ORIGINAL ARTICLE

16-Year Survival of the Canadian Collaborative Cohort of Related Dementias

Maya L. Lichtenstein, Nader Fallah, Benita Mudge, Ging-Yuek R. Hsiung, Dean Foti, B. Lynn Beattie, Howard H. Feldman

ABSTRACT: ***Background:*** Survival estimates are integral to care for patients diagnosed with dementia. Few Canadian studies have carried out long-term follow-up of well-described cohorts, analyzing survival related to multiple risk factors. ***Methods:*** Survival analysis of an inception cohort enrolled at a British Columbia (BC) tertiary dementia referral clinic between 1997 and 1999 was undertaken. Vital status was completed for 168 patients diagnosed with dementia. An evaluation of the effects of demographics, vascular risk factors, cognitive and functional ratings, apolipoprotein 4-status, and cholinesterase use on survival was performed using a log-rank test and time-dependent Cox regression. Survival of this dementia cohort was compared with the age-matched life expectancy of persons in BC. ***Results:*** In all, 158/168 (94.0%) subjects died over 16.6 years, with a median survival of 7.08 years. Risk factors associated with shorter survival in dementia groups included age of onset ≥80 (hazard ratio [HR] 1.56, 95% confidence interval [CI] 1.05-2.32); greater functional disability (Disability Assessment for Dementia < 55% [HR 1.47, 95% CI 1.04-2.08]); and cumulative medical illness severity (Cumulative Illness Rating Scale ≥ 7 [HR 1.51, 95% CI 1.08-2.12)]. Compared with the BC population, years of potential life lost for dementia subjects aged <65 was 15.36 years, and for dementia subjects aged ≥80 it was 1.82 years. ***Conclusions:*** Survival in dementia subjects is shorter than population life expectancies for each age strata, with greatest impact on younger patients. For people diagnosed with dementia, age ≥80 years, cumulative medical illness severity, and functional disabilities are the most significant survival predictors and can be used to guide prognosis.

RÉSUMÉ: Estimations de survie dans le cadre d'une étude de cohorte canadienne portant sur les démences. ***Contexte:*** Les estimations de survie font partie intégrante des soins prodigués à des patients chez qui la démence a été diagnostiquée. Peu d'études canadiennes reposent néanmoins sur un suivi à long terme de cohortes décrites et analysées en profondeur en tenant compte de l'espérance de survie et de plusieurs facteurs de risque. ***Méthodes:*** De 1997 à 1999, dans une clinique de soins tertiaires de la Colombie-Britannique spécialisée dans le traitement des démences, une analyse de la survie d'une cohorte, à son démarrage et selon le mode d'installation de la maladie, a été entreprise. On a ainsi établi le statut vital de 168 patients chez qui on avait diagnostiqué la démence. On a ensuite évalué les possibles effets des caractéristiques démographiques, des facteurs de risque vasculaires, des scores cognitifs et fonctionnels, de la présence d'allèles de l'ApoE et de l'utilisation d'inhibiteurs de la cholinestérase (ICh) sur la survie au moyen du test de Mantel-Haenszel et de la régression de Cox. L'espérance de survie de cette cohorte de patients atteints de démence a été finalement comparée à celle de personnes du même âge vivant aussi en Colombie-Britannique. ***Résultats:*** Sur un total de 168 patients, 158, soit 94,0 %, sont décédés il y a plus de 16,6 ans, l'espérance médiane de survie étant de 7,08 ans. Parmi les facteurs de risque associés, dans notre groupe de patients, à une survie plus courte, mentionnons : l'âge au moment de l'apparition de la maladie (≥80) (RR 1,56 ; IC 95 % : 1,05-2,32); une plus grande incapacité fonctionnelle (IFD < 55% ; RR 1,47 ; IC 95 % : 1,04-2,08); et la sévérité des antécédents pathologiques (Échelle du pointage cumulatif des maladies ≥7 ; RR 1,51 ; IC 95 % : 1,08-2,12). Si l'on compare nos patients à la population de la Colombie-Britannique, les années potentielles de vie perdues en raison de la démence chez des sujets âgés de plus de 65 ans ont été de 15,36 ans et de 1,82 ans chez ceux âgés de 80 ans ou plus. ***Conclusions:*** L'espérance de survie chez les patients atteints de démence est moins longue que celle qui correspond à la population générale, et ce, pour chaque couche d'âge comparée, le plus grand impact étant observé chez les patients plus jeunes. Dans le cas d'individus âgés de 80 ans chez qui l'on a diagnostiqué une démence, la sévérité de leurs antécédents pathologiques cumulatifs, de même que leurs incapacités fonctionnelles, demeurent les facteurs prédicteurs de survie les plus importants et peuvent ainsi être utilisés dans l'établissement d'un pronostic.

Keywords: Dementia, Alzheimer's, Clinical epidemiology

doi:10.1017/cjn.2018.6 Can J Neurol Sci. 2018; 45: 367-374

Background

The largest single risk factor for developing dementia is aging. As longevity increases, more people are diagnosed with dementia. In Canada, 24.8% of the population aged ≥65 years lives with dementia or mild cognitive impairment,[1] with annual estimated costs of $8.8 billion.[2] Accurate determination of life expectancy after dementia diagnosis is important for patients, families, and communities for planning

From the Department of Medicine, Division of Neurology, University of British Columbia Hospital, Clinic for Alzheimer Disease and Related Disorders, The Center for Brain Health, Vancouver, British Columbia, Canada (MLL, NF, BM, G-YRH, DF, BLB, HHF).

Received May 25, 2017. Final Revisions Submitted October 26, 2017. Date of Acceptance November 8, 2017.

Correspondence to: Howard H. Feldman, Department of Neurosciences, University of California San Diego, 9500 Gilman Drive, MC 0949, La Jolla, CA 92093. Email: hhfeldman@ucsd.edu

services, estimating costs of forthcoming care, and community support needs.

Previous studies indicate that survival rates vary considerably. Although the previous commonly cited survival estimate in dementia are 8-12 years,[3] more recent prospective studies using published diagnostic criteria estimate median survival after dementia diagnosis from 3.2[4] to 8.3[5] years. These differences may be attributed to study design and population, but individual patient factors also influence survival.

Canadian survival studies following dementia diagnosis are limited.[6-8] The studies are older, with shorter follow-up, and without systematic investigation of potentially important contributing risk factors. The Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD) was an eight-center study across Canada that included subjects referred to dementia specialty clinics for assessment of cognitive impairment. All subjects received comprehensive neurological, cognitive, and functional ability assessments before being classified as being "cognitively normal," "cognitively impaired but not demented" (CIND), or "dementia."[9]

The present study evaluates the long-term survivorship of the inception cohort referred to the lead and coordinating ACCORD site, at the University of British Columbia Hospital's Clinic for Alzheimer Disease and Related Disorders (CARD). Clinic for Alzheimer Disease and Related Disorders is a tertiary dementia referral clinic for the province of British Columbia (BC). This study aimed to evaluate the effects of demographics, genetic and vascular risk factors, dementia treatment, and comorbid medical illness on survival, and to compare survival of this cohort with a reference BC population.

Methods

Subjects

Canadian Cohort Study of Cognitive Impairment and Related Dementias enrolled an inception cohort of 1136 subjects from eight centers across Canada between 1997 and 1999. All participants were enrolled and consented consecutively, after referral by family physicians or other specialists. Detailed description of the methods have been previously published.[9] There were 229 newly referred patients enrolled through CARD, 169 of whom were initially diagnosed with dementia. For the current study, we undertook a survival analysis of this inception dementia cohort in 2015. One subject was removed because of significant missing baseline data, allowing an evaluable sample of 168 subjects.

Diagnosis

Diagnostic classification was made by CARD site investigators as cognitively normal, CIND, or dementia according to DSM-IIIR criteria[10] after evaluation of all clinical, laboratory, and neuroimaging data. Dementia etiology was ascertained in the following manner: Alzheimer's disease (AD) by NINCDS-ADRA criteria;[11] vascular dementia (VaD) was diagnosed on the basis of history of stroke, neurological signs consistent with cerebrovascular accidents, history of vascular risk factors or neuroimaging evidence of ischemic changes and Hachinski Ischaemic Score (HIS) score; frontotemporal dementia (FTD) was diagnosed on the basis of Lund and Manchester group criteria;[12] and dementia with Lewy bodies (DLB) using the criteria by McKeith et al.[13] All dementia diagnoses besides AD were grouped as "Other Dementias" (OD) for this analysis owing to small numbers.

Baseline demographic information included date of birth; sex; education; living status (alone or with others); and cholinesterase inhibitor (AchEI) use. Vascular risk factors, including diabetes mellitus, hypertension, hypercholesterolemia, atherosclerosis, and smoking, were assessed by nurse clinical interview or the presence of those risk factors through evaluation of medical records and current medications. These risk factors were recorded as dichotomous variables (yes/no). For a subset of participants (43%) within a separate consent, apolipoprotein 4 (ApoE-4) carrier status was analyzed.

Baseline scores of standardized assessments were also collected: Mini-Mental Status Examination (MMSE)[14] screens global cognition, with lower scores indicating more severe impairment (range 0-30); Cumulative Illness Rating Scale (CIRS)[15] rates impairment of 14 organ systems (including neurological, where the question was changed to "brain and spinal cord, *excluding dementia*" in order not to confound results given our cognitively impaired cohort), with higher scores indicating more severe comorbid medical disease (range 0-56); HIS[16] identifies underlying vascular components for dementia (range 0-18), with scores >7 indicating significant cerebrovascular contribution; Disability Assessment for Dementia (DAD)[17] rates everyday functioning including activities of daily living, with lower percentages indicating greater disability (range 0%-100%); Functional Rating Scale (FRS),[18] a derivative of the Clinical Dementia Rating Scale,[19] provides global staging of dementia severity, where higher scores indicate greater cognitive and functional impairment (range 8-32); and Neuropsychiatric Inventory (NPI)[20] assesses frequency and severity of neuropsychiatric disturbances (range 0-144), with higher scores indicating greater burden.

Determination of Vital Status

We obtained vital status for every subject on June 20, 2015 through the BC Medical Service Plan records, which has a record of all citizens in BC. Death dates and moves from BC are registered at the first of the new month after which a person died or moved. The 14th day of the previous month was used as censor date. Survival was calculated from the date of baseline assessment to censor date. Six participants left BC during follow-up time and were counted as censored at the time of their move.

Statistical Methods

Baseline characteristics were compared between diagnostic groups using independent *t*-test for continuous variables, using Levene's test to verify equality of variances in the samples. We used Pearson's χ^2 to compare categorical data. Significance was defined as two-tailed $p < 0.05$.

We performed separate unadjusted Kaplan-Meier curves and log-rank tests to determine survival from diagnosis for AD and OD groups for each variable. Continuous variables were stratified for these analyses. For age, we initially looked at 5-year age strata and found significant difference between groups of those under and over 80, but not for any other age strata. We then used ≥80 as a binary cut-off point to maximize statistical power to examine for group differences. For the MMSE and FRS, which have published cut-offs that are indicative of clinical differences,[21,22] those scores were used as strata. For the DAD, NPI, CIRS, and Hachinski

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press

scores, which do not have validated cut-off points marking severity, we initially divided the sample into quartiles. Given our small sample, quartiles without significant difference were grouped together to form a dichotomized variable to evaluate severity. Stratified groups were tested for proportional hazards, but assumptions were not met with diagnosis (AD vs. OD), and thus time-dependent Cox regression was used. Survival by 5-year age group was compared with BC population life expectancies for years 1990-1999,[23] reflecting the period of recruitment.

All analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Cohort Characteristics

Of the 168 participants diagnosed with dementia, 135 had a primary diagnosis of AD; 33 had a primary diagnosis that was non-AD, including 8 VaD, 9 DLB, and 12 FTD; and 4 were diagnosed with another dementia. As the numbers in each subtype of dementia were small, they were grouped as "OD" for the purpose of comparison. Table 1 lists the characteristics of the cohort. Mean age at diagnosis was 78.24 (SD 8.76). The groups differed significantly from each other in that the AD group was significantly older at the time of diagnosis, more likely to be female, and had lower MMSE scores than the OD group; the OD group in turn had significantly higher total CIRS, NPI, and Hachinski scores and lower DAD scores than the AD group. When comparing all dementia types by age strata <80 and ≥80, we found no significant difference between groups, except that those ≥80 were more likely to live alone (40% vs. 17%, $p = 0.004$) and there was a trend toward lower DAD scores (59 vs. 68, $p = 0.052$); data not shown.

Table 1: Baseline characteristics of cohort

	AD ($n = 135$)	OD ($n = 33$)	p-value
Age at assessment (mean [SD])	80.74 (7.79)	74.00 (7.12)	**≤0.001**
Event (death) (n [%])	128 (94.8)	30 (90.9)	0.395
Female sex (n [%])	89 (65.9)	9 (27.3)	**≤0.001**
Education in years (mean [SD])	11.61 (3.47)	12.58 (3.25)	0.148
Lives alone (n [%])	31 (23.0)	6 (18.2)	0.539
MMSE (mean [SD])	19.52 (5.45)	21.61 (5.18)	**0.048**
CIRS (mean [SD])	4.64 (2.70)	8.33 (3.95)	**≤0.001**
Hachinski (mean SD])	3.15 (1.56)	4.36 (2.54)	**0.012**
DAD (mean [SD])	68.23 (21.07)	58.17 (26.10)	**0.046**
FRS (mean [SD])	22.88 (4.67)	24.55 (3.87)	0.060
NPI (mean [SD])	10.09 (10.92)	19.39 (15.90)	**0.004**
Atherosclerosis (n [%])	15 (13.6)	7 (22.6)	0.225
Hypertension (n [%])	33 (28.2)	8 (30.8)	0.794
Dyslipidemia (n [%])	14 (17.5)	6 (26.1)	0.359
Diabetes mellitus (n [%])	9 (6.7)	4 (12.1)	0.299
Ever-smoked (n [%])	77 (57.0)	20 (60.6)	0.710
AchEI use (n [%])	75 (57.3)	12 (38.7)	0.063
ApoE-4 allele (n [%])	31 (60.8)	10 (71.4)	0.465

AchEI = cholinesterase inhibitor; AD = Alzheimer's disease; ApoE = apolipoprotein E; CIRS = Cumulative Illness Rating Scale; DAD = Disability Assessment for Dementia; FRS = Functional Rating Scale; MMSE = Mini-Mental Status Exam; NPI = Neuropsychiatric Inventory; OD = other dementias.

Percentages for dichotomous data are valid percent accounting for missing data. Bolded text indicates significant values.

Cognitive Diagnosis, Mortality, and Survival

In total, 158/168 (94.0%) subjects died during the mean follow-up time of 16.61 years (SD 0.82): 128/135 (94.8%) of AD, and 30/33 (90.9%) of OD. Unadjusted median survival was 7.08 years (SE 0.41) for all-cause dementia. There was no significant difference in the unadjusted median survivorship between AD (7.33 years, SE 0.25) and OD (4.33 years, SE 1.44, log-rank 1.72, $p = 0.190$).

We found that older age at diagnosis, higher CIRS, and lower DAD scores were significantly associated with shorter survival (Table 2; Figures 1A-1D). There was no interaction between DAD and CIRS scores. There was a trend toward significance between smoking ($p = 0.070$) and shorter survival. There was no significant association between other variables including AchEI use and survival. Given the relatively small sample size, only whole-sample significant factors were included in the subsequent regression model.

A model was built using time-dependent Cox regression adjusting for diagnosis (AD, OD), age at diagnosis (<80, ≥80), CIRS (<7, ≥7), and DAD scores (<55%, ≥55%). Shorter survival was associated with age ≥80 years (hazard ratio [HR] 1.56, 95% confidence interval [CI] 1.05-2.32); DAD scores <55% (HR 1.47, 95% CI 1.04-2.08); and CIRS scores ≥7 (HR 1.51, 95% CI 1.08-2.12). There was no difference in survival by group (AD vs. OD) in this model.

Median survival times by 5-year strata were compared with population life expectancies in BC[23] (Table 3). Survival decreased with each stratum, but years of potential life lost after a dementia diagnosis was particularly compromised for younger subjects: 15.36 years lost for those diagnosed <65 years, tapering to 1.82 years for those ≥80 years.

Discussion

In the current study, we report on the survival analysis of a well-characterized cohort referred to a tertiary-care dementia clinic in the province of BC, Canada. The median survival from diagnosis for all-cause dementia was 7.08 years. Important predictors of shorter survival within the dementia groups included older age, lower DAD, and higher CIRS scores. Comparing the median dementia survival with BC general population life expectancies, there was a reduction in survivorship across all age groups, with strongest effect on younger subjects.

Although survival time was reduced in subjects ≥80 years with dementia, the effect of reduced survival was strongest for those <80 years, consistent with other studies.[5,7,24-27] Age at diagnosis (≥80) was a significant risk factor for survival (HR = 1.56), a finding that is consistent with most[4,28-33] but not all[34-36] other studies.

Our cohort had relatively long survivorships after diagnosis—roughly 7 years compared with published median survival times of 3-8 years—but direct comparison with other studies is difficult. Differences can be at attributed to community sample;[4,6,28,34,37-39] older population age;[4,6,28,37,39-41] shorter

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press

Table 2: Survival table by characteristics for Alzheimer's disease (AD) and other dementia groups

Characteristic (*n*)	Median survival in years (SE)	χ^2 (df)	Unadjusted *p*-value (log-rank)
Age (years) at assessment		5.12 (1)	**0.024***
<80 (133)	7.25 (0.33)		
≥80 (35)	4.58 (1.40)		
Diagnostic group		1.72 (1)	0.190
AD (135)	7.33 (0.25)		
Other dementias (33)	4.33 (1.44)		
Sex		1.23 (1)	0.268
Male (70)	5.83 (0.52)		
Female (98)	7.42 (0.21)		
Education (years)		1.40 (1)	0.237
<12 (76)	7.33 (0.22)		
≥12 (92)	5.83 (0.89)		
Lives alone		0.03 (1)	0.855
Yes (37)	7.42 (0.19)		
No (130)	6.58 (0.61)		
CIRS strata		7.04 (1)	**0.008***
1st-3rd quartile (1-6 [114])	7.50 (0.17)		
4th quartile (≥7 [54])	4.17 (0.88)		
Hachinski strata		0.13 (1)	0.715
1-3 (106)	7.33 (0.31)		
≥4 (62)	6.17 (0.84)		
MMSE strata		1.56 (2)	0.458
≤17 (47)	6.33 (1.54)		
18-23 (70)	7.33 (0.56)		
≥24 (49)	7.08 (0.95)		
DAD strata		5.38 (1)	**0.020***
1st quartile (<55% [49])	4.00 (1.16)		
2nd-4th quartile (≥55% [116])	7.33 (0.27)		
FRS strata		2.15 (1)	0.143
Normal to mild: 8-23 (97)	7.17 (0.44)		
Moderate to severe: 24-40 (71)	6.58 (0.52)		
NPI strata		0.13 (1)	0.720
1st-2nd quartile (<7 [72])	7.17 (0.97)		
3rd-4th quartile (≥7 [90])	6.83 (0.39)		
Hypertension		0.73 (1)	0.395
Yes (41)	6.83 (0.56)		
No (102)	7.33 (0.38)		
Dyslipidemia		0.75 (1)	0.386
Yes (13)	6.83 (1.74)		
No (154)	7.17 (0.50)		
Diabetes		1.67 (1)	0.196
Yes (14)	3.75 (1.40)		
No (164)	7.08 (0.36)		
Smoking		3.30 (1)	0.070
Ever (97)	6.17 (0.70)		
Never (71)	7.42 (0.35)		

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press

Table 2. *Continued*

Characteristic (*n*)	Median survival in years (SE)	χ^2 (df)	Unadjusted *p*-value (log-rank)
Atherosclerosis		2.23 (1)	0.135
Yes (22)	4.25 (1.66)		
No (119)	7.17 (0.48)		
AchEI use		0.48 (1)	0.490
No (75)	7.08 (0.76)		
Yes (87)	6.83 (0.56)		
ApoE-4 carrier		2.64 (1)	0.104
Yes (41)	6.83 (0.53)		
No (24)	8.17 (1.07)		

AchEI = cholinesterase inhibitor; ApoE = apolipoprotein E; CIRS = Cumulative Illness Rating Scale; DAD = Disability Assessment for Dementia; FRS = Functional Rating Scale; MMSE = Mini-Mental Status Exam; NPI = Neuropsychiatric Inventory; OD = other dementias.
*Remain significant after time-dependent Cox regression adjustment for diagnosis, age, CIRS, and DAD.
Bolded text indicates significant values.

follow-up times;[4,6,37-40,42] different methods of ascertainment; and definitions of diagnoses.[4,34,38,40,41] Furthermore, our findings may be influenced by a secular trend where overall life expectancy[43] is increasing in recent years. Of particular note, BC has the longest life expectancy in Canada and one of the highest in the world.[44]

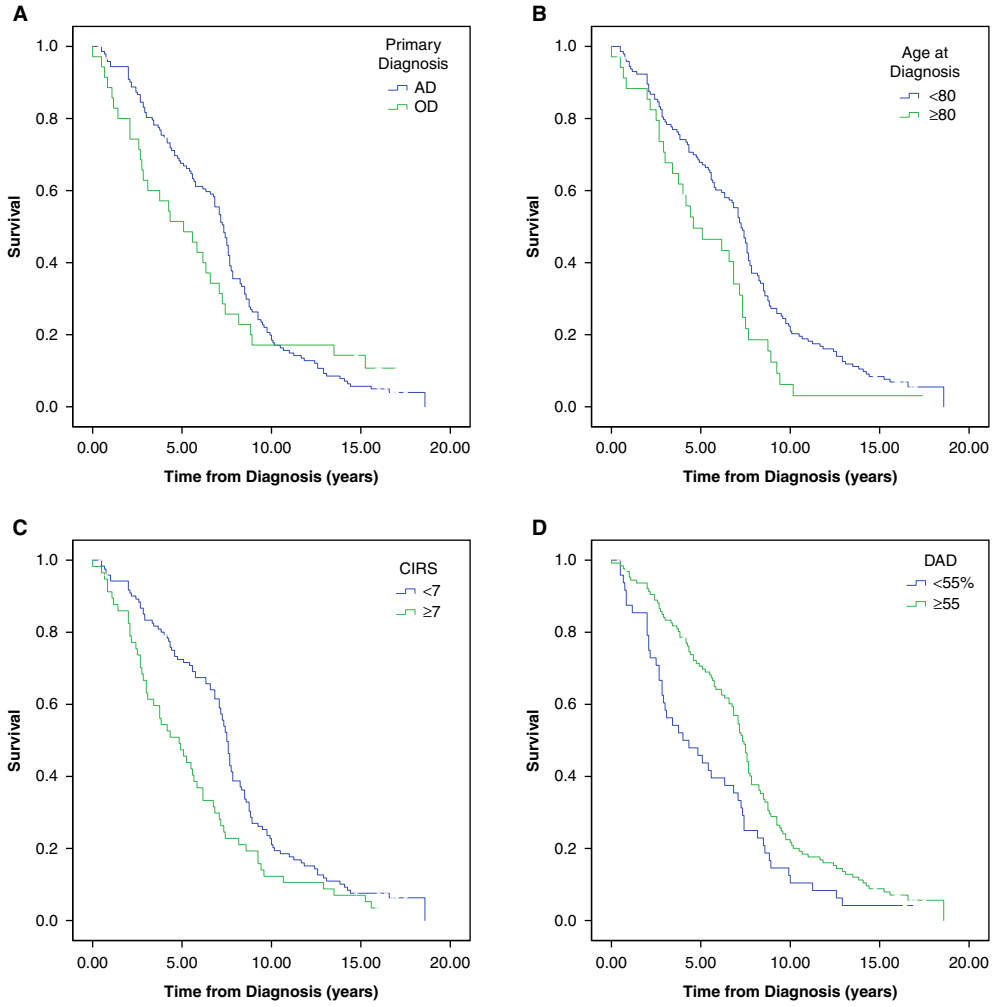

Figure 1: *(A-D) Kaplan-Meier survival curves. AD = Alzheimer's disease; CIRS = Cumulative Illness Rating Scale; DAD = Disability Assessment for Dementia; OD = other dementias.*

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press

Table 3: Comparison of median survival in Alzheimer's disease and other dementias with life expectancy in British Columbia

Age group	Number of subjects (number of events)	Median survival in years (SE)	Life expectancy in British Columbia in years by age group*	Years of potential life lost
<65	21 (20)	7.25 (0.64)	22.61**	15.36
65-69	27 (24)	7.33 (0.36)	18.60	11.27
70-74	42 (40)	7.08 (0.89)	14.91	7.83
75-79	43 (42)	7.17 (1.15)	11.53	4.36
≥80	35 (32)	4.58 (1.40)	6.40***	1.82

*Data from Human Mortality Database.
**Data from age group 60-64.
***Life expectancy averaged from age groups 80-84 (8.58 years), 85-90 (6.20 years), and 90-94 (4.41 years).

A cumulative medical comorbidity index (CIRS) was a strong predictor of mortality (HR = 1.51). The CIRS, a composite measure of medical comorbidity severity, is sensitive to the effects of age, education, and cognitive impairment,[45] factors that affect performance on scales such as these. Not surprisingly, the degree of functional disability associated with dementia, measured by the DAD, was also found to be a significant and independent predictor of survival (HR = 1.47). This finding recognizes that functional disability better predicts survival than cognitive impairment on screening cognitive measures such as the MMSE.[46,47] Our study suggests that a global health assessment such as the CIRS and a functional disability rating such as the DAD are useful adjuncts to predicting survival with dementia.

The OD group had substantially shorter median survival compared with the AD group (4.33 years vs. 7.33 years). This difference did not reach significance, possibly due to the small sample numbers in the OD group. Consistent with other studies,[25,47] individual vascular risk factors did not predict survival in dementia. However, studies are needed that measure the presence and degree of control of vascular risk factors during midlife as differentiated from the presence or absence at the time of dementia assessment. This inception cohort was unique for its enrollment when AchEIs were first becoming available in Canada for use in AD, but not covered by government health insurance in BC. Only about half of the participants were taking AchEIs; no survival difference was found ($p = 0.490$). There have been conflicting reports about the effects of AchEIs on survival, with some reporting no difference,[47,48] and others reporting a survival benefit,[49,50] but studies showing prolonged survival were retrospective within nursing-home populations. Although consistent with a number of other studies,[39,51,52] we found no significant survival difference overall with ApoE-4 ($p = 0.104$), similar to a previous study.[53] Apolipoprotein 4's lack of significant survival overall effect may indicate that ApoE-4 has a progression effect earlier in the disease course. It is noteworthy that prevalence of ApoE-4 carriers was higher in the OD group compared with the AD group. We believe that there may be two elements at play to explain this: selection bias of OD subjects willing to undergo genetic testing, which may be driven by family history, with only 10 of the 33 in the OD group consenting to genetic testing. The second element is that, in this study, we used primary clinical diagnoses, reflecting usual clinical paradigms. A previous study using this British Columbia ACCORD cohort[54] has shown that that out of the 45 cases that went to autopsy, 47% had mixed pathologies. Of these, 86% of them were mixed Alzheimer's pathology, which may also account for the higher prevalence of ApoE-4 carriers among the OD group. Further studies with larger samples using integrated clinical, genetic, and pathological data would be helpful in clarifying this issue. Sex is often cited as a significant predictor of survival in dementia,[6,28,30,33] which we did not find to be the case, along with a number of others studies.[5,29,35,52]

The strengths of this study include the complete survivorship data on a cohort of consecutively referred individuals 16 years after initial recruitment. As a provincial tertiary care center, the CARD receives a broad range of referrals, and multiple etiologies of cognitive change are encountered. All diagnoses were made according to a uniform set of research criteria and reviewed for inconsistencies within the diagnostic algorithm. We have previously reported CARD's clinical-pathological diagnostic accuracy,[54] with very high accuracy for primary pathologies, and lower accuracy for multiple mixed and secondary etiologies, an effect that was not evaluated within this current study. Further strengths of the current study include our ability to include a large number of potential risk factors and long follow-up time in our survival analyses.

There are several potentially important limitations. As a referred sample, there may be selection bias, which may result in either underestimation or overestimation of survival times. Survival may be underestimated, as referred individuals may be farther along in disease course. Length-time[6] and referral bias may contribute to overestimating survival. This study design did not allow for the recruitment of a cognitively normal control group, and within the study we had only a small group of participants who were classified as being not cognitively impaired. Another constraint is our relatively small sample size, which limits our ability to address differential survival across CIND, OD, and a more fine-grained assessment of dementia of mixed etiologies. To date, the other study centers of the ACCORD have had high loss to follow-up, and therefore are not able to undertake a similar survival analysis. Comparisons with BC population data is of interest, but must be interpreted with caution: by nature, these data do not represent a recruited sample and include people with dementia, although these factors would serve to strengthen the survival differences found.

Conclusion

A diagnosis of dementia confers a shorter survival than population life expectancy in BC in any age stratum, with greatest impact on younger patients. Age at diagnosis, higher number of medical comorbidities, and greater disability predict shortened survival better than cognitive impairment. Instruments such as CIRS and DAD may be more valuable indicators for survival in dementia than the MMSE, and would be useful in mapping the patient journey and shaping family and societal expectations.

Acknowledgments

The authors thank all of the subjects who participated in the study, and the study staff at the CARD, as well as all of the investigators and staff members of the ACCORD.

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press

Funding

The ACCORD study was funded by the Medical Research Council of Canada (now CIHR) and the Pharmaceutical Manufacturers Association of Canada, MRC PMAC program (grant-in-aid no. PA14197), with partner support from Sandoz, SmithKline Beecham, Pfizer Canada Inc., Hoffman LaRoche Ltd., Janssen Pharmaceutical Inc., and Astra. A further extension for ACCORD-II added sponsors Eisai, Hoechst Marion Roussel Canada Research Inc, Bristol Myers Squibb (US), and Eli Lilly Canada.

Disclosures

NF, BLB, and BM have nothing to disclose. MLL reports grant support from the Association for Frontotemporal Degeneration.

G-YRH reports receiving funding support for conducting clinical trials from Eli Lilly, AstraZeneca, Tau-Rx, and Roche, outside the submitted work. DF reports personal fees and non-financial support from Pfizer Canada, personal fees and non-financial support from Novartis Canada, personal fees and non-financial support from Lundbeck Canada, personal fees and non-financial support from Janssen Pharmaceuticals, and personal fees from Eli Lilly, during the study.

HHF reports grants from Canadian Institutes of Health Research (CIHR) and Pharmaceutical Manufacturers Association of Canada (PMAC) Partnership Program (ACCORD-I), and grants from Pharmaceutical Company Grant in Aid Funding (ACCORD-II), during the study, as well as clinical trial funding and service agreement with Lilly Pharmaceuticals, service agreement with Eisai Pharmaceuticals, and service agreement with Banner Institute and Genentech Pharmaceuticals, outside the submitted work. Before 2009, during the ACCORD study period (unrelated to the ACCORD), he received personal fees from Pfizer Inc, Sandoz (now Novartis), SmithKline Beecham (now GlaxoSmithKline), Hoffman LaRoche, Janssen Pharmaceuticals, Astra (now Astra Zeneca), Hoechst Marion Rousel (now Sanofi Aventis), Eli Lilly, Eisai, and Bristol Meyers Squibb. Before 2009, UBC site payments were received for sponsored clinical trials with Pfizer Inc, Novartis, GlaxoSmithKline, Hoffman LaRoche, Janssen Pharmaceuticals, and Sanofi Aventis. On leave from UBC between 2009 and 2011, HHF was a full-time employee of Bristol Myers Squibb.

Statement of Authorship

MLL: study concept and design, acquisition of data, analysis and interpretation of data, drafting, revising, and final approval of the manuscript. NF: study concept and design, analysis and interpretation of data, and revising and final approval of the manuscript. BM: acquisition of data, and revising and final approval of the manuscript. G-YRH: acquisition of data, and revising and final approval of the manuscript. DF: acquisition of data, and revising and final approval of the manuscript. BLB: acquisition of data, and revising and final approval of the manuscript. HHF: study concept and design, acquisition of data, analysis and interpretation of data, and revising and final approval of the manuscript.

References

1. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet. 1997;349:1793-6.
2. Wimo A, Winblad B, Jonsson L. The worldwide societal costs of dementia: estimates for 2009. Alzheimers Dement. 2010;6: 98-103.
3. Stubendorff K, Hansson O, Minthon L, Londos E. Differences in survival between patients with dementia with Lewy bodies and patients with Alzheimer's disease – measured from a fixed cognitive level. Dement Geriatr Cogn Disord. 2011;32:408-16.
4. Jagger C, Clarke M, Stone A. Predictors of survival with Alzheimer's disease: a community-based study. Psychol Med. 1995;25:171-77.
5. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. Arch Neurol. 2002; 59:1764.
6. Wolfson C, Wolfson DB, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med. 2001;344:1111-16.
7. Ostbye T, Hill G, Steenhuis R. Mortality in elderly Canadians with and without dementia: a 5-year follow-up. Neurology. 1999; 53:521.
8. Hogan DB, Thierer DE, Ebly EM, Parhad IM. Progression and outcome of patients in a Canadian dementia clinic. Can J Neurol Sci. 1994;21:331-38.
9. Feldman H, Levy AR, Hsiung GY, et al. A Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD): Study Methods and Baseline Results. Neuroepidemiology. 2003;22:265-74.
10. Fratiglioni L, Grut M, Forsell Y, Viitanen M, Winblad B. Clinical diagnosis of Alzheimer's disease and other dementias in a population survey. Agreement and causes of disagreement in applying Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, Criteria. Arch Neurol. 1992;49:927-32.
11. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34:939-44.
12. Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1994;57:416-18.
13. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47:1113-24.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
15. Conwell Y, Forbes NT, Cox CEDC. Validation of a measure of physical illness burden at autopsy: The Cumulative Illness Rating Scale. J Am Geriatr Soc. 1993;41:38-41.
16. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol. 1975;32:632-7.
17. Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. Am J Occup Ther. 1999;53: 471-481.
18. Crockett D, Tuokko H, Koch W, Parks R. The assessment of everyday functioning using the Present Functioning Questionnaire and the Functional Rating Scale in elderly samples. Clin Gerontol. 1989;8:3-25.
19. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988;24:235-41.
20. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44: 2308-2314.
21. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922-35.
22. Feldman H, Schulzer M, Wang S, Tuokko H, Beattie BL. The functional rating scale (FRS) in Alzheimer disease assessment: a longitudinal study. Neurobiol Aging. 1994;15:S8.
23. Human Mortality Database. Available at: http://www.mortality.org/. Accessed June 20, 2015.
24. Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. Int Psychogeriatr. 2012;24:1034-45.

25. Larson EB, Shadlen MF, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004;140: 501-9.
26. Hsiung GY, Donald A, Grand J, et al. Outcomes of cognitively impaired not demented at 2 years in the Canadian Cohort Study of Cognitive Impairment and Related Dementias. Dement Geriatr Cogn Disord. 2006;22:413-20.
27. Rizzuto D, Bellocco R, Kivipelto M, Clerici F, Wimo A, Fratiglioni L. Dementia after age 75: survival in different severity stages and years of life lost. Curr Alzheimer Res. 2012;9:795-800.
28. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol. 2005;62:779-84.
29. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Prognostic factors in very old demented adults: a seven-year follow-up from a population-based survey in Stockholm. J Am Geriatr Soc. 1998;46:444-5.
30. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age. J Clin Epidemiol. 1999;52:737-43.
31. Heyman A, Peterson B, Fillenbaum G, Pieper C. The consortium to establish a registry for Alzheimer's disease (CERAD). Part XIV: Demographic and clinical predictors of survival in patients with Alzheimer's disease. Neurology. 1996;46:656-60.
32. Schaufele M, Bickel H, Weyerer S. Predictors of mortality among demented elderly in primary care. Int J Geriat Psychiatry. 1999; 14:956.
33. Xie J, Brayne C, Matthews FE, Medical Research Council Cognitive FASc. Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. BMJ. 2008;336:258-62.
34. Mölsä PK, Marttila RJ, Rinne UK. Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand. 1995;91:159-64.
35. Guhne U, Matschinger H, Angermeyer MC, Riedel-Heller SG. Incident dementia cases and mortality. Results of the leipzig Longitudinal Study of the Aged (LEILA75+). Dement Geriatr Cogn Disord. 2006;22:185-93.
36. Stern Y, Tang M, Albert MS, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA. 1997;277:896-12.
37. Aevarsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol. 1998;55:1226-32.
38. Mölsä PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand. 1986;74:103-7.
39. Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007;69:1084-93.
40. Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ. 2010;341:c3584.
41. Rascovsky K, Salmon DP, Lipton AM, et al. Rate of progression differs in frontotemporal dementia and Alzheimer disease. Neurology. 2005;65:397-403.
42. Mehta KM, Yaffe K, Pérez-Stable EJ, et al. Race/ethnic differences in AD survival in US Alzheimer's Disease Centers. Neurology. 2008;70:1163-70.
43. World Health Organization. Life expectancy data by WHO region. Available at: http://apps.who.int/gho/data/view.main.SDG2016 LEXREGv?lang=en. Accessed March 9, 2017.
44. Zhang LR, Rasali D. Life expectancy ranking of Canadians among the populations in selected OECD countries and its disparities among British Columbians. Arch Public Health. 2015;73:17.
45. Borson S, Scanlan JM, Lessig M, DeMers S. Comorbidity in aging and dementia: scales differ, and the difference matters. Am J Geriatr Psychiatry. 2010;18:999-1006.
46. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. Int J Geriatr Psychiatry. 2013;28:1109-24.
47. Rountree SD, Chan W, Pavlik VN, Darby EJ, Doody RS. Factors that influence survival in a probable Alzheimer disease cohort. Alzheimer's Res Therapy. 2012;4(3):16
48. Lopez OL, Becker JT, Wahed AS, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurol Neurosurg Psychiatry. 2009;80:600-7.
49. Ott BR, Lapane KL. Tacrine therapy is associated with reduced mortality in nursing home residents with dementia. J Am Geriatr Soc. 2002;50:35-40.
50. Gasper MC, Ott BR, Lapane KL. Is donepezil therapy associated with reduced mortality in nursing home residents with dementia? Am J Geriatr Pharmacother. 2005;3:1-7.
51. Wattmo C, Londos E, Minthon L. Response to cholinesterase inhibitors affects lifespan in Alzheimer's disease. BMC Neurol. 2014;14:173.
52. Helzner EP, Scarmeas N, Cosentino S, Tang MX, Schupf N, Stern Y. Survival in Alzheimer disease: a multiethnic, population-based study of incident cases. Neurology. 2008;71:1489-95.
53. Dal Forno G, Carson KA, Brookmeyer R, Troncoso J, Kawas CH, Brandt J. APOE genotype and survival in men and women with Alzheimer's disease. Neurology. 2002;58:1045-50.
54. Woodward M, Mackenzie IRA, Hsiung GYR, Jacova C, Feldman H. Multiple brain pathologies in dementia are common. Eur Geriatr Med. 2010;1:259-65.

https://doi.org/10.1017/cjn.2018.6 Published online by Cambridge University Press