Journal of Alzheimer's Disease 75 (2020) 581–593
DOI 10.3233/JAD-200078
IOS Press

Mortality Rates and Mortality Risk Factors in Older Adults with Dementia from Low- and Middle-Income Countries: The 10/66 Dementia Research Group Population-Based Cohort Study

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Accepted 9 March 2020

Abstract.

Background: Dementia is the main cause of disability in older people living in low- and middle-income countries (LMIC). Monitoring mortality rates and mortality risk factors in people with dementia (PwD) may contribute to improving care provision.

Objective: We aimed to estimate mortality rates and mortality predictors in PwD from eight LMICs.

Methods: This 3–5-year prospective cohort study involved a sample of 1,488 older people with dementia from eight LMIC. Total, age- and gender-specific mortality rates per 1,000 person-years at risk, as well as the total, age- and gender-adjusted mortality rates were estimated for each country's sub-sample. Cox's regressions were used to establish the predictors of mortality.

Results: At follow-up, vital status of 1,304 individuals (87.6%) was established, of which 593 (45.5%) were deceased. Mortality rate was higher in China (65.9%) and lower in Mexico (26.9%). Mortality risk was higher in males (HR = 1.57; 95% CI: 1.32,1.87) and increased with age (HR = 1.04; 95% CI: 1.03,1.06). Neuropsychiatric symptoms (HR = 1.03; 95% CI: 1.01,1.05), cognitive decline (HR 1.04; 95% CI: 1.03,1.05), undernutrition (HR = 1.55; 95% CI: 1.19, 2.02), physical impairments (HR = 1.15; 95% CI: 1.03,1.29), and disease severity (HR = 1.43; 95% CI: 1.22,1.63) predicted higher mortality risk.

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ISSN 1387-2877/20/$35.00

Conclusion: Several factors predicted higher mortality risk in PwD in LMICs. Males, those with higher age, higher severity of neuropsychiatric symptoms, higher number of physical impairments, higher disease severity, lower cognitive performance, and undernutrition had higher mortality risk. Addressing these indicators of long-term adverse outcomes may potentially contribute to improved advanced care planning, reducing the burden of disease in low-resourced settings.

Keywords: Dementia, low- and middle-income countries, mortality risk, population-based studies

INTRODUCTION

Dementia is a globally prevalent neuropsychiatric syndrome that affects 50 million people worldwide [1]. Approximately 66% of all people with dementia live in low- and middle-income countries (LMIC) and this proportion is expected to rise to more than 70% by 2050 [2]. Dementia is caused by several brain diseases, such as Alzheimer's disease and vascular-related problems, causing progressive and incapacitating cognitive, behavioral, and motor dysfunctions [3]. Dementia is overwhelmingly the most important and independent cause of disability and mortality in older people living in LMIC and there is a need for further research to better understand how this could be improved [1, 4, 5].

According to the Global Burden of Disease study of the period from 1990 to 2016 [6], dementia represented the fifth leading cause of death globally, accounting for 2.4 million deaths. People with dementia have an average mortality risk of 2.6 times higher than that of the people in the same age group without dementia [7]. In LMIC, mortality rates are approximately 1.6 to 5.7 higher in people with dementia compared to people without dementia [5]. However, there is a current lack of understanding around the factors contributing to these differences. In addition, the number of people with undetected dementia in LMIC is often high, which precludes accurate registration of causes of death and contributes to an underestimation of dementia as a cause of death in such contexts [8].

A previous systematic review [9] of the predictors of mortality in people with dementia included only one study from a LMIC (Brazil) [10]. This review found a high heterogeneity in how predictors of mortality in dementia were assessed and reported, which hinders the establishment of a consensus based on current estimates. The review indicated, however, that some mortality risk factors in people with dementia seem to be consistent across studies and countries and include both dementia severity and levels of disability. The establishment of reliable and comparable evidence on the predictors of mortality in people with dementia is of interest to individuals living with the condition and their families, as well as to those responsible for planning appropriate services throughout the course of this disabling and progressive condition. To date, no interventions have been capable of slowing dementia progression. Therefore, acknowledging dementia as a life limiting condition with diverse predictors of death may currently contribute to end of life planning and discussions targeting palliative care approaches among family members, caregivers and people with dementia.

This prospective cohort study aimed to provide a detailed description of patterns of mortality in a large sample of 1,488 older people with dementia living in catchment areas of Latin America, India and China, and to assess whether several socio-economic-, health-, and dementia-related factors predict mortality risk in dementia.

METHODS

Design and settings

This is a 3–5-year follow-up prospective cohort study (10/66 Dementia Research Group population-based cohort study) [11] involving eight LMIC (India, China, Cuba, Dominican Republic, Venezuela, Mexico, Puerto Rico, and Peru).

Sample and procedures

Baseline assessments of all residents aged $\geq$65 were undertaken in geographically defined catchment areas of eight LMIC. Both urban and rural catchment areas were included. Middle-class or professional areas with high-income earners were avoided [11]. Individuals meeting the inclusion criteria and who provided informed consent to take part received a household-based full assessment, which consisted of participant and informant interviews as well as physical examination.

After an average time of 3–5 years, participant vital status was checked, and follow-up assessments were repeated. When the death of a participant was regis-

tered, the circumstances of such event were checked through interviews with key informants (usually a family member) and the World Health Organization's "Standard Verbal Autopsy Questionnaire 3: Death of a Person Aged 15 Years and Above" was also used to ensure reliability [12]. The same procedures were used in each country. A total of 14,960 older individuals were interviewed at baseline (between 2,000 and 3,000 participants per country). The sample investigated in the current study included those identified as having any type of dementia at baseline ($n = 1,488$), which was established either by the 10/66 dementia criteria and/or by the DSM-IV criteria. More details about this can be found in a previously published study protocol [11].

Measurements

Socio-demographic information was collected at baseline and included age (years), gender (female, male), educational level (none or minimal, completed primary, completed secondary, completed tertiary), and household assets index (calculated based on the number of cars, number of televisions, number of refrigerators, number of telephones, existence of mains water, mains electricity, and plumbed toilet). Cardiovascular disease (CVD) risk factors were collected via self-report of any of the following conditions: hypertension, smoking, diabetes, and obesity. Physical impairments included self-report of stroke, angina, heart attack, increased blood pressure, arthritis/rheumatism, eyesight problems, hearing difficulties, chronic cough, breathlessness, asthma or trouble breathing, fainting, weakness, paralysis or loss of a limb.

Depressive episodes were established according the ICD-10 criteria [13]. Measurement of the Mid-Upper Arm Circumference (MUAC) was a proxy measure for nutritional status [14]. The instruments and procedures used to measure the MUAC are described elsewhere [15, 16]. MUAC of the entire sample was divided into quarters in order to identify the mean arm circumference of the first quarter. Data was then dichotomized, establishing 22 cm as the cut-off point for nutritional status (undernutrition: <22 cm; adequate nutrition: ≥ 22 cm). Participants or their informants were also asked about having received any type of community healthcare, and any medical service (including in patient), up to three months before the interview. Those who answered affirmatively to this question were classified as having had "access to any treatment" [17].

Dementia diagnosis was established according to the 10/66 protocol [18] and/or DSM-IV criteria [19]. We obtained information to establish the diagnosis from: the Community Screening Instrument for Dementia (CSI-D COGSCORE Scale) [20], incorporating both the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) animal-naming verbal fluency task and the modified CERAD ten word list learning task with delayed recall [21]; the Geriatric Mental State examination informant interview [13]; evidence of cognitive and functional decline from the CSID informant interview (RELSCORE scale) [22]; and from a structured neurological examination including the Luria three step motor sequencing fist-edge-palm test [23].

Dementia subtype diagnosis consisted of applying a computer algorithm derived from specific elements of validated research diagnostic criteria for each of the dementia subtypes. NINCDS-ADRDA criteria were applied for possible or probable Alzheimer's disease (AD) [24]. NINDS/AIREN criteria were applied for possible vascular dementia (VaD) [25]. Dementia with Lewy bodies (DLB) was diagnosed according to the Consortium on DLB [26]. Frontotemporal dementia (FTD) diagnostic criteria were determined according to the Work Group on FTD and Pick's disease [27]. This algorithm allows for co-morbidities to exist between AD and VaD, as well as AD and DLB.

The severity of dementia (classified as questionable, mild, moderate, or severe) was assessed in all participants in line with the Clinical Dementia Rating scale (CDR) [28]. Global cognitive status was defined by the CSI-D COGSCORE Scale, which comprises 32 items assessing orientation, comprehension, memory, naming and language expression. Higher scores represent better cognitive function [20]. Neuropsychiatric symptoms were evaluated using the abbreviated version of the Neuropsychiatric Inventory (NPI-Q) [29].

Data analysis

The 10/66 Dementia Research Group data archive (mortality 3.4) and the Stata® 12.1 statistical software were used for data analysis. We described the sociodemographic profile, health status, and clinical characteristics of dementia for the total cohort and for each country. Total- and gender-stratified crude mortality rates, as well as age- and gender-standardized mortality rates per 1,000 person-years at risk were estimated for each country. For the latter, we used

direct standardization using the age and gender distributions of Cuba's sample as the reference population. Comparative Mortality Ratios (CMR) were calculated for each country by dividing their age- and gender-adjusted mortality rates by the rate in Cuba.

We used Cox's proportional hazards regression to estimate the effect of potential predictors on mortality. We ran five sets of models: Model 1 adjusted for socio-demographic variables (age, gender, education, and assets); Model 2 adjusted for the same socio-demographic variables, plus number of impairments, CVD risk factors, nutrition status, access to any treatment, depression, and dementia subtypes. Three further models were used to estimate the effect of dementia severity on mortality, each adjusting for all the variables in Model 2, plus dementia severity (CDR) (Model 3), behavioral symptoms (NPI) (Model 4), or total cognitive score (COGSCORE) (Model 5). Each Model was tested separately for each country. Fixed-effects meta-analyses were then used to combine effect sizes for each country. Higgin's I^2 was used to estimate the degree of heterogeneity among countries. All the analyses were conducted using 95% confidence intervals (CI).

Ethical approval

All the procedures contributing to this work complied with the ethical standards of the relevant national and international committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the participants. People with dementia who lacked capacity to consent were enrolled through a signed agreement from a next of kin. Illiterate participants gave oral consent, which was witnessed in writing by a literate person, and by the researcher. Each country's local ethical committees and the King's College London Research Ethics' committee approved the study protocol.

RESULTS

Sociodemographic profile

Among the 1,488 individuals with dementia at baseline, vital status was established at follow up for 1,304 individuals (87.6%), of which 593 (45.5%) were deceased and 184 (12.4%) were not traced (Table 1). The total sample contributed 3,858.80 person-years for the study. The mean follow-up time was 3.0 (SD = 1.3) years among all countries. Mean age at baseline was similar among countries, ranging from 75.5 (SD = 8.1) years old in India to 83.3 (SD = 8.4) in Puerto Rico. The proportion of deaths over the follow-up period was higher in China (65.9%; $n = 89$) and Cuba (57.4%; $n = 159$), and lowest in Mexico (26.9%; $n = 43$) and Peru (29.5%; $n = 43$). Mean age at death was 84.7 years (SD = 7.9), highest in Puerto Rico (87.1; SD = 8.8) and lowest in India (76.1; SD = 8.0). The proportion of women was higher than the proportion of men in all countries, representing two thirds ($n = 880$; 67.5%) of the total sample. Around 35% ($n = 450$) of all individuals in the sample were married or cohabited with a partner. Around 55% ($n = 695$) had none or minimum education, constituting the majority in Mexico ($n = 140$; 87.5%), Dominican Republic ($n = 167$; 78.8%), and India ($n = 38$; 70.4%).

Health status

Undernutrition was identified in 16.2% ($n = 194$) of the total sample, most of whom were from India ($n = 25$; 48.1%), Mexico ($n = 38$; 24.1%), and Cuba ($n = 65$; 23.6%). Nearly 70% ($n = 888$) of all participants had one or more physical impairment, with higher prevalence in China ($n = 106$; 78.5%) and Dominican Republic ($n = 169$; 75.5%). Of the total sample, 78.9% ($n = 1,029$) had at least one CVD risk factor and 40.3% ($n = 525$) had two or more of them, with the highest prevalence in the Dominican Republic (84.9% with one or more, and 51.4% with two or more). About 11.5% ($n = 150$) had depression, with the highest prevalences recorded in Dominican Republic ($n = 52$; 23.2%) and Venezuela ($n = 21$; 17.1%). At baseline, 47% of the total sample reported having had access to any type of treatment, and with Puerto Rico having the highest proportion ($n = 29$; 82.9%).

Clinical characteristics of dementia

The majority of participants had mild dementia ($n = 558$; 42.8%), representing 24.1% ($n = 13$) of the sample in India (lowest) and 47.3% ($n = 106$) in Dominican Republic (highest). Severe dementia represented 7.8% ($n = 101$) of the total sample and was highest in Cuba ($n = 52$; 18.8%). One third ($n = 411$; 31.5%) met the criteria for pure AD subtype (highest rate in Cuba: $n = 130$; 46.9%) and 16.7% ($n = 218$) met the criteria for VaD (highest rate in China: $n = 36$;

Table 1
Sociodemographic and health characteristics of people with dementia from eight LMIC

Variables	Country								
	Cuba	Dominican Republic	Puerto Rico	Peru	Venezuela	Mexico	China	India	All
Cohort characteristics									
Baseline Sample: *n*	296	242	244	166	145	180	140	75	1,488
Vital Status determined: *n* (% of baseline sample)	277 (93.6)	224 (92.6)	185 (75.8)	146 (88.0)	123 (84.8)	160 (88.9)	135 (96.4)	54 (72.0)	1,304 (87.6)
Deaths: *n* (% of those with status determined)	159 (57.4)	97 (43.3)	98 (53.0)	43 (29.5)	39 (31.7)	43 (26.9)	89 (65.9)	25 (46.3)	593 (45.5)
Person-years of follow-up	818.9	668.2	536.1	386.6	408.0	418.5	478.7	143.8	3,858.8
Years of follow-up: mean (SD)	3.0 (1.4)	3.0 (1.3)	2.9 (1.5)	2.6 (1.0)	3.3 (1.4)	2.6 (0.7)	3.5 (1.4)	2.6 (1.1)	3.0 (1.3)
Sociodemographic data									
Mean age at baseline (SD)	82.0 (7.1)	80.7 (8.0)	83.3 (8.4)	81.6 (8.7)	79.2 (8.8)	80.7 (7.1)	79.2 (6.8)	75.5 (8.1)	80.9 (8.0)
Mean age at death (SD)	85.3 (6.8)	85.1 (7.6)	87.1 (8.8)	86.0 (8.7)	82.7 (8.7)	83.8 (7.5)	83.3 (6.6)	76.1 (8.0)	84.7 (7.9)
Female gender: *n* (%)	196 (70.8)	157 (70.1)	119 (64.7)	97 (66.4)	86 (69.9)	110 (68.8)	82 (60.7)	33 (61.1)	880 (67.5)
Married/cohabiting: *n* (%)	76 (27.6)	50 (22.5)	83 (45.1)	59 (41.3)	32 (32.7)	57 (35.6)	69 (51.1)	24 (44.4)	450 (35.4)
None/minimal education: *n* (%)	113 (41.2)	167 (78.8)	75 (40.5)	33 (23.4)	46 (46.9)	140 (87.5)	83 (61.5)	38 (70.4)	695 (55.2)
Mean assets at baseline (SD)	5.61 (0.94)	4.75 (1.53)	6.57 (0.59)	5.73 (1.27)	6.01 (1.33)	4.63 (1.95)	5.49 (1.03)	3.69 (1.61)	5.46 (1.49)
Health status									
Undernutrition: *n* (%)	65 (23.6)	26 (11.7)	9 (7.1)	17 (12.0)	12 (13.0)	38 (24.1)	2 (1.5)	25 (48.1)	194 (16.2)
One or more physical impairment: *n* (%)	174 (63.3)	169 (75.5)	137 (74.5)	95 (65.5)	72 (73.5)	117 (73.1)	106 (78.5)	18 (33.3)	888 (69.7)
At least one CVD: *n* (%)	221 (79.8)	188 (83.9)	157 (84.9)	111 (76.0)	90 (73.2)	118 (73.8)	104 (77.0)	40 (74.1)	1,029 (78.9)
Two or more CVD: *n* (%)	101 (36.5)	90 (40.2)	95 (51.4)	51 (34.9)	48 (39.0)	71 (44.4)	62 (45.9)	7 (13.0)	525 (40.3)
Depression: *n* (%)	24 (8.7)	52 (23.2)	8 (4.3)	15 (10.3)	21 (17.1)	17 (10.6)	7 (5.2)	6 (11.1)	150 (11.5)
Access to any treatment: *n* (%)	101 (36.3)	107 (47.8)	29 (82.9)	59 (40.7)	63 (64.3)	98 (61.3)	44 (32.6)	26 (48.1)	527 (46.8)
Dementia-related assessments									
Mean COGSCORE (SD)	18.7 (18.4)	20.6 (7.4)	14.3 (11.8)	18.2 (9.8)	19.3 (8.7)	21.3 (6.7)	14.9 (10.6)	20.1 (7.8)	18.4 (9.3)
Mean NPI severity (SD)	6.7 (5.3)	9.9 (7.1)	5.0 (5.4)	6.6 (5.9)	6.9 (6.2)	5.6 (6.0)	1.9 (3.5)	3.7 (4.4)	6.3 (6.1)
Dementia severity (CDR): n (%)									
Questionable dementia	57 (20.6)	53 (23.7)	46 (24.9)	34 (23.3)	28 (22.8)	66 (41.3)	31 (23.0)	34 (63.0)	349 (26.8)
Mild dementia	104 (37.6)	106 (47.3)	85 (46.0)	63 (43.2)	56 (45.5)	70 (43.8)	61 (45.2)	13 (24.1)	558 (42.8)
Moderate dementia	63 (22.7)	40 (17.9)	41 (22.2)	35 (24.0)	35 (28.5)	18 (11.3)	39 (28.9)	3 (5.6)	274 (21.0)
Severe dementia	52 (18.8)	21 (9.4)	7 (3.8)	13 (8.9)	4 (3.3)	2 (1.25)	2 (1.5)	0 (0)	101 (7.8)
Subtype diagnosis: n (%)									
AD	130 (46.9)	53 (23.7)	47 (25.4)	50 (34.3)	39 (31.7)	40 (25.0)	43 (31.9)	9 (16.7)	411 (31.5)
VaD	31 (11.2)	52 (23.2)	38 (20.5)	20 (13.7)	23 (18.7)	16 (10.0)	36 (26.7)	2 (3.7)	218 (16.7)
LBD	9 (3.2)	14 (6.3)	7 (3.8)	8 (5.5)	4 (3.3)	3 (1.9)	0 (0)	2 (3.7)	47 (3.6)
FTD	6 (2.2)	11 (4.9)	3 (1.6)	11 (7.5)	9 (7.3)	10 (6.3)	3 (2.2)	1 (1.9)	54 (4.1)
Mixed	26 (9.4)	34 (15.2)	10 (5.4)	11 (7.5)	9 (7.3)	14 (8.8)	3 (2.2)	2 (3.7)	109 (8.4)
Not allocated	75 (27.1)	60 (26.8)	80 (43.2)	46 (31.5)	39 (31.7)	77 (48.1)	50 (37.0)	38 (70.4)	465 (35.7)

CVD, cardiovascular disease; AD, Alzheimer's disease; VaD, vascular dementia; LBD, Lewy body dementia; FTD, frontotemporal dementia; CDR, Clinical Dementia Rating; NPI, Neuropsychiatric Inventory.

26.7%). The mean COGSCORE was 18.4 (SD = 9.3) in the total sample, with highest scores in Mexico (mean score = 21.3; SD = 6.7) and lowest scores in Puerto Rico (mean score = 14.3; SD = 11.8).

Mortality rates

General crude and adjusted rates

Crude mortality rate (per 1,000 person-years) for the total sample was 153.5 (95%CI: 141.6–166.3) (Table 2). Crude mortality rates ranged from 95.6 (95%CI: 69.8–130.8) in Venezuela to 195.2 (95%CI: 166.2–226.8) in Cuba (per 1,000 person-years). In the gender-specific crude mortality rates, men had higher total mortality rate 188.4 (95%CI: 165.2–214.8) than women 138.4 (95%CI: 125.0–153.3). In all the eight countries, rates were higher in men, ranging from 117.7 (95%CI: 70.9–195.2) in Venezuela to 304.6 (95%CI: 180.4–514.3) in India. After direct standardization for age and gender, mortality rate was higher in China (rate = 208.8; 95%CI: 116.2–371.7); followed by Cuba (rate = 200.6; 95%CI: 132.09–31.09) and Puerto Rico (rate = 183.4; 95%CI: 109.4–325.1); and lower in the other five countries, with the lowest rate in Mexico (rate = 109.9; 95%CI: 47.5–306.4). Supplementary Table 1 presents rates according to different age and gender groups.

Predictors of mortality

Among the covariates included in model 2, pooled estimates for all countries (Table 3) showed mortality rates were predicted by increased age (HR = 1.04; 95%CI: 1.03–1.06), male gender (HR = 1.57; 95%CI: 1.32–1.87), higher number of physical impairments (HR = 1.15; 95%CI: 1.03–1.29), and undernutrition (HR = 1.55; 95%CI: 1.19–2.02). The association of higher number of physical impairments and undernutrition with higher mortality rates was explained by dementia severity (CDR, NPI, or COGSCORE). All dementia severity indicators predicted higher mortality rates. Model 3 showed that dementia severity given by the CDR (HR = 1.43; 95%CI: 1.22–1.63), gender (HR = 1.39; 95%CI: 1.07–1.72), and age (HR = 1.03; 95%CI: 1.02–1.05) remained predictors of mortality, in addition, AD (HR = 0.70; 95%CI: 0.51–0.88) and FTD (HR = 0.35; 95%CI: 0.00–0.77) were predictors of lower mortality. When adjusting by dementia severity given by the NPI in model 4 (HR = 1.03; 95%CI: 1.01–1.05), only gender (HR = 1.37 95%CI: 1.05–1.70) and age (HR = 1.04; 95%CI: 1.03–1.06) remained significant predictors. Finally, in model 5 when adjusting by dementia severity given by the COGSCORE (HR = 0.96; 95%CI: 0.95–0.97), gender (HR = 1.40; 95%CI: 1.07–1.72) and age (HR = 1.04; 95%CI: 1.02–1.05) remained significant predictors, while those with FTD presented a reduced mortality risk (HR = 0.35; 95%CI: 0.00–0.74). Supplementary Table 2 presents individual estimates for each country. Gender (male) was a particularly strong contributor to the pooled estimates of mortality risk in Peru (HR = 2.31; 95%CI: 1.22–4.38) and in India (HR = 2.74; 95% CI: 1.16–6.48). Similarly, undernutrition (Model 2) was a particularly strong contributor to the pooled estimates of mortality in Peru (HR = 3.53; 95%CI: 1.37–9.12) and in Venezuela (HR = 6.51; 95%CI:1.63–26.07). Dementia severity (CDR) (Model 3) was a particularly strong contributor to the pooled estimates of mortality in Venezuela (HR = 3.52; 95%CI: 1.13–10.96) and in China (HR = 2.05; 95%CI: 1.26–3.33). Heterogeneity test was significant for undernutrition ($Q = 9.36$; df = 7; $p = 0.03$) and cognitive function (COGSCORE) ($Q = 16.32$; df = 7; $p = 0.02$).

Table 2
Total- and gender-specific mortality rates among people with dementia by country*

Country	Total mortality rates		Gender-specific crude mortality rates		CMR***
	Crude mortality rates	Standardized mortality rates**	Female	Male	
Cuba	195.2 (166.2–226.8)	195.2 (166.2–226.8)	184.4 (153.0–223.3)	220.2 (166.5–291.4)	1.0
Dominican Republic	145.2 (119.0–177.1)	157.0 (93.4–276.9)	129.0 (100.8–165.2)	188.9 (135.0–264.4)	0.80
Puerto Rico	182.8 (150.0–222.8)	183.4 (109.4–325.1)	170.3 (132.2–219.3)	214.4 (156.0–294.7)	0.94
Peru	111.2 (82.5–150.0)	116.9 (42.8–270.5)	91.7 (61.5–136.8)	152.1 (97.0–238.4)	0,60
Venezuela	95.6 (69.8–130.8)	116.3 (44.8–303.5)	85.6 (57.3–127.6)	117.7 (70.9–195.2)	0.60
Mexico	102.0 (76.2–138.5)	109.9 (47.5–306.4)	92.6 (63.5–134.9)	126.2 (77.3–206.0)	0.56
China	185.9 (151.0–228.9)	208.8 (116.2 –371.7)	170.2 (129.4–224.0)	212.2 (154.4.–291.6)	1.07
India	173.8 (117.4–257.2)	149.4 (42.3–605.2)	112.4 (62.2–202.9)	304.6 (180.4–514.3)	0.77
Total	153.5 (141.6–166.3)	—	138.4 (125.0– 153.3)	188.4 (165.2–214.8)	—

*Rates are given per 1,000 person-years (95%CI). **Directly Standardized for age and gender using the distribution of the Cuban sample as reference population. ***Comparative Mortality Ratio: comparison of adjusted mortality rates for each country in relation to Cuba's rates.

Table 3
Pooled estimates of the association between the sample characteristics and the mortality risk

	Model 1	Model 2	Model 3	Model 4	Model 5
Age (per year)	**1.04 (1.03–1.06)**	**1.04 (1.03–1.05)**	**1.03 (1.02–1.05)**	**1.04 (1.03–1.06)**	**1.04 (1.02–1.05)**
Gender (male)	**1.57 (1.32–1.87)**	**1.36 (1.05–1.67)**	**1.39 (1.07–1.72)**	**1.37 (1.05–1.70)**	**1.40 (1.07–1.72)**
Education (per level)	1.01 (0.94–1.09)	0.97 (0.88–1.06)	0.98 (0.90–1.08)	0.99 (0.90–1.08)	0.99 (0.90–1.08)
Assets (per asset)	0.96 (0.89–1.03)	0.97 (0.89–1.06	0.96 (0.88–1.05)	0.97 (0.90–1.06)	1.06 (0.97–6.88)
Number of impairments		**1.15 (1.03–1.29)**	1.04 (0.79–1.30)	1.05 (0.80–1.30)	1.06 (0.81–1.31)
CVD risk factors		0.94 (0.84–1.05)	0.92 (0.81–1.04)	0.92 (0.79–1.05)	1.06 (0.81–1.31)
Undernutrition		**1.55 (1.19–2.02)**	1.10 (0.74–1.46)	1.11 (0.75–1.48)	0.94 (0.83–1.05)
Access to any treatment		1.05 (0.86–1.28)	0.96 (0.75–1.18)	0.88 (0.68–1.07)	1.00 (0.66–1.33)
Depression		1.17 (0.86–1.60)	0.99 (0.57–1.41)	0.85 (0.51–1.19)	0.95 (0.74–1.16)
AD		1.01 (0.82–1.26)	**0.70 (0.51–0.88)**	0.97 (0.74–1.20)	0.98 (0.60–1.37)
VaD		1.26 (0.96–1.65)	0.90 (0.61–1.19)	1.18 (0.83–1.54)	0.88 (0.67–1.09)
LBD		1.18 (0.66–2.12)	0.68 (0.06–1.29)	0.60 (0.09–1.11)	0.94 (0.64–1.24)
FTD		0.59 (0.31–1.14)	**0.35 (0.00–0.77)**	0.36 (0.00–0.78)	**0.35 (0.00–0.74)**
Dementia severity (CDR)			**1.43 (1.22–1.63)**		
NPI				**1.03 (1.01–1.05)**	
COGSCORE					**0.96 (0.95–0.97)**

CVD, cardiovascular disease; AD, Alzheimer's disease; VaD, vascular dementia; LBD, Lewy body dementia; FTD, frontotemporal dementia; CDR, Clinical Dementia Rating; NPI, Neuropsychiatric Inventory. [1]Adjusted for age, gender, education, and assets. [2]Adjusted for all variables in model (1) plus number of impairments, CV risk factors, undernutrition, access to any treatment, depression, AD, VAD, LBD, and FTD. [3]Adjusted for all variables from models (1) and (2) plus dementia severity (CDR). [4]Adjusted for all variables from models (1) and (2) plus NPI. [5]Adjusted for all variables from models (1) and (2) plus COGSCORE.

DISCUSSION

Previous 10/66 study compared the mortality rates between people with and without dementia in urban areas of Cuba, the Dominican Republic, and Venezuela, and in urban and rural areas of Mexico, Peru, China, and India [5]. However, to our knowledge, the current study is the first to examine the mortality rates and the effect of several potential risk factors for mortality in people with dementia from eight LMIC over a period of 3–5 years. We found that standardized mortality rates varied up to 2-fold between countries and were highest in Cuba and China, and lowest in Peru, Venezuela, and Mexico. Men had higher mortality rates in all countries. Increased age, male gender, and dementia severity (evaluated in three distinct dimensions: cognitive, behavioral, and clinical) were independently associated with significant increased mortality rates in the total sample. Higher number of physical impairments and undernutrition were also predictors of increased mortality. However, this was explained by dementia severity given by any of the measured domains. FTD was a predictor of lower mortality risk when adjusting by CDR or COGSCORE, and AD was a significant protective factor when adjusting by CDR. Educational status, household assets, access to any treatment, depression, CVD, and dementia subtypes were not significantly associated with mortality rates. Heterogeneity on the countries' pooled estimates was moderately high for undernutrition and cognition, but not for other domains of severity.

Overall, our study identified a higher mortality rate (153.5 deaths per 1000 person-years for the total sample) compared to most studies of older people with dementia conducted in high-income countries. For instance, in a Spanish community-based cohort of people aged ≥75, the mortality rate related to dementia was 10 per 1000 person-years [30]. However, this is a community-based cohort study where mortality rates were estimated based on incident cases, which may partly account for lower rates. In a study from the United States, a death rate of 90 deaths per 1000 person-years was found [31], and a cohort study from Sweden found as low rates as 24 per 1000 person-years in people with dementia aged ≥75 [32]. A multi-ethnic population-based study in the United States (aged ≥65) (based on incident AD cases) also identified a lower mortality rate than ours (107 per 1000 person-years) [33].

Mortality estimates from other cohort studies in LMIC vary greatly in comparison to each other and to those of high-income countries. For example, the mortality rate per 1000 person-years in people with dementia aged ≥65 in the Ibadan Study of Ageing in Nigeria [34] was 83.1, which was similar to the estimates we found in Venezuela, Mexico, and Peru. A Chinese study conducted in Beijing found a higher crude mortality rate of 236 per 1000 person-years among people with dementia [35]. A

previous study by the 10/66 Dementia Research Group, focusing on dementia incidence and mortality, compared people with and without dementia at baseline and found increased mortality hazards in those with dementia in all the countries studied (Cuba, the Dominican Republic, Venezuela, Peru, Mexico, and China). Age and gender-adjusted Cox's proportional hazards models identified hazard of death as being 1.6 to 5.7 times higher in those with dementia compared to those without dementia with a pooled estimate of HR = 2.77 (95% CI: 2.47–3.10) [5]. Higher mortality rates in people with dementia in LMIC, as also with the general population, may derive from social determinants and poorer healthcare assistance. In people with dementia, there is also the issue of delay in establishing a dementia diagnosis.

As found in our sample, other studies have shown that age may play a significant role in predicting mortality risk in people with dementia [9]. Higher mortality risk in men have also been found in some studies [36–39], but not in others [32, 33, 40, 41], While lower education has been considered to be a strong risk factor for dementia onset [42, 43] and a previous study has found that increased education was a protector factor against mortality risk in dementia [32], data from a prospective population-based cohort study of older adults in Spain suggested that high educational attainment was related to higher mortality risk in people with dementia. More advanced neuropathology associated with higher education at any level of disease severity might lead to an earlier death after diagnosis [44]. Corroborating our findings, several studies have reported no association between educational level and mortality [30, 36, 39–41, 45, 46]. Although high cognitive reserve and formal education may have protective effects on delaying the disease onset and disease progression, older people from LMIC have on average received less formal education throughout their lives and the association between educational level and mortality rates in people with dementia warrants further investigation in similar settings [47].

In our study, we also found that undernutrition was a predictor of higher mortality risk in people with dementia in LMIC; however, it was no longer significant when controlled by dementia severity. This finding suggests undernutrition would significantly contribute to mortality when dementia is assessed as being more severe either in the cognitive, behavioral, or clinical tests. Only a few previous studies have analyzed undernutrition as a potential mortality risk factor among people with dementia. Recently, a cohort study including older residents with dementia of a rural area in the USA reported that those who were malnourished had faster cognitive deterioration and worse functional decline, as well as three times higher mortality rate [48, 49]. Poor nutrition is frequently observed in people with dementia and has been found to be associated with higher functional impairment [50], rapid cognitive decline, more neuropsychiatric symptoms, and higher caregiver burden [51]. Additionally, cachexia and dehydration are highly reported causes of death in people with dementia [52] and studies have shown that the association between weight loss and high dementia severity contribute to an increase in mortality risk [4, 5, 10]. Improving nutritional status may lead to a decrease in morbidity and mortality, although the implications of this approach to improve the end of life care quality are controversial [53]. Dementia is a life-limiting condition and there is no evidence of effective measures to prolong life expectancy. A palliative care approach, including an advanced care planning that involves people with dementia, family members, and healthcare staff in the decision-making process regarding factors that may lead to increased risk of unfavorable outcomes, may be the only solution to reduce the overall burden related to the condition.

Even though long-term depression has been associated with a heightened risk of mortality in the general population [54, 55], our study and others have found no significant association between depression and mortality rate in people with dementia [56, 57]. It might be that other predictors, such as undernutrition, poor physical capacity, and disease severity, which are often consequences of advanced depressive states, might be more strongly related to short-term mortality, thus buffering the impact of depression itself on mortality risk in a combined-effect model. Furthermore, a single evaluation at baseline may not necessarily have detected those who developed depression along the course of the study in our cohort. Another prospective study with people without dementia has demonstrated that depressive symptoms measured at several occasions, but not at baseline, were associated with mortality [58]. Further longitudinal research on the association between mortality risk and depression measured at several points throughout the study in people with dementia could help clarify this potential association.

Previous studies have shown that having CVD risk factors in midlife may lead to a higher risk for dementia later in life [59, 60] and that having hypertension

and diabetes may lead to a higher mortality risk in people with dementia [33]. However, our study did not find any significant association between CVD risk factors and mortality risk. Late life development of these risk factors and a shorter follow-up period may explain our results. Other possible explanations might be, for instance; that our data did not adequately detected midlife exposure to CVD risk factors, which would be more related to higher mortality rates in late life dementia; midlife CVD risk factors may be underrepresented in our sample because of survival bias [61]; or that dementia itself or its consequences may go beyond well-established midlife risk factors for mortality [61]. Despite the lack of direct association between CVD risk factors and mortality risk, people with VaD subtype tended to have a higher risk of death, suggesting that past CVD could have a higher effect on the mortality risk of those individuals.

Dementia subtypes did not predict mortality in our sample and other studies have also found conflicting results regarding this variable [62]. For example, VaD subtype has been considered to be a predictor of higher mortality in dementia in some studies [63, 64], but not in others [65, 66]. Heterogeneity in diagnostic criteria defining VaD cases and, consequently, the diversity of pathological and clinical presentations into the VaD subtype in the various studies, may explain this disparity. Moreover, specific characteristics related to the neuropathological processes in some dementia subgroups, such as clinical manifestations at onset of the brain damage or fluctuant cognition due to small stroke events, may explain higher mortality rates in some patients with VaD, but not in others [67]. However, our study design and diagnostic framework did not allow us to address such issues.

Similarly to the results observed in our total sample, dementia severity and functional impairment have been shown to predict mortality in other studies, though a few have found that none of these factors has led to a higher mortality risk in people with dementia [32, 68]. Other studies have shown that dementia severity was an independent risk factor for reduced life expectancy. This has important implications to clinical practice as improving palliative and end of life care quality for people with this condition has become a priority in face of the increasing global burden of dementia [69, 70]. By including three different measurements of disease severity in our study, each one of them representing a dimension of dementia progression, it was possible to demonstrate that cognitive decline, behavioral worsening and functional impairment may have specific roles in the cascade leading to death among older adults with dementia. Particularly in LMIC, where malnutrition in people with dementia tends to be even higher at baseline than in high-income countries due to lower socioeconomic resources, our results point out to the relevance of recognizing this issue in the care provided to people with dementia in such settings to aid in the decision-making process involved in the advanced care planning towards an improved care in end of life in people with dementia.

Methodological strengths and limitations

This study was conducted using standardized and cross-culturally validated methods to assess mortality in people with dementia in LMIC. Response rate for the baseline survey was high and only nearly 10% of the sample was lost to follow-up, which allowed prospective evaluation of the main predictors of death. In addition, the prospective nature of the study reduced the likelihood of reverse causality in our analysis. However, the follow-up was restricted to a 3–5-year period and, since dementia cases were prevalent at cohort inception, the survival rate after the onset of symptoms could not be determined. Even though dementia is a chronic condition and longer follow-up periods might optimize mortality assessments, data from other studies show that the median survival rate after onset of dementia may be of only 3.3 years, which indicates that our study has considered a significant amount of time to detect meaningful changes in the majority of participants who were in mild and moderate stages of dementia [71].

All study participants were living in catchment areas of LMIC and may not be representative of the national population of older people in each country. Most catchment areas were restricted to lower socioeconomic status or mixed neighborhoods, which might constrain the variance of socioeconomic exposures, limiting the power to detect the effects of social factors, such as low to high education and low to high number of assets. Cultural differences among countries also mean that cross-country comparisons should be made with caution. Sample characteristics were more homogeneous among Latin American countries, and the smaller samples from India and China may have generated less accurate figures about these countries. The low mortality rates observed in Peru and Venezuela possibly derived from under ascertainment, leading to overrepresentation of deaths among those not traced and whose

vital status was not determined. Specific characteristics of the selected catchment areas may also explain the differences in mortality rates. However, the low proportion of people who could not be traced at follow up may have helped reduce this source of bias in most countries.

Although MUAC was defined a proxy measure for nutritional status in this study, ROC analysis performed in previous research indicates that MUAC is a good measurement of undernutrition in older adults from LMIC [72]. Ethnic differences among countries may generate anthropometric patterns that require different cut-offs for MUAC undernutrition criteria and previous standardization for such differences has not been defined for older adults. The use of body mass index would have facilitated the comparative analyses with previous studies, however this measure is currently not age-standardized reducing its applicability to older adults [2]. Body mass index does not account for loss in muscle mass, which is key precursor of frailty [73], and it depends on the accuracy of two measures (height and weight), which are both difficult to obtain in frail older people with dementia and in home-based assessments.

Conclusions and implications

This study examined patterns of mortality rates and mortality risk factors in a cohort of 1,488 older adults with dementia living in catchment areas of eight LMIC. China had the highest age and gender standardized mortality rate; however, it was not statistical. Older age, male gender, higher number of physical impairments, undernutrition, and higher dementia severity were independently associated with higher mortality risk in the total sample. Educational status, household assets, access to any treatment, depression, CVD, and dementia subtypes were not associated with mortality, warranting further investigation considering inconsistencies found in the literature. The identification of factors increasing the risk of unfavorable outcomes in older adults with chronic, progressive, and incapacitating conditions is essential for the establishment of better end of life care strategies, reducing suffering and costs related to the assistance of people with dementia in low-resourced settings.

ACKNOWLEDGMENTS

This is a secondary analysis of data collected by the 10/66 Dementia Research Group (http://www.alz.co.uk/1066). The 10/66 DRG is led by Martin Prince from Institute of Psychiatry, Psychology and Neuroscience, King's College London. The other principal investigators, data custodians and responsible for research governance in each site are Juan Llibre Rodriguez (Cuba), Daisy Acosta (Dominican Republic), Mariella Guerra (Peru), Aquiles Salas (Venezuela), Ana Luisa Sosa (Mexico), KS Jacob (Vellore, India), Joseph D Williams (Chennai, India), Ivonne Jimenez (Puerto Rico), and Yueqin Huang (China). The 10/66 Dementia Research Group's research has been funded by the Wellcome Trust Health Consequences of Population Change Programme (GR066133 – Prevalence phase in Cuba and Brazil; GR080002- Incidence phase in Peru, Mexico, Argentina, Cuba, Dominican Republic, Venezuela, and China), the World Health Organization (India, Dominican Republic, and China), the US Alzheimer's Association (IIRG–04–1286 - Peru, Mexico, and Argentina), the Puerto Rico State Legislature (Puerto Rico), and FONACIT/CDCH/UCV (Venezuela).

The European Research Council (DA, MJP) has funded ongoing data collection, and further analyses of existing data – ERC-2013-ADG340755 LIFE2YEARS1066.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0078r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-200078.

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