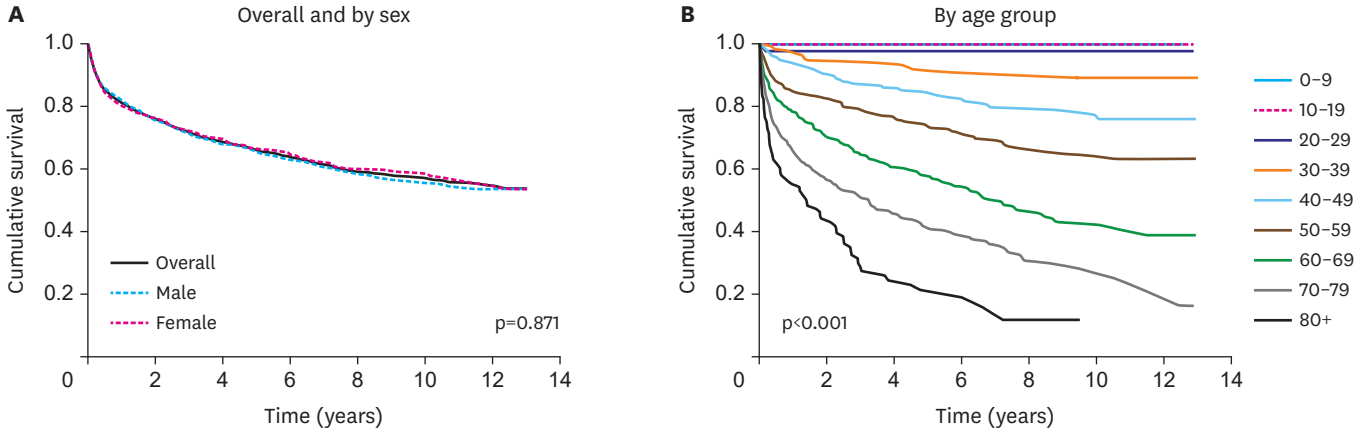

Figure 2. Survival curve for amyloidosis in Korean from 2006 through 2018. (A) Amyloidosis survival curve overall and by sex (p=non-significant); overall (middle), by sex (male: lower; female: upper) and (B) by age group (p<0.001)

The overall 10-year SR was about 58% in this study. Our results revealed higher SRs than another study of 159 light-chain amyloidosis patients from 1996 to 2003 at 40%.[8] The Australian study showed that overall SR by age group improved over 15 years.[9] Unfortunately, we could not show life expectancy for amyloidosis in this study. However, we calculated estimated survival mean years that was around 8 years by overall and sex.

Although the age-standardized incidence increased overall and by sex during a decade in this study, the incidences of Australian amyloidosis[6] and Swedish amyloidosis[10] were higher than those found in our study. In this study, the three major causes of death for amyloidosis were endocrine, nutritional, and metabolic diseases (ICD-10: E code), malignant neoplasm (ICD-10: C code), and diseases of the circulatory system (ICD-10: I code). We did not observe more specific causes of death using ICD-10 codes due to limited data. However, in additional observation, we showed the E8 code (range of genetic disorders including amyloidosis) had the highest proportion among the codes starting with ICD-E and the C9 code (range of blood cancer disease including multiple myeloma) among ICD-C codes. For socioeconomic position, we found a higher HR in the medium-level socioeconomic position group.

Our study has several limitations. First, the National Health Insurance benefit records might have missed amyloidosis patients who did not use medical services or who paid for their own medical expenses.[11] Therefore, the incidence and SR of amyloidosis in this study might be under- or overestimated. Because of the increasing incidence of amyloidosis, Korea needs a well-designed hospital-based amyloidosis registry. Second, due to data limitations we did not analyze by amyloidosis subtype.

In conclusion, we found that the age-standardized incidence of amyloidosis in Korea was about 0.5 persons per 100,000 persons in 2017. The SR across a decade was about 58%. Specifically, the older age groups showed lower SRs than the younger age groups. The three major causes of death for amyloidosis were endocrine, nutritional, and metabolic disease; malignant neoplasm; and diseases of the circulatory system. The death risk for amyloidosis was higher with age and medium socioeconomic status. These patterns in incidence, cause of death, and SR should be considered in future research designs and policies for amyloidosis healthcare services.

ACKNOWLEDGEMENTS

This study used data from the Korean National Health Insurance Service (KNHIS; research management number NHIS-2019-1-147), but the study results are not related to the KNHIS.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Age-standardized incidence* and 95% CI of amyloidosis overall and by sex (per 100,000)

Click here to view

Supplementary Table 2

SR (%) and 95% CI of amyloidosis overall, by sex, and by age group

Click here to view

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