

DETERMINANTS OF FURTHER SURVIVAL IN CENTENARIANS FROM THE PROVINCE OF MANTOVA

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1. INTRODUCTION

The interest in centenarians as a study model for ageing and longevity on one hand (IMUSCE, 1995; Franceschi, 1993) and the demographic explosion of centenarians (Vaupel and Jeune, 1995) with its consequences on society, economy and welfare on the other, encouraged several Italian research groups in the mid Nineties to undertake multidisciplinary studies on population-based samples of extremely old people (Deiana *et al.*, 1999; INRCA, 1999).

Among these was the MALVA study which addressed subjects aged 98+ residing in the province of Mantova (Northern Italy) at the 1st April 1998. The aims of the project were to add to the knowledge about geographic distribution, demographic and socio-economic characteristics and state of health of extremely old people as well as to contribute to the establishment of a biological bank containing cells and DNA of centenarians, useful for investigating the immunological and genetic bases of longevity.

We would like to mention here that Prof. Antonio Parmeggiani, to whom this paper is dedicated, was greatly interested in the topic of longevity which led him to act as supervisor on an undergraduate thesis entitled (“La misura della popolazione centenaria in alcuni comuni dell’Emilia Romagna (1990-1996)” by Daniela Bertuccini, 1996-97). Based on data obtained from Registry offices regarding residents and deceased between 1990 and 1996 in some municipalities of Emilia-Romagna, the work supervised by Prof. Parmeggiani defined a framework for comparison of demographic data on centenarians from the province of Mantova. Moreover it also provided life tables distinguished by age classes on an annual basis for the male and female population aged 85+.

In comparison with previous studies, MALVA’s objective was also to evaluate the health status of the oldest old reducing as far as possible the bias caused by the extremely high mortality rate, as required by a cross-sectional study. The percentage of 98+ subjects in good mental and physical conditions (category A of the health status classification proposed by Franceschi *et al.*, 2000) recorded in the MALVA study was 12% (Guerese *et al.*, 2003), therefore lower than that observed

in the previous Italian studies which had not been able to enrol the frailer subjects.

In the Mantova province, 49% of the severely disabled subjects did not benefit from any kind of assistance, neither in an institution or at their home, and were therefore dependent on their family members. However, the subjects whose functional status was heavily compromised fell into a condition of severe disability at a median age of 95.5 with 83 and 99.8 years as the 5th and 95th percentile, and therefore generally enjoyed a state of good health right into very old age (Gueresi *et al.*, 2008).

With the extinction of the cohort of participants in the MALVA project (the last female having died in April 2008 at the age of 109), to conclude the study it seemed interesting to evaluate which variables pertaining to socio-demographic characteristics, functional and nutritional status and predictors of mortality in the younger elderly influenced further survival in the subjects aged 98+ of the Mantova province.

The data were analysed using Cox regression models estimated on a set of predefined variables and considering methods for multiple imputation of missing values.

2. SAMPLE AND METHODS

2.1. *Sample*

The eligible subjects for the Malva study were the subjects resident in the Mantova province aged 98 years at 1st April 1998 according to the lists of residents provided by the Registry offices of the 70 municipalities in the province.

At that time residing in the Mantova province were 117 subjects aged 98+ (about 32 every 10000 residents) among which 101 were females and 16 males, with a female/male ratio of 6.3.

Of the 117 eligible subjects, 84 agreed to participate in the study, 29 refused to be interviewed, while 4 were in actual fact domiciled outside the province and were unobtainable.

In order to preserve as far as possible the characteristics of a cross-sectional study, reducing the bias due to the extremely high mortality rate at advanced ages, the strategy of enrolment (detailed in Gueresi *et al.*, 2003) included choosing a circumscribed geographical area, identifying and contacting the potential participants before the starting date of the survey, containing as far as possible the time required for data collection (a three month period between April and June 1998) and interviewing firstly the frailer subjects according to indications by their general practitioners. As a result, only 7 of the 84 (i.e. 8%) subjects who agreed to participate in the study died before the interview.

The age of participants was validated by the Census registry and other documents.

Age and gender distribution of the participants in the MALVA study is shown in table 1.

TABLE 1
Age and gender distribution of the participants in the MALVA study

Age	Females	Males	Total
98	29	5	34
99	12	0	12
100	12	0	12
101	3	3	6
102	2	1	3
103	3	1	4
104	5	0	5
105	1	0	1
Total	67	10	77

As discussed thoroughly elsewhere (Gueresi *et al.*, 2003), the participants can be considered representative of the whole 98+ population residing in the Mantova province as regards age range, sex ratio and territorial distribution. Moreover, it can be observed that the survival after six months from the interview was 79.8% among those who agreed to participate in the study and 79.3% among the refusals, suggesting a similar health status in the two groups.

The study protocol comprising inclusion criteria, informed consent form, collecting procedure and questionnaire was submitted to and approved by the Ethical Committee of the Italian National Research Centre on Ageing (INRCA), Ancona.

Data were collected at the subjects' homes by a physician and a biologist, both specifically trained for the task. The participants were administered an interview and various tests to evaluate physical and cognitive functions and underwent a medical examination, anthropometric measuring and blood sampling. The questionnaire, much of which shared with other Italian studies on centenarians (IMUSCE, 1995; Deiana *et al.*, 1999; INRCA, 1999), is specified in Gueresi *et al.*, 2003.

2.2. Methods

Data were analysed using different Cox proportional hazard regression models using first a set of predefined variables as will be described. Each model adjusts for the effects of gender and age.

Assume we observe time to the event of interest for n independent subjects, and let (t_i, δ_i) denote the observed time and the event indicator for the i -th subject. Denote also by \mathbf{X}_i the vector of subject specific covariate. The Cox proportional hazard regression assumes that the individual hazard function $\lambda(t, \mathbf{x}_i)$ has a multiplicative form that models the effects of covariates:

$$\lambda(t, \mathbf{x}_i) = \lambda_0(t) \exp(\beta' \mathbf{x}_i) \quad (1)$$

$\lambda_0(t)$ is the baseline hazard function at time t . The regression parameters β are estimated by maximizing the partial likelihood $l(\beta)$ (Collett, 1994).

A key assumption of the Cox regression model is proportional hazards. The proportional hazards assumption means that the hazard ratio is constant over

time, or that the hazard for an individual is proportional to the hazard for any other individual. Proportional hazards assumption for each Cox regression model was assessed using test based on the Schoenfeld partial residuals which is a measure of the difference between the observed and expected value of the covariate at each time (Shoenfeld, 1982; Therneau and Grambsch, 2000).

The analysed data contain missing values, however, and standard casewise deletion would result in an important reduction in sample size. In this paper Multivariate Imputation by Chained Equations (MICE, van Buuren et al, 1999) has been used. Following this approach a conditional distribution is specified for the missing data of each incomplete variable, for example in the form of a linear or (polytomous) logistic regression of the incomplete covariate given a set of predictors. Predictors themselves can be incomplete. It is assumed that a multivariate distribution exists from which these conditional distributions can be derived, and that iterative Gibbs sampling from the conditionals can generate draws from it.

The method of multiple imputation (MI) is used increasingly for analyzing data-sets with missing observations.

The basic idea of data analysis with multiple imputation is to create a small number, m , of copies of the data, each of which has the missing values suitably imputed. It is usual to choose $m=3$ or 5, in this paper $m=5$ have been used. Then, each complete dataset is analysed independently. Estimates of parameters of interest are averaged across the m copies to give a single estimate. Standard errors are computed according to the "Rubin rules" (Rubin, 1987).

Suppose that initially our primary interest lies in a scalar estimand Q . In a typical case, this might be a regression coefficient, for example, the log hazard ratio in a Cox regression model. Suppose that we have imputed m complete data-sets using an appropriate model. In each of these data-sets, we use standard complete-data methods to obtain an estimate of Q with an associated estimated variance.

Let $\theta^{(k)}$ and $V^{(k)}$ denote the point estimate and variance respectively from the k -th ($k = 1, 2, \dots, m$) data-set.

As might be expected, the multiple imputation point estimate of θ is the average of the m complete-data estimates $\bar{\theta}$.

Combining information on within-imputation and between-imputation variation is required to obtain a valid standard error for this estimate (Carlin *et al.*, 2003). Between-imputation variation is important in reflecting variability due to imputation uncertainty.

The within-imputation variance component is obtained as the average of the complete-data variance estimates:

$$W = \frac{1}{m} \sum_{k=1}^m V^{(k)} \quad (2)$$

While the between-imputation variance is calculated by a simple empirical combination of the complete-data point estimates:

$$B = \frac{1}{m-1} \sum_{k=1}^m (\hat{\theta}^{(k)} - \bar{\theta})^2 \quad (3)$$

The total variance in the combined estimate of θ is then given by

$$T = W + \left(1 + \frac{1}{m}\right) B \quad (4)$$

and Rubin (1987) shows that, approximately,

$$T^{-1/2}(\theta - \bar{\theta}) \sim t_\gamma \quad (5)$$

where

$$\gamma = (m-1) \left\{ 1 + \frac{W}{(1+1/m)B} \right\}^2 \quad (6)$$

Therefore a $100(1 - \alpha)\%$ interval estimate for θ is

$$\bar{\theta} \pm t_{\gamma, 1-\alpha/2} \sqrt{T} \quad (7)$$

The simple methods described above for scalar estimands do not generalize immediately for a multidimensional (vector) quantity, but Li, Raghunathan, and Rubin (1991) have proposed an approximate method to give a p-value for the null hypothesis that all components of a vector Q are equal to zero.

The overall estimates incorporate the missing data uncertainty as well as sampling variation. An essential requirement for the MI method to work in practice is that imputation should be performed under a model that is general enough to make the missing at random (MAR) assumption defensible, even if this model uses variables that are not of substantive interest for later data analysis.

Adopting methods for multiple imputation of missing value, four distinct Cox regression models were estimated, as will be described below. Finally two complete models have been considered: the first one included the statistically significant variables in the previous analyses, while the second one was obtained with a backward selection procedure using a p-value of 10% for removal. Analyses were carried out using STATA (ver. 9.0).

The four estimated models refer to groups of features which may have a significant impact on survival of the elderly as reported in the literature: socio-demographic characteristics, functional status, nutritional status, cardiovascular risk factors.

Among the very numerous variables collected during the course of the survey, included were those variables which according to previous studies have been shown to be predictive of survival in the elderly, focusing on factors that may be still relevant in the extreme stages of life. Not taken into consideration instead

were certain features of potential interest to the analysis due to their reduced variability in the examined group (e.g. only four out of the 77 participants in the study were or had been smokers) or to the great number of missing data (e.g. the Geriatric Depression Scale could not be administered to 43% of the participants due to serious cognitive or sensory impairment).

“Socio-demographic” model.

Included in the “socio-demographic” model are the following variables: gender, age, offspring (has living offspring, had offspring now deceased, never had offspring) institutionalization (yes/no), civil status (widowed, unmarried), level of education (schooling years), financial support from relatives, acquaintances or the social services (yes/no).

“Functional” model.

The variables included in the “functional” model (ADL-Activities of Daily Living, walking 400m, MMSE- Mini Mental State Examination, Self-rated health) are considered salient aspects in any classification of the health status at very old age.

The degree of autonomy was determined by the WHO scale that assesses the degree of self-maintenance considering 21 different activities of daily living. Among these, five items covering Katz’s ADL scale were examined: bathing, dressing, feeding, toileting and transfer. Each activity was rated on a 4-point scale: 1, the subject carries out the activity without difficulty; 2, with some difficulty but without assistance; 3, with partial assistance; and 4, with total assistance. In order to summarize the information on the ability of the elderly to perform daily activities, subjects have been classified as follows: “independent or moderately dependent” (the subject needs assistance in performing 0-2 activities) and “severely or completely dependent” (the subject needs assistance in performing 3-5 activities).

Not considered were performance-based measures included in the MALVA protocol, due to the high number of subjects who did not perform the tests. However, to examine more thoroughly the functional status of the subjects beyond their capacity to perform the basic activities of daily living, considered was the ability to walk 400 m, as evinced by their answers to the WHO questionnaire.

Cognitive function was assessed by the “Mini Mental State Examination” test (Folstein *et al.*, 1975). The crude score was adjusted for years of schooling. Subjects unable to carry out the test since they were classified by physicians as suffering from dementia were assigned score 0. Categorization of cognitive impairment was made according to the classification criteria proposed by Franceschi *et al.*, 2000, where a score of 12 or more points indicates absence of severe cognitive impairment, while a score <12 points suggests the presence of severe cognitive impairment.

General self-rated health was evaluated according to a 5-point scale; to the question “How do you feel about your health?” the interviewees could answer: “very well”, “well”, “not too bad”, “bad” or “very bad”. The analysis considered three groups: “very well or well”, “not too bad”, “bad or very bad”.

For this group of variables it was not possible to estimate a single model because of the high association between variables. In fact, almost all the subjects with cognitive problems are seriously limited in their daily activities or in walking, whereas the subjects with severe limitations in daily activities are not able to walk 400m without assistance. Different models have therefore been considered including alternatively ADL, MMSE and the WHO question about the ability to walk 400 m. Each of these models comprises, as usual, age, gender and, in addition, the self-rated health scale.

“Cardiovascular” model

This model included several known factors representing risk or protection for cardiovascular diseases: hypertension (in presence of therapy for hypertension or blood pressure values above 140/90 mmHg), previous cardiovascular or cerebrovascular disease (angina, myocardial infarction, stroke), serum total cholesterol levels (>200 mg dl⁻¹/ ≤ 200 mg dl⁻¹), serum HDL (>60 mg dl⁻¹/ ≤ 60 mg dl⁻¹) and serum triglycerides (>150 mg dl⁻¹/ ≤ 150 mg dl⁻¹).

Also considered was pulse rate (beats min⁻¹), given that a fast heart rate has been recognized as a precursor of hypertension and atherosclerosis and a predictor for cardiovascular and non-cardiovascular mortality (Kannel *et al.*, 1987; Fujiura *et al.*, 2001).

To record pulse rate and blood pressure mean values of at least three consecutive measurements were used.

Finally, added to the model was Body Mass Index¹. Subjects were divided into three BMI categories: “underweight” (BMI <18.5), “normal weight” (BMI ≥ 18.5 and <25), “overweight - obese” (BMI ≥ 25).

In 44% of cases it was not possible to measure height and weight directly and therefore the values referred by the participant or their proxy were used.

“Nutritional” model

The variables in the “nutritional” model included haematochemical parameters used as indicators of the protein, carbohydrate and lipid supply (serum albumin (mg/dl), blood glucose (mg/dl) and total cholesterol (mg/dl) respectively), besides the information directly provided by the subjects concerning their consumption of fruit/vegetables rich in vitamins and minerals (yes/no) and their consumption of liquids (“less than 3 glasses”, “3-5 glasses” and “over 5 glasses”). Other items in the questionnaire were not used given a certain uniformity in the diet of the centenarians: for example 87% of the subjects had pasta or rice and 95% had milk, cheese or yoghurt every day. Considered lastly were several anthropometric characters: to BMI were added the arm circumference (cm) and triceps skinfold thickness (mm) according to Lohman *et al.* (1988).

¹ Here the definition for BMI = Weight (kg) / Stature² (m²).

3. RESULTS AND DISCUSSION

Figure 1 depicts the Kaplan Meier estimates of the survival function for the entire follow-up: the median survival time is equal to 21 months, while after about 35 months 75% of subjects were died. Tables 2 and 3 report some descriptive statistics for the variables used in the Cox models.

Table 4 shows the results obtained from the Cox models that used as covariates the four set of variables illustrated in the previous paragraph. All the estimated models satisfy the proportional hazard assumption.

In the “socio-demographic” model institutionalization is the only variable significantly related to survival time, with an increase in the risk of death of 247% and quite a large confidence interval (95% CI=80-669).

It has previously been reported that in the MALVA study the only significant determinant for institutionalization was the absence of living offspring, however among the participants in the study about 83% of institutionalized subjects were severely disabled (Gueresi *et al.*, 2008). Since institutionalization concerns often frail and dependent individuals who cannot receive support at home from the family, being institutionalized can involve unfavourable conditions such as a deteriorated state of health, reduced environmental, social and affective stimuli, a worsened psychological state and increased risk of malnutrition, all of which may have repercussions on survival.

In the “functional” models the variables that significantly influence survival are those describing cognitive function (MMSE test), the ability to walk and the self-rated health scale, showing that only two of the three estimated models appear of interest in the analysis of survival. Table 4 shows the results for the “functional” framework: in the first model (model a) the absence of severe cognitive impairment reduces the hazard rate by 48% (95% CI 2-72), while an increase in the hazard rate of 282% (95% CI 2-1340) is shown when comparing “bad or very bad” with respect to “very well or well” categories of the self-rated health scale. The model including the WHO item (model b) shows an increase in the hazard rate of 87% (95% CI 5-233) when comparing centenarians unable to walk 400m without assistance with those able to, and an increase of 368 % (95% CI 16-1783) when comparing health self-rating “bad or very bad” with “very well or well”.

Despite the fact that the ADL score did not here predict survival, the significant influence on mortality of the ability to walk 400m confirms that disability, which represents a common outcome for acute and chronic diseases, can be considered a valuable indicator of worsened health in the oldest old. On the whole, the results of the “functional” model are in agreement with the findings from Nybo *et al.* (2003), reporting that in Danish nonagenarians mortality was predicted by high disability level, poor physical and cognitive performance, and self-rated health (in women).

Interestingly, in the “cardiovascular” model the conditions recognized as cardiovascular risk factors in the middle-aged and younger elderly do not represent a risk for centenarians. On the contrary, a total serum cholesterol level above 200

mg/dl has an hazard ratio of 0.6, however not statistically significant (p -value = 0.16). The relative risk associated with higher serum total cholesterol seems to decline with age and in older persons cholesterol might be inversely associated with total mortality (Weverling-Rijnsburger *et al.*, 1997; Brescianini *et al.*, 2003). The well-known protective effect of high serum HDL concentration, which has also been reported for centenarians (Hagberg and Samuelsson, 2008), does not reach the statistical significance in the extremely aged people from the Mantova province, probably because here the generally high HDL values suggested the use of a decidedly high threshold.

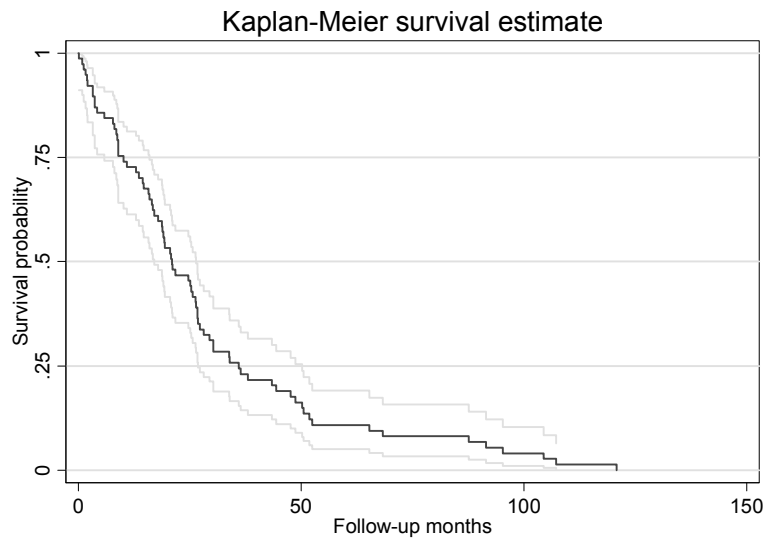


Figure 1 – Kaplan Meier estimates of the survival function.

TABLE 2
Descriptive statistics for quantitative variables

	N.	Mean	Std. Dev.	Min	Max
Age	77	100.20	1.86	98.01	105.58
Serum albumin (mg/dl)	73	3.63	0.47	2.17	4.49
Serum total cholesterol (mg/dl)	73	199.40	43.21	100.00	313.00
Arm circumference (cm)	69	21.06	2.60	15.60	27.30
Education (schooling years)	67	5.04	3.04	2.00	14.00
Pulse rate (beats/min)	73	71.45	11.47	47.00	108.00
Blood glucose (mg/dl)	74	82.68	21.00	44.00	165.00

TABLE 3
Descriptive statistics for qualitative variables

	N.	Percent
Offspring	72	
had offspring now deceased		11.11
has living offspring		69.44
never had offspring		19.44
Institutionalization	77	
no		62.34
yes		37.66
Gender	77	
female		87.01
male		12.99
Civil status	76	
unmarried		11.84
widowed		88.16
Financial support from relatives, acquaintances or the social services	77	
no		50.65
yes		49.35
MMSE	71	
presence of severe cognitive impairment		53.52
absence of severe cognitive impairment		46.48
ADL	77	
severely or completely dependent		74.03
independent or moderately dependent		25.97
Hypertension	75	
no		73.33
yes		26.67
High density lipo-protein (HDL)	73	
<=60 mg/dl		53.42
>60 mg/dl		46.58
Triglycerides	71	
<= 150 mg/dl		77.46
> 150 mg/dl		22.54
Previous cardiovascular or cerebrovascular diseases	75	
no		61.33
yes		38.67
BMI	77	
<18.5		9.09
18.5-24.9		63.64
>= 25		27.27
Consumption of fruit/vegetables	75	
no		21.33
yes		78.67
Daily liquid intake	77	
less than 3 glasses		24.68
3 - 5 glasses		68.83
over 5 glasses		6.49
WHO 4: walking 400m without assistance	69	
yes		28.99
no		71.01

TABLE 4
Variables predicting survival after 98 years of age. Models for group of prognostic factors

	HR	[95% CI]		P-value
Socio-demographic characteristics				
Has living offspring [had offspring now deceased]	0.87	0.36	2.09	0.76
Never had offspring [had offspring now deceased]	0.68	0.24	1.93	0.47
Institutionalization [no]	3.47	1.80	6.69	<0.001
Education (schooling years)	0.89	0.69	1.14	0.35
Gender [female]	1.82	0.87	3.82	0.11
Age	1.23	0.93	1.63	0.15
Financial support [no]	1.06	0.65	1.73	0.81
Civil status [unmarried]	1.89	0.87	4.11	0.11
Functional status (model a)				
MMSE: presence of severe cognitive impairment [yes]	0.52	0.28	0.98	0.04
Perceived health "not too bad" ["very well or well"]	0.87	0.47	1.61	0.66
Perceived health "bad or very bad" ["very well or well"]	3.82	1.02	14.40	0.05
Gender [female]	1.64	0.82	3.29	0.16
Age	1.22	0.93	1.61	0.15
Functional status (model b)				
WHO 4 : walking 400m without assistance [yes]	1.87	1.05	3.33	0.03
Perceived health "not too bad" ["very well or well"]	1.18	0.68	2.05	0.55
Perceived health "bad or very bad" ["very well or well"]	4.68	1.16	18.83	0.03
Gender [female]	1.30	0.63	2.65	0.48
Age	1.16	0.90	1.51	0.25
Cardiovascular risk factors				
Hypertension [no]	1.19	0.65	2.20	0.58
Serum total cholesterol [≤ 200 mg/ dl]	0.60	0.29	1.22	0.16
Serum HDL [≤ 60 mg/ dl]	0.82	0.41	1.62	0.57
Serum triglycerides [≤ 150 mg/dl]	0.86	0.42	1.75	0.67
BMI < 18.5 [18.5-24.9]	3.83	1.45	10.11	0.01
BMI ≥ 25 [18.5-24.9]	1.09	0.58	2.06	0.80
Previous cardiovascular or cerebrovascular diseases [no]	1.02	0.59	1.77	0.95
Gender [female]	1.31	0.60	2.86	0.50
Age	1.10	0.80	1.50	0.53
Pulse rate (beats/min)	0.94	0.70	1.26	0.67
Nutritional status				
Serum albumin (mg/dl)	0.62	0.43	0.88	0.01
Blood glucose (mg/dl)	1.14	0.83	1.58	0.41
Serum total cholesterol (mg/dl)	0.74	0.56	0.99	0.04
Consumption of fruit/vegetables[no]	0.83	0.40	1.72	0.62
Daily liquid intake: 3 - 5 glasses [less than 3 glasses]	0.83	0.36	1.95	0.68
Daily liquid intake: over 5 glasses [less than 3 glasses]	1.39	0.47	4.08	0.55
BMI < 18.5 [18.5-24.9]	2.33	0.78	6.91	0.13
BMI ≥ 25 [18.5-24.9]	1.25	0.67	2.36	0.49
Triceps skinfold (mm)	1.14	0.78	1.65	0.50
Arm circumference (cm)	0.72	0.49	1.06	0.10
Gender [female]	1.63	0.68	3.88	0.27
Age	0.92	0.68	1.25	0.61

Note: for polychotomous variables the reference category is reported in brackets; HR=hazard ratio; HDL=High-density lipoprotein. Hazard ratios for quantitative variables relate to a variation of 1 SD in each variable

TABLE 5
Variables predicting survival after 98 years of age. Synthetic model

	Hazard ratio	[95% CI]		P-value
Institutionalization [no]	2.65	1.49	4.70	<0.001
MMSE: presence of severe cognitive impairment [yes]	0.52	0.29	0.91	0.02
Serum albumin (mg/dl)	0.74	0.52	1.06	0.10
Serum total cholesterol (mg/dl)	0.78	0.58	1.03	0.08
BMI < 18.5 [18.5-24.9]	4.33	1.75	10.72	<0.001
BMI ≥ 25 [18.5-24.9]	1.44	0.80	2.59	0.22
Gender [female]	2.30	1.04	5.06	0.04
Age	1.23	0.91	1.67	0.18

Note: for polychotomous variables the reference category is reported in brackets; HDL=High-density lipoprotein. Hazard ratios for quantitative variables relate to a variation of 1 SD in each variable.

The only factor that confirms a protective role at a younger age is having a BMI within normal values vs. being underweight, with an increment in risk for people with BMI below 18.5 of 283% (95% CI=45-1011). A U-shaped relationship between BMI and mortality has been often reported for the middle-aged but it is emerging that the WHO BMI thresholds for overweight and obesity may be too restrictive for older people. Indeed, among the oldest old the highest BMI is often associated with the lowest mortality (Nybo *et al.*, 2003; Allard *et al.*, 2000). Nevertheless, risk factors measured at old age do not necessarily reflect lifetime exposure to these factors (Nybo *et al.*, 2003).

It has been put forward that the decreasing effect of some risk factors with advancing age can be due to selective survival into very old age of “disease-resistant” phenotypes (Perls, 1995). Several studies have shown, in fact, that centenarians have better cardiovascular risk profiles compared to younger old people, as reviewed in Galioto *et al.* (2008). This can depend on a favourable genetic profile, as suggested by the lower prevalence of cardiovascular diseases in centenarians’ offspring compared to controls without centenarian parents (Terry *et al.*, 2003), together with a healthy past lifestyle, which seems widespread among subjects who have reached extreme longevity (Perls and Terry, 2003).

In the “nutritional” model serum albumin is a predictor of survival along with total cholesterol, with a reduction of 38 % (95% CI= 12-57) and 26 % (95% CI=1-44) respectively for a variation of 1 SD each (0.5 and 43). The protective effect of a BMI within normal values has shown to be not significant in this model, probably because BMI was included together with more predictive variables that are related to it. Indeed, closer to statistical significance is arm circumference (p-value=0.10), a measure that has a biological meaning not unlike that of BMI (higher values indicate greater mass, without distinction between fat or lean mass) but seems to be more suitable for evaluating the elderly, being easy to measure.

On the whole, these results seem to confirm the importance of maintaining adequate nutrition in the oldest old. Chan *et al.* (1999) observed that centenarians have a poorer nutritional status compared to elderly and young subjects, which may be due to their decreased metabolism or to the selective advantage of slenderness in achieving old age. However, malnutrition is one of the principal determinants of mortality in the very elderly.

Serum albumin has been recognized as an independent risk factor for mortality in the elderly (Sahyoun *et al.*, 1996). In the study of Shimizu *et al.* (2001) on a sample of Japanese centenarians, serum albumin was the only significant factor influencing survival, after adjustment for clinical variables.

Besides malnutrition, there are several medical conditions predisposing to low levels of serum albumin (Fuhrman, 2002; Rozzini *et al.*, 1997), which can be therefore considered an indicator of health status. However, a significant association between serum albumin and ageing has recently been observed (Gomi *et al.*, 2007).

Low serum albumin concentration has also been associated with an increased risk of disability, suggesting a relation between hypoalbuminaemia and sarco-

penia, i.e. the loss of peripheral muscle tissue (Baumgartner *et al.*, 1996). Incidentally, sarcopenia can be also related to a low BMI or low arm circumference, both emerging, in the “cardiovascular” or in the “nutritional” model, as unfavourable conditions for survival in the MALVA study participants.

Poor muscle strength consequent to loss of muscle mass is an important component of “frailty” and may be a predictor for adverse outcomes (Bergman *et al.*, 2007). “Frailty” is considered a useful concept by geriatricians but there is still uncertainty and debate regarding its definition (Bergman *et al.*, 2007). Widely used criteria include exhaustion, low handgrip strength, low gait speed, low physical activity and weight loss (Fried *et al.*, 2001). However, an association between obesity and frailty syndrome has been reported in older women (Blaum *et al.*, 2005). According to Rockwood (2005) frailty is likely to be correlated with disability, comorbidity and self-rated health, and should identify a group that is vulnerable to adverse outcomes.

A low serum total cholesterol too can be seen as a marker of frailty in the oldest old (Spada *et al.*, 2007), having been associated with unfavourable conditions such as a compromised cognitive function, comorbidity, disability, or malnutrition (Ranieri *et al.*, 1998). Moreover, a combination of low albumin and low total cholesterol levels may identify subjects at risk of future functional decline (Schalk *et al.*, 2004).

It is worth noting that all the variables which have been shown to be significant in the “socio-demographic”, “functional”, “cardiovascular” or “nutritional” model – institutionalization, MMSE score, ability to walk, perceived health, BMI, serum albumin, serum total cholesterol- can be seen as markers of frailty or correlated conditions, so that the final model including these variables can be defined as a “frailty” model. In this model the functional status was represented by the MMSE variable, since it seemed to be of more general interest than the WHO questionnaire variable relating to the ability to walk 400m.

As can be seen in table 5, almost all the variables included in the final model confirmed their importance in predicting survival. Only the perceived health variable was excluded since it was no longer associated with survival. Furthermore, a significant disadvantage in terms of survival emerged for the male gender.

The same variables included in this final “frailty” model, with the addition of the civil status, were kept in the final model obtained with a backward selection procedure. Whatever path is selected for the final model, the best predictors of mortality are a Body Mass Index less than 18.5 and institutionalization. These characteristics emerge therefore as the best “frailty” indicators in the centenarians from the province of Mantova.

It has been suggested that frailty, favouring fractures, infections or other diseases, may amplify the role of “accidental” risk factors for death in the oldest old (Hagberg and Samuelsson, 2008; Rockwood and Mitnitski, 2007). Nevertheless, as Nybo *et al.* (2003) observed, death at extremely advanced age is not an entirely stochastic phenomenon simply because factors predicting survival do exist.

Indeed, it is emerging that survival of centenarians is influenced by factors on the whole similar even in geographical areas that are far apart, despite the differ-

ent genetic background and different climate, nutrition, economic status, social and medical services to which the subjects have been exposed during the course of their whole life. Several studies (Shimizu *et al.*, 2001; Allard *et al.*, 2000; Nybo *et al.*, 2003; Hagberg and Samuelsson, 2008 and present study) agree on the finding that factors predicting mortality in centenarians are not the same well-known predictors of mortality in the middle-aged and younger elderly.

Further research on predictors of mortality at advanced ages may help in better defining the state of health and the condition of “frailty” in the oldest old as well as in planning interventions for improving their survival and quality of life.

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ACKNOWLEDGEMENTS

Thanks are due to Claudio Franceschi, coordinator of the MALVA project, to Leonarda Troiano, Gabriella Pini, Ciro Lenti and Beniamino Coppa who collected the data and to Giulia Cavrini, Elisabetta Bonafede and Elisa Cevenini who collaborated in the preliminary phases of this study. Data collection in the MALVA study was supported by a grant from ‘Fondazione Cassa di Risparmio di Verona Vicenza Belluno e Ancona’.

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SUMMARY

Determinants of further survival in centenarians from the province of Mantova

The MALVA project, one of the first Italian studies on population-based samples of centenarians, was addressed to the subjects aged 98+ residing in the province of Mantova (Northern Italy) at the 1st April 1998. The present study aims at analyzing the impact of selected clinical and socio-demographic variables on further survival of the 77 participants in the MALVA study.

Adopting methods for multiple imputation of missing value, four distinct Cox regression models were estimated using groups of predefined variables describing socio-demographic characteristics, functional status, nutritional status, cardiovascular risk factors. Each model was adjusted for the effects of gender and age. Finally two complete models have been considered: the first one including the statistically significant variables in the previous analysis, and the second one obtained with a backward selection procedure. The variables included in the final models can be seen as markers of “frailty” or correlated conditions. Most of these variables maintained a significant influence on survival, however belonging to the “underweight” BMI category and being institutionalized emerged as the best “frailty” indicators in the centenarians from the province of Mantova. The results of this study are in agreement with several previous studies in recognizing that factors predicting mortality in centenarians are not the same well-known predictors of mortality in the middle-aged and younger elderly.