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PREDICTORS OF 4-YEAR MORTALITY AMONG NONAGENARIANS AND CENTENARIANS IN DUJIANGYAN, CHINA

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Abstract: *Objectives*: To identify predictors of mortality in a long-lived Chinese population. *Design:* Four-year follow up mortality data of a previously performed cross-sectional observational study. *Setting:* Dujiangyan, China. *Participants:* Eight-hundred eight Han Chinese aged 90-108 years. *Measurements*: Trained researchers performed face-to-face interviews and physical and geriatric assessments to obtain information on sociodemographic factors, self-reported medical diseases, geriatric-specific conditions, number of hospitalizations and biomedical measurements (systolic/diastolic blood pressure, body mass index (BMI) and blood tests for albumin, fasting glucose, creatinine clearance, hemoglobin and lipid panel). *Results:* Of 808 participants, 424 (52.5%) died during the 4-year period. In univariate analyses, age, 3 out of 10 medical diseases (osteoarthritis, respiratory illnesses and diabetes), increasing number of medical diseases (comorbidities), 4 out of 8 geriatric-specific conditions (ADL impairment, hearing problems, cognitive impairment and weight loss), and two biomedical measurements (albumin <40.0 g/L; creatinine clearance <1200 mL/s) were significantly associated with mortality. In multivariate Cox regression analysis, none of the medical diseases that were significant in the univariate analyses, nor comorbidities, were associated with mortality. Three geriatric conditions were significant: ADL impairment [hazard ratio (HR) = 1.42, 95% confidence interval (CI) = 1.14-1.78, P=.002], cognitive impairment (HR = 1.51, 95% CI = 1.18-1.92, P=.001) and weight loss (HR = 1.41, 95% CI = 1.05-1.90, P=.022). Female gender (HR =.75, 95% CI =.59-.95, P=.018) also reached statistical significance. Two biomedical measures were significantly associated with mortality: albumin <40.0 g/L (HR=1.39, 95% CI=1.02-1.88) and CrCl <1200 mL/s (HR=1.41, 95% CI=1.06-1.88). *Conclusion:* Among a long-lived cohort of Chinese, several geriatric conditions (functional disability, cognitive impairment and weight loss) predict mortality. Comorbidities and specific medical diseases do not. Adding objective biomedical measures does not seem to add substantial information to the risk profile for mortality.

Key words: Mortality, long-lived, comorbidities, geriatric conditions, China.

Introduction

There are several reasons to investigate predictors of mortality in populations of long-lived individuals. Mortality is often considered the final common pathway for many underlying causes of decline associated with age (1). Studying long-lived populations "provides a magnified view of the aging process" (2) and understanding factors associated with mortality among this group can direct future research and preventive treatments for age-related diseases for adults at any age (3, 4). Studies in this age group can also shed light on the challenge that clinicians, researchers and policy-makers face, namely, where to focus efforts and resources for long-lived individuals, on the traditional medical-disease models (e.g. cardiac disease, stroke and cancer) or models based on geriatric-specific conditions (e.g. functional disability and dementia) (6-11).

The majority of studies of long-lived populations have been done in developed countries (10, 12-15). As the world ages, more information will be needed from populations in developing countries. The fastest growing segment of the world's population is the group older than 85 years. By 2050, this group will account for 20% of all older persons in the world (16, 17). Much of this group will come from developing countries. Currently over 60%

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of the world's population 60 years of age and above live in developing countries and by 2050, this will approach 80%. As this 60+ group grows, it will naturally impact the very elderly group.

One country with a particular concern for population aging is China. In absolute numbers, China has the world's largest 60+ group now. This will have great consequences in the future. In 2000, there were 3.7 million people age 85 years and above, but this is expected to grow to over 42 million by 2050 (18).

Methods

Location, Sampling and Recruitment of Participants

The present study is based on 4-year follow-up mortality data of a previously performed cross-sectional study of a very elderly population from Dujiangyan, China. Dujiangyan is 30 kilometers from Chengdu, the capital of Sichuan province. In the summer of 2005, researchers from the Department of Geriatrics, Sichuan University, conducted a cross-sectional study called the Project of Longevity and Aging in Dujiangyan (PLAD). The PLAD aimed to investigate the relationship between environmental factors, lifestyle factors, genetics, age-related diseases and longevity (19, 20). With the help of government officials and the population registry, researchers recruited 62.1% (870/1401) of the population age 90 years and above. Face-to-face interview questionnaires were administered by trained researchers to collect self-reported health information and perform physical and geriatric assessments. Over 95% of participants were accompanied by family members who served as proxies when necessary. Informed consent was obtained from all participants or their legal proxies. The Sichuan University Research Ethics Committee approved the study.

Sociodemographic Variables

Sociodemographic variables included age, gender, education (dichotomized as "any education" or "no education" since none of the participants had an educational level above middle school), and main profession (farmers and non-farmers) before 60 years of age. Tea drinkers, alcohol drinkers and smokers were categorized as current or not current. Participants were asked if they practiced any religion (dichotomized as yes or no).

Medical Diseases

Information on ten medical diseases was collected by asking subjects or caregivers using the following question: "Have doctors ever told you that you have had any of the following diseases or health problems in the past year"? The ten medical diseases were: osteoarthritis, gastrointestinal diseases, respiratory diseases, hypertension, heart problems, chronic renal disease, cerebrovascular disease, peripheral vascular disease, cancer and diabetes. Respiratory diseases included asthma, pneumonia, tuberculosis, emphysema, bronchitis and breathing problems. Cancer excluded skin cancer. For the purpose of this paper, comorbidities was defined as the number of medical diseases. Number of hospitalizations in the past year was also asked about.

Geriatric Conditions

The eight geriatric conditions included: activities of daily living (ADL) impairment (defined as impairment in one or more of six basic ADLs: feeding, dressing, grooming, bathing, walking, toileting (21)), hearing problems (per participant or according to accompanying family member), vision problems, (eye troubles not relieved by glasses), fall (in the past year), fracture (any kind of fracture), weight loss (>1 kilogram in the past month), loss of appetite, and cognitive impairment (23).

Cognitive function was measured using a Chinese version of the 30-item Mini-Mental State Examination (MMSE) (22). Since none of the participants had an educational level above middle school, a cut-off score lower than 18 was used to define cognitive impairment.

Objective Biomedical Measurements

The mean of two blood pressure readings was recorded. For the analyses, systolic blood pressure and diastolic blood pressure were considered elevated if >159mm/Hg or >89mm/Hg, respectively (24). Body mass index (BMI) was calculated using measured weight and height; low was considered <18 kg/m^2 (25).

Venous blood samples were collected after an overnight fast and analyzed in the biochemistry laboratory of Sichuan University. The following values were considered abnormal: albumin <40.0 g/L, fasting (26) plasma glucose >5.54 mmol/L, creatinine clearance (CrCl) <1200 mL/s (Cockcroft-Gault equation) and hemoglobin <100.0 mg/L. A cut point of CrCl <1200 mL/s was chosen instead of 1300 mL/s because such a large percentage of participants had CrCl <1300 mL/s. A hemoglobin cut point of <100 g/L was used to identify people for whom anemia might have some clinical consequence of a low hemoglobin. For lipids, the following were chosen as cut points: LDL >3.36 mmol/L, HDL <1.03 mmol/L and triglycerides >2.26 mmol/L (27).

Mortality Data

In 2009, monthly mortality data were requested (only for original PLAD participants) from local government registries for the period from summer 2005 (original date of the PLAD study) up through summer of 2009. Of the original 870 participants, 808 could accurately be verified as alive or dead. Reasons for not knowing the vital status of the other 62 original participants included residents who moved away from the region and inability of the local government to complete the search in the given time. Data on reasons for death were not available.

Statistical Analysis

Risk for mortality was modeled using Cox regression survival analyses to calculate unadjusted and adjusted hazard ratios (HRs) [(with 95% confidence intervals (CI)] with survival in months as the dependent variable. All variables were treated as dichotomous variables except age, comorbidities and hospitalizations, which were analyzed as linear variables in order to retain as much information as possible. Age, gender and variables that were significant at a P value <0.1 in the unadjusted analyses were entered into the adjusted (multivariate) Cox regression analysis. The area under the receiver operating characteristics curve (C statistic) was used to evaluate model fit. Data were analyzed using IBM SPSS Statistics, version 17.0 (SPSS, Inc., Chicago, IL).

Results

Characteristics of the Participants

Participants' (N=870) mean age was 94 years (range 90-108). Approximately 68% were female, 73% had no formal education, 78% were farmers and <25% practiced religion of any kind. The percentages of current tea drinkers, alcohol drinkers and smokers were 42%, 26% and 42%, respectively. The most prevalent medical diseases were osteoarthritis (29.4%), gastrointestinal problems (17.7%), and respiratory problems (14.1%). The remaining medical diseases were all less than 10% prevalent. Overall, 42.4% reported no medical diseases, 57.6% reported one or more and 20.0% reported two or more. More than half of the participants had not been hospitalized in the past one year, with 24.4% having one hospitalization and 21% having two or more hospitalizations. The most prevalent geriatric conditions were hearing problems (54.9%), falls (52.3%), cognitive impairment (50%), vision problems (43.7%) and ADL disability (33.8%).

Although less than 10% of participants reported hypertension on the interview, 23.6% had a systolic blood pressure >159mmHg, and 13.6% had a diastolic blood pressure >89mmHg. Similarly, although a very small percentage of participants reported diabetes and chronic kidney disease, 15.0% had fasting glucose >5.54 mmol/L and 15.9% had a calculated CrCl clearance <1200 mL/s. Almost 40% of participants had a BMI <18kg/m^2, but only 12.4% had albumin <40.0 g/L. Anemia was not queried in the interview, but 16.3% had hemoglobin <100.0 g/L. Lipid profiles on the group revealed small percentages of participants with laboratory values outside the acceptable range.

Table 1
Comparison of Baseline Characteristics of Chinese Nonagenarians and Centenarians Alive or Deceased after 4-Year Follow-up and Cox regression analyses (Unadjusted HR and 95% CI) with Mortality as Dependent Variable[a]

Variable[b]	Alive N=384	Deceased N=424	HR (95% CI)	P Value
Sociodemographics				
Age (years)	93.4+3.5	93.8+3.3	1.03 (1.00-1.06)	.047
Female	70.6	66.0	0.87 (0.71-1.07)	.182
Education (any)	27.0	27.5	1.01 (0.81-1.25)	.960
Profession[c]	78.3	78.8	1.02 (0.81-1.29)	.865
Religion (any)	24.3	23.6	0.99 (0.79-1.24)	.911
Tea Drinker[d]	44.4	40.9	0.89 (0.74-1.08)	.253
Alcohol Drinker[d]	27.3	25.3	0.91 (0.73-1.13)	.387
Smoker[d]	44.8	41.4	0.91 (0.75-1.10)	.339
Medical diagnoses				
Osteoarthritis	26.7	33.3	1.27 (1.03-1.55)	.023
Gastrointestinal diseases	16.4	19.3	1.16 (0.91-1.48)	.236
Respiratory diseases	12.0	16.6	1.36 (1.05-1.76)	.019
Hypertension	8.7	11.4	1.29 (0.96-1.75)	.093
Heart problems	5.0	4.5	0.92 (0.65-1.62)	.917
Chronic renal disease	1.9	3.1	1.29 (0.75-2.25)	.360
Cerebrovascular disease	2.4	1.4	0.74 (0.33-1.66)	.463
PVD	1.6	0.9	0.63 (0.24-1.69)	.358
Cancer	0.8	1.5	1.37 (0.61-3.06)	.446
Diabetes	0.3	1.9	2.51 (1.25-5.06)	.010
Comorbidites[e]	0.74+.88	0.95+1.02	1.19 (1.08-1.20)	<.001
Hospitalizations[f]	1.06+1.99	1.25+2.27	1.03 (0.99-1.07)	.160
Geriatric Conditions				
ADL impairment	27.7	38.9	1.55 (1.27-1.88)	<.001
Hearing problems	52.6	58.7	1.24 (1.02-1.51)	.029
Fall	50.8	53.1	1.09 (0.90-1.31)	.396
Cognitive impairment	44.0	55.2	1.44 (1.17-1.77)	<.001
Cognitive impairment unknown	12.0	11.6	1.22 (0.88-1.69)	.225
Vision problems	41.9	45.8	1.39 (0.94-1.38)	.183
Loss of appetite	14.0	16.7	1.22 (0.94-1.58)	.129
Weight loss (>1kg in one month)	11.0	15.9	1.47 (1.13-1.92)	.004
Fracture	10.7	10.1	1.00 (0.73-1.36)	.976
Biomedical measurements				
Systolic BP >159 mmHg	23.4	23.7	0.99 (0.79-1.24)	.930
Diastolic BP >89	12.8	14.5	1.05 (0.80-1.39)	.708
BMI (<18kg/m2)	36.8	40.6	1.08 (0.88-1.32)	.459
Hemoglobin (<100.0 g/L)	15.5	17.3	1.15 (0.89-1.49)	.291
Albumin (<40.0 g/L)	8.9	15.3	1.52 (1.16-2.00)	.002
Fasting glucose (>5.54 mmol/L)	16.6	13.5	0.85 (0.64-1.14)	.271
CrCl (<1200 mL/s)	11.0	19.6	1.52 (1.18-1.95)	.001
LDL(>3.36 mmol/L)	4.4	5.5	1.21 (0.79-1.86)	.382
HDL <1.03 mmol/L	5.3	4.0	0.88 (0.53-1.45)	.614
TG (>2.26 mmol/L)	8.0	4.7	0.69 (0.44-1.10)	.116

a. Abbreviations: HR: hazard ratio; CI: confidence interval; PVD: peripheral vascular disease; BP: blood pressure; BMI: body mass index; CrCl: creatinine clearance; LDL: low density lipoprotein; HDL: high density lipoprotein; TGs: triglycerides. Completeness of data: The maximum percent of missing data points for variables in various categories were as follows: sociodemographics (1.2%), medical diagnosis (3.1%), hospitalizations (0.5%), geriatric conditions other than cognitive impairment (1.4%), blood pressure measurements (4.5%), BMI (8.4%), lab measurements (10.8%). For cognitive impairment, 12.3% of participants did not have a completed MMSE. Since this was higher than most other data, a dummy variable, "cognition unknown" was created for the analyses; b. Values are means+SDs or percentages of patients. Percentages are valid percentages; c. Profession defined as farmer; d. Tea Drinker, Alcohol Drinker and Smoker all defined as current; e. Comorbidities is number of self-reported medical diagnoses; f. Hospitalizations is number of hospitalizations in 1 year.

Cox Unadjusted Logistic Regression Analyses (Table 1)

Of 808 participants included in the analyses, 424 (52.5%) died during a 4-year period. In the unadjusted Cox regression analyses, age was the only sociodemographic variable that was significantly associated with risk of mortality (HR=1.03, 95% CI=1.00-1.06). Three of ten medical diseases were significantly associated with risk of mortality, [diabetes (HR=2.51, 95% CI=1.25-5.06), respiratory disease (HR=1.36, 95% CI=1.05-1.76) and osteoarthritis (HR=1.27, 95% CI=1.03-1.55)], as well as number of comorbidities (HR=1.19, 95% CI=1.08-1.20). Four of eight geriatric conditions were significantly associated with risk of mortality: ADL impairment (HR=1.55, 95% CI=1.27-1.88), hearing problems (HR=1.24, 95% CI=1.02-1.51), cognitive impairment (HR=1.44, 95% CI=1.17-1.77), weight loss (HR=1.47, 95% CI=1.13-1.92). Lastly, two of ten objective biomedical measurements were significantly associated with risk of mortality in the unadjusted Cox regression analyses: albumin <40.0 g/L (HR=1.52, 95% CI=1.16-2.00); creatinine clearance <1200 mL/s (HR=1.52, 95% CI=1.18-1.95).

Table 2
Predictors of Mortality According to Cox multivariate regression analysis (Adjusted HR and 95% CI)a

Variables	HR (95% CI)	P Value
Sociodemographics		
Age (years)	1.03 (1.00-1.06)	.091
Female	0.75 (0.59-0.95)	.018
Medical diagnoses		
Osteoarthritis	1.03 (0.75-1.41)	.860
Respiratory	1.18 (0.82-1.69)	.377
Hypertension	1.27 (0.85-1.89)	.244
Diabetes	1.93 (0.83-4.49)	.126
Comorbiditesb	1.09 (0.90-1.32)	.379
Geriatric Conditions		
ADLs	1.42 (1.14-1.78)	.002
Hearing problems	1.12 (0.90-1.39)	.306
Cognitive Impairment	1.51 (1.18-1.92)	.001
Cognitive Impairment Unknown	0.99 (0.66-1.48)	.948
Weight loss (>1kg in one month)	1.41 (1.05-1.90)	.022
Biomedical measurements		
Albumin (<40.0 g/L)	1.39 (1.02-1.88)	.036
CrCl (<1200 mL/s)	1.41 (1.06-1.88)	.017

a. Abbreviations: Abbreviations: HR=hazard ratio; CI=confidence interval; BP=blood pressure; CrCl=creatinine clearance; HRs are based on SI Units. b. Comorbidities is number of self-reported medical diagnoses.

Cox Adjusted Logistic Regression Analyses (Table 2)

In the adjusted analysis, three geriatric conditions were associated with increased risk of mortality: ADL impairment (HR=1.42, 95% CI=1.14-1.78), cognitive impairment (HR=1.51, 95% CI=1.18-1.92) and weight loss (HR=1.41, 95% CI=1.05-1.90). None of the four medical diagnoses, nor comorbidities, were associated with increased risk of mortality. Female gender (HR=0.75, 95% CI=.59-.95) was protective and age was predictive (HR=1.03, 95% CI=1.00-1.06) but this effect was not significant (P=.091). Of the biomedical measures, albumin (HR=1.39, 95% CI=1.02-1.88) and CrCl (HR=1.41, 95% CI=1.06-1.88) were significantly associated with mortality.

Discussion

In this study of Chinese nonagenarians and centenarians, three geriatric conditions and two biomedical measurements predicted risk of mortality: cognitive impairment, ADL impairment, weight loss, low albumin and low CrCl. Several previous studies of very elderly support these findings (28-30).

Although international experts in aging have recently emphasized the prevention of dementia, more attention is needed (31). As of 2010, nearly two-thirds of the world's 35.6 million people with dementia live in low and middle income countries, with almost one-fifth of these (6.35 million) living in China (32).

Previous studies also support the finding that ADL impairment predicts mortality risk (5, 33, 34). Although frailty is not synonymous with ADL impairment, in a study investigating the association of frailty with mortality among older Chinese age 65-109 years, a frailty index was associated with mortality risk, especially among older cohorts (35).

Although the causes of weight loss and low albumin are often multifactorial and not always related to nutritional issues, the results of this study support previous findings that it is still a very important marker of risk for mortality (26, 36-38).

Neither increasing number of medical diseases (comorbidities) nor individual medical diseases predicted mortality. Whether this was because groups like the one here are a special group of "escapers" or resilient to common diseases (such as cardiovascular diseases), or there was a survival bias (those with disease died early), or even if medical diseases were underdiagnosed (39, 40), this study supports future directions in clinical care and research that focus on the geriatric conditions such as those found in this study as opposed to the classic medical model, which is disease focused (5, 6, 41-43)

There are several limitations to this study. It included individuals from one region of China. Although it cannot be used to extrapolate for the rest of China, many studies on long-lived populations from which aging research has benefited have come from limited regions within one country (30, 44, 45). Another limitation is the duration of follow up. Four years was chosen arbitrarily by two of the researchers (BD, JHF). Although this study was similar in length to some in the literature (5, 12, 13, 30) it is not as long as others (46).

It is likely that there is inclusion bias in this study.

Although the capture rate of this population was 62%, which is similar to other population studies of very elderly (a Danish study of nonagenarians and the NonaSantfeliu study in Spain had capture rates of 63% and 61%, respectively) (12, 30), health status and mortality data was not available on those not included in the study. This could have affected the results. For example, if older individuals not included in this study had lower prevalence of cognitive impairment, ADL impairment and weight loss, but similar or higher mortality rates, these conditions might not have been significant predictors in the analyses.

Similarly, recruitment (and volunteerism) of older individuals in population studies such as this one may be affected by poor health status of potential volunteers. This may explain the low prevalence of medical diseases, and thus lack of association with mortality. Other possible explanations for the low prevalence rate of medical diseases include survival bias or under-reporting or under-diagnosing of medical diseases. The list of self-reported medical diseases was as extensive as in other studies of the very elderly (12, 29, 45, 47-50). The addition of the biomedical objective measures, especially laboratory values, aided in capturing some medical conditions (for example, only about 2.5% of patients said they had chronic renal disease, but 15% had low CrCl). However, these measurements did not seem to add substantial information to the risk profile for mortality. This may have been different if more detailed tests of cardiovascular health had been done (such as cardiac echocardiogram, electrocardiogram or carotid ultrasound) (51).

Conclusion

Among a long-lived cohort of Chinese, several geriatric conditions (functional disability, cognitive impairment and weight loss) predict mortality. Accumulation of comorbidities and specific medical diseases do not. Adding basic objective biomedical measures does not seem to add substantial information to the risk profile for mortality.

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