Hospital incidence, mortality and costs of Alzheimer's disease in Spain: a retrospective multicenter study

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Author contributions

JD contributed to the investigation by analyzing and interpreting the burden associated to Alzheimer's disease in Spain and was a major contribution in the intellectual content revision. AM analyzed the current situation of dementia and Alzheimer's disease in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Abstract

Background: Alzheimer's disease (AD) is the most common form of dementia. Its neurodegenerative nature and the lack of a curative treatment result in a substantial burden for healthcare systems and society. This study aimed to analyze the hospital incidence and mortality of AD in Spain and to evaluate patients' use of healthcare resources and direct medical costs.

Methods: Admission records of patients with AD treated in hospitals in Spain between 2011 and 2016 were selected from a Spanish hospital discharge database.

Results: Records of 7,894 patients with diagnosed AD were analyzed. Hospital incidence was 3.7 per 10,000 persons over the study period, 2.9 and 4.4 for males and females, respectively. In-hospital mortality was 9.5%; both hospital incidence and in-hospital mortality increased over the study period. Mortality was principally associated with acute respiratory failure and other diseases of the respiratory system and heart failure. Annual medical costs of specialized care increased slightly during the study period, with a mean annual cost per patient of €4,969.

Conclusions: AD is responsible for an increasing proportion of hospitalizations in Spain and raising medical costs, which highlights the importance of early detection and optimized care.

Keywords: Alzheimer's disease; incidence; mortality; medical costs; Spain.

1. Introduction

Dementia is a multifactorial syndrome characterized by a significant cognitive decline, noticeable as a decline of memory, language and other abilities that hamper the individual's autonomy [1, 2]. The most common cause of dementia is Alzheimer's disease (AD), a terminal neurodegenerative condition accounting for 60-80% of dementia cases [3]. The estimated incidence rate of AD in southern Europe is 8.97 cases per 1000 person-years (95% CI, 8.13-9.86), with a prevalence of the 6.88% (95% CI, 6.19-7.61) [4]. In 2016, AD was the ninth cause of death in Spain, responsible for 36,027 deaths; 70% of the deaths were in women [5].

Primary care plays a central role in the diagnosis of the first symptoms of dementia and its possible association with AD [6]. A survey among primary care physicians in Europe indicated that, although some practitioners often try to establish a diagnosis on their own, about 56% of physicians immediately refer suspected dementia cases to a secondary care specialist [7]. Diagnosing AD generally requires a more exhaustive medical evaluation that is often conducted by neurologists [8]. The understanding of its neuropathology has increased substantially in the past quarter century, enabling the establishment of a set of criteria for its diagnosis [9, 10]. In general terms, AD is diagnosed when the patient presents cognitive impairment of a gradual onset, impaired functioning, and deficit in language and spatial cognition, in the absence of reversible causes. In addition, several biomarkers can be evaluated, as the presence of beta-amyloid protein or indices of neuronal damage [8, 11-13]. The guideline for the diagnosis and management of AD published by the European Federation of the Neurological Societies (EFNS) of Alzheimer's disease in 2010 supports the use of screening tests to assess cognitive impairment in patients with

70 dementia, followed by a set of more specific neuropsychological tests [14]. Once an AD

71 diagnosis is established, patients can receive pharmacological treatment, which may include

72 cholinesterase inhibitors, N-methyl D-aspartate (NMDA) antagonist and including non-

73 steroidal anti-inflammatory drugs, estrogens and statins; complementarily, non-

74 pharmacological treatment is highly recommended [10, 14]. The number of clinical trials

75 investigating new treatments and earlier diagnostic methods has risen in the past years [15,

76 16], which increases the interest on obtaining updated AD epidemiology data and a clear

77 definition patients' characteristics, comorbidities and current treatments.

78 Previous studies analyzing the situation of Alzheimer in Spain have focused on describing

79 risk factors [17]. Additionally, the MapEA Project analyzed the current diagnosis protocols

80 and management of the disease [18]; its conclusions, published in 2017, revealed great

81 deficiencies in early detection plans, diagnosis and disease follow-up [18]. Epidemiology

82 data is scarce in the country, with data available from one-prospective observational study

83 investigating societal costs in 2013 that collected patient and caregiver data [2].

84 This study aims to describe patient characteristics, hospital incidence and mortality of

85 Alzheimer's disease in Spain, to evaluate patients' use of medical resources and to estimate

86 the direct medical cost of AD in hospitals from the perspective of the National Spanish

87 Healthcare System.

88 2. Methods

89 *2.1. Study setting*

90 Healthcare records from patients with Alzheimer's disease were analyzed in a retrospective

91 multicenter study. Details of both inpatient and outpatient admissions were obtained from a

92 Spanish National hospital discharge database that includes records from public and private

93   hospitals, covering 90% of hospitals in Spain across Spanish regions. Data is codified at the

94   hospital level by means of the International Statistical Classification of Diseases and

95   Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) the

96   year 2016. Centers are responsible for data codification, evaluation and confidentiality. The

97   database is validated internally and subjected to periodic audits; in this process, errors and

98   unreliable data are eliminated. Data inclusion was limited to patients with a specialist

99   diagnosis of Alzheimer's disease attended in hospitals in Spain between 1 Jan 2011 and 31

100   Dec 2016.

101   *2.2. Data extraction*

102   Admission files corresponding to patients with AD were identified from the specialized

103   care database using one ICD-9 codes (331.0) and four ICD-10 codes (G30.0, G30.1, G30.8,

104   G30.9), specific for early onset AD, late onset AD, other AD and unspecified AD. Only

105   admissions in which AD was registered as the admission motive were included in the study.

106   Admission records did not contain any parameters identifying healthcare centers or medical

107   history that were previously re-coded to maintain records anonymized, in accordance with

108   the principles of Good Clinical Practice and the Declaration of Helsinki. This research did

109   not involve human participants and there was no access to identifying information; in this

110   context the Spanish legislation does not require patient consent and ethics committee

111   approval [19].

112   *2.3. Study variables*

113   The variables analyzed were: patients' sex and age, date of admission, type of admission,

114   date of discharge, type of discharge (including death), service that discharged the patient,

115   readmission rate (defined as a subsequent readmission for the same cause within 30-days

116   after discharge), admission motive, secondary diagnoses registered during the admission,

117 medical procedures performed codified with the ICD Procedure Classification System

118 (ICD9-PCS and ICD10-PCS) and cost of the admission.

119 ## 2.4. Data analysis

120 Only the first admission registered per patient in the study period was used for the analysis

121 of patients' characteristics; all admission files were used to analyze data on the nature of

122 admission, length of stay, readmission rate, medical procedures and admission costs.

123 Hospital incidence (hospitalization rate) was defined as the annual rate of AD related

124 admissions by the total number of hospital admissions. In-hospital mortality was calculated

125 as the annual number of hospital deaths registered in patients with AD by the total number

126 of patients admitted with AD. Direct medical costs of specialized healthcare were extracted

127 from the database, where they are assigned according to the standardized average expenses

128 of admissions and medical procedures determined by the Spanish Ministry of Health

129 (include all expenses related to the admission: examination, medication, surgery, diet, costs

130 associated to personnel, medical equipment and resources). The costs of prescribed

131 medication were not available.

132 Frequencies and percentages are presented for dichotomous variables and mean and

133 standard deviation or range were calculated for quantitative variables. The characteristics of

134 deceased patients were analyzed for the admission in which death was registered. The

135 association of secondary conditions to hospital mortality was assessed using the odds ratio

136 (OR) with 95% confidence interval (CI), with the group of patients non-deceased during the

137 hospitalization as the reference group. Two-tailed T-student or one-way analysis of

138 variance were used as appropriate and two-sample Z tests were used to test for differences

139 in sample proportions, with a $p<0.05$ considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

3.1. Patient characteristics

In total, 8,300 admission files were obtained, corresponding to 7,894 single patients treated in secondary care settings. The majority of the patients (61.97%) were females. Mean age was 80.40 years (SD=8.29) and female patients were significantly older (p<0.001), with a mean age of 81.17 years (SD=8.13) (Table 1). The most common secondary diagnoses registered upon admission were hypertension, disorders of lipoid metabolism (hypercholesterolemia and hypertriglyceridemia) and diabetes.

3.2. Incidence and mortality

Hospital incidence of AD in Spain between 2011 and 2016 was 3.68 per 10,000 patients, 2.94 and 4.36 per 10,000 males and females, respectively (Figure 1A). Hospital incidence increased significantly over the study period, from 3.47 per 10,000 in 2011 to 3.86 per 10,000 in 2016 (p<0.001).

In-hospital mortality rate was 9.53% during the study period, 8.89% in males and 9.92% in females (Figure 1B). The global in-hospital mortality rate increased significantly over the study period from 7.27% in 2011 to 10.74% in 2016 (p<0.001). Deceased patients displayed a higher frequency of acute respiratory failure (OR=4.71; 95%CI=3.69-6.01), other diseases of the respiratory system (OR=1.56; 95%CI=1.16-2.10), pneumonitis due to inhalation of food (OR=3.15; 95%CI=2.52-3.94) and heart failure (OR=1.92; 95%CI=1.39-2.66) (Table 1).

163 *3.3. Use of healthcare resources and medical costs*

164 The 81.80% of the admissions registered in Spanish hospitals were urgent or non-scheduled

165 and the readmission rate was 10.02%. Outpatient consultations were only the 1.42% of all

166 admissions, while mean length of hospital stay was of 10.47 days (0-785). The services to

167 discharge the patients were internal medicine services (46.20%), neurology (19.13%),

168 geriatrics (10.77%) and psychiatrics (10.64%).

169 Additionally, the most common medical procedures performed during the admission were

170 evaluated (Table 2). Diagnostic imaging techniques were predominant for these patients,

171 whereas psychiatric evaluation appeared underrepresented.

172 Finally, the imputed admission cost was used to estimate the direct medical costs of the

173 disease. The mean annual cost per patient was €4,969, increasing significantly over the

174 study period from €4,819 in 2011 to €5,393 in 2016 (p<0.001) (Figure 2). Patients'

175 deceased in hospital facilities, likely to have reached advanced stages of AD, resulted in a

176 mean cost per patient that reached the €6,022, significantly higher to that in patients non-

177 deceased during the admission, of €4,683 (p<0.001) (Table 3). The use of mechanical

178 ventilation dramatically increased admission costs; however, it was only registered in

179 3.53% of admissions.

180 **4. Discussion**

181 AD is one of the most important medical challenges worldwide; while an effective

182 treatment is still not available, its incidence maintains an increasing tendency, which

183 intensifies the need of enhancing care at all levels [20]. This study was centered in patients

184 with AD diagnosed by a specialist, admitted in hospitals in Spain. Patients' age was around

185   80 years and the percentage of females was over 60%. This higher incidence of AD among

186   females has been described in many occasions and for all age groups [10].

187   In-hospital mortality was 9.5%, although overall mortality rates are presumably higher; in

188   fact, AD was the ninth cause of death the year 2016 in Spain [5]. In addition, in-hospital

189   mortality increased over the years, a trend that has been observed in several European

190   countries, including Spain between 1994 and 2013 [21]. Generally, an advanced or severe

191   state of the disease can be assumed in deceased patients, reflected herein in the secondary

192   diagnoses registered including respiratory failure, pneumonitis due to inhalation of food

193   and heart failure that could ultimately be the direct causes of death [22].

194   When considering all patients, hypertension, hypercholesterolemia and diabetes were the

195   most frequent conditions, found in 43%, 25% and 24% of the patients, respectively; in the

196   Spanish population between 75 and 84 years of age these conditions were found in 57%,

197   41% and 26% of the population, respectively [23]. Urinary tract infections, urinary

198   incontinence and thyroid disorders have been directly linked with AD in previous studies

199   [24, 25]; similarly, depression can follow an AD diagnosis and has been found in 40-50%

200   of patients with AD [26]. The comorbidities described in a previous observational study in

201   Spain in 2013 included hypertension (50%), hypercholesterolemia (43%), depression

202   (31%), diabetes mellitus (21%), urinary tract disorders (12%), ischemic heart disease (8%)

203   and obstructive pulmonary disease (7%) [2]. In addition, a broad Spanish study, focusing

204   on the population with AD and senile dementia over 70 years of age, identified a large

205   number of hospital admissions due to other causes in this population, including

206   dehydration, malnutrition, pneumonia, urinary tract infection, pressure ulcer and

207   confusional state [27].

208   Mean annual hospitalization cost was €4,969 per patient. Data from the Spanish ministry of

209   health indicates that the overall medical cost per citizen was €2,033 the year 2016 in the

210   general population, €1,300 spent in specialized care [23]. Admission costs increased

211   between 2014 and 2016. One of the factors that could explain this increase is the upward

212   revision of unit costs of medical procedures and for the treatment of conditions as declared

213   by the Spanish Ministry of Health [28]. In addition, the extraordinary level of dependency

214   reached by patients with AD, particularly in advanced stages of the disease, and the

215   extended hospitalization time have been argued to increase these costs [29]. This is

216   reflected in the admission cost calculated in those admissions requiring mechanical

217   ventilation, increasing with length of hospital stay. Additionally, AD represents a great

218   burden for caregivers that goes beyond indirect or informal care costs, reporting health and

219   leisure-related issues and professional problems, which must be considered when

220   evaluating the total burden of this disease [30].

221   This study was limited by a series of factors. The recent update to ICD10-CM codes limits

222   the number of patients codified by this system, impeding the separate analysis of early

223   onset and late onset AD. Psychiatric evaluation appeared under registered, which limits the

224   interpretation of this data. Further studies will be required to estimate the total burden of

225   this disease.

226   Overall, this study provides a description of the characteristics of patients admitted with

227   Alzheimer's disease in Spanish hospitals, and evaluates medical costs and the factors

228   associated to the largest admission costs. Recommendations to avoid unnecessary

229   admissions, and to shorten hospitalization time when patient condition cannot be improved,

230   are expected to reduce the total medical cost of this disease. . In the upcoming years,

231   Alzheimer's increasing incidence is likely to translate in a growth of medical costs.

Multidisciplinary care should be promoted taking into account the complex needs of these patients, following early detection and optimized care for this incurable and terminal disease, while new treatments are investigated.

5. Declarations

6.1. Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

6.2. Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm

6.3. Funding

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6.4. Declaration of financial and other interest

The authors declare that they have no competing interests.

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354   Papers of special note have been highlighted as:

355   * of interest

356   ** of considerable interest

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369 # 8. Tables

370 **Table 1 Patient characteristics, in-hospital mortality and secondary diagnoses**

371 **registered in more than 5% of admissions in all files and in deceased patients.**

	Total admissions	Admissions of deceased patients
Admission files, N	8,300	796
Mean age, years (SD)	80.40 (8.29)	83.90 (7.69)
Female patients, %	61.97	64.32
Mean age female patients, years (SD)	81.17 (8.13)	85.35 (7.41)
Male patients, %	38.03	35.68
Mean age male patients, years (SD)	78.87 (8.55)	81.29 (7.51)
In-hospital mortality rate, %	9.5	-
Unspecified essential hypertension**, %**	42.73	28.14
Disorder of lipoid metabolism**, %**	24.96	12.69
Diabetes mellitus**, %**	23.72	16.96
Cardiac dysrhythmias**, %**	13.89	15.45
Urinary tract infection**, %**	13.19	10.18
Osteoarthrosis and allied disorders**, %**	11.45	6.91
Dementia**, %**	10.54	6.78
Other and ill-defined cerebrovascular disease**, %**	10.29	4.15
Anemia**, %**	9.15	7.16
Depression and anxiety**, %**	8.60	3.52
Thyroid disorders**, %**	8.09	5.28
Other forms of chronic ischemic heart disease**, %**	6.32	4.77
Urinary incontinence**, %**	6.28	5.65
Other diseases of respiratory system**, %**	4.50	7.04
Pneumonitis due to inhalation of food**, %**	3.64	12.44
Heart failure**, %**	3.07	5.90
Acute respiratory failure**, %**	2.94	13.82

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Table 2 Admission details and medical procedures performed in more than 5% of admissions.

	Total admissions
Urgent or non-scheduled admissions, %	81.80
Readmission rate, %	10.02
Mean length of hospital stay, days	10.47
Internal medicine services	46.20
Neurology services	19.13
Geriatrics	10.77
Psychiatric services	10.64
Medical procedures	-
Computerized axial tomography of head, abdomen or thorax	30.64
Injection or infusion of a therapeutic or prophylactic substance	29.63
Skeletal x-ray	22.25
Electrocardiogram	13.64
Microscopic examination of blood	11.90
Diagnostic ultrasound	8.34
Microscopic examination of specimen from bladder, urethra, prostate, seminal vesicle, perivesical tissue, and of urine and semen	7.51
Magnetic resonance imaging of brain and brain stem or spinal canal	7.22
Ambulatory cardiac monitoring	6.30
Percutaneous [endoscopic] gastrostomy [PEG]	6.27
Enteral infusion of concentrated nutritional substances	5.43
Psychiatric interview and evaluation	5.83

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Table 3 Mean direct medical costs of specialized care according to length of hospital stay (LOHS) per patient groups, type of admission and level of care.

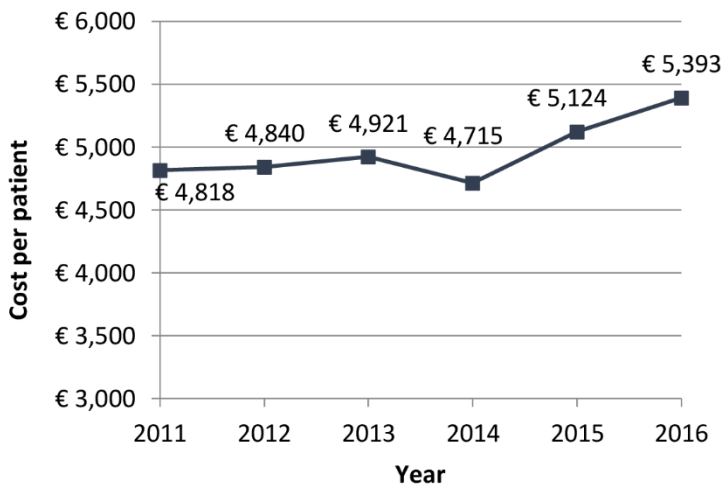|	Mean admission cost, LOHS ≤7 days	Mean admission cost, LOHS >7 days
Total patients	€4626	€5051
Patients deceased during the admission	€5880	€6197
Patients non-deceased during the admission	€4495	€4926
Urgent admission	€4653	€5057
Scheduled admission	€4516	€5036
Readmission	€4880	€5476
Internal medicine services	€4848	€5531
Neurology and neurosurgery services	€4088	€4421
Geriatrics	€4890	€5158
Psychiatric services	€4069	€4065
Non-invasive mechanical ventilation	€4911	€6271
Continuous invasive mechanical ventilation	€6651	€44,974
Other oxygen enrichment techniques	€6512	€7441

402 9. Figures

403 **Figure 1 A) Hospital incidence and B) in-hospital mortality of Alzheimer's disease in**

404 **Spain (2011-2016).**
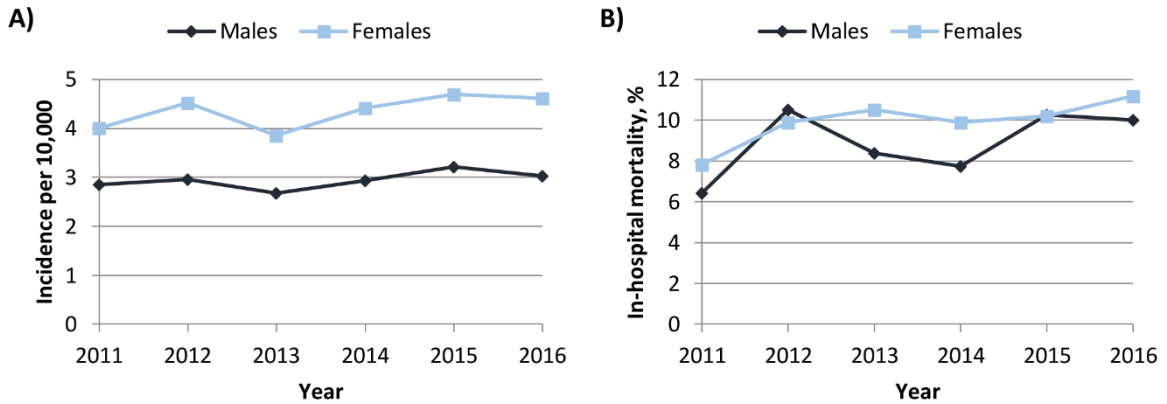
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406 **Figure 2 Annual direct medical cost of secondary healthcare per patient.**

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