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Could the EQ-5D be Used to Predict Mortality and Hospitalization Over a Long Term Period?

Giulia Cavrini[1] · J. Zamberletti[1] · M. Zoli[2]

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Abstract The evaluation of the relationship between health related quality of life (HRQoL) and the occurrence of negative events such as deaths and hospitalizations in the elderly is well established for short-term periods, but underexplored in the longterm. We aim to assess the capacity of HRQoL to predict mortality and hospitalization in an elderly population over an 8-year period. Data were collected by means of the "Pianoro Study", through a questionnaire, which contained the EQ-5D and EQ-VAS instruments to measure the HRQoL. Deaths and hospitalizations occurring over the following 8 years were collected from the registers of the Health Authority. The Cox proportional hazard model and the zero-inflated negative binomial regression model were used to verify the capacity of the EQ-5D to predict deaths and first hospitalizations and the number of hospitalizations respectively, controlling for socio-demographic and clinical variables. High values on the EQ-VAS were significantly associated with a lower risk of death and first hospitalization, whilst the EQ-5D classes of problems and the EQ-5D dimensions were associated with a greater risk (less consistent in predicting mortality). Moreover, the EQ-VAS was found to be significantly associated with both the probability of a zero hospitalization rate and the number of hospitalizations, whereas the EQ-5D classes of problems and the EQ-5D single dimensions were significantly associated with the number of hospitalizations but not with a zero hospitalization probability rate. HRQoL, measured by the EQ-5D questionnaire, is an important prognostic factor in predicting long-term mortality and hospitalization.

Keywords EQ-5D · Elderly · Mortality · Hospitalization · Survival analysis

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✉ Giulia Cavrini
gcavrini@unibz.it

[1] Faculty of Education, Free University of Bolzano/Bozen, Viale Ratisbona 16, 39042 Bressanone, Bolzano, Italy

[2] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

1 Introduction

Identifying risk factors associated with mortality and hospitalization is one of the main functions of epidemiology, and an effective method of forecasting negative health events in the elderly is through measuring self-perceived quality of life. Of particular interest is the study of health related quality of life (HRQoL), which has been described as the impact of health status 'on an individual's ability to function and his or her perceived well-being in the physical, mental and social domains of life' (Nordlund et al. 2005). This concept is tied to the WHO definition of health, which is not only determined by the physical status of an individual but is also multidimensional, 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (WHO 1948). The monitoring of self-perceived Quality of Life (QoL) is becoming increasingly important in the implementation of social and health-related policies. Growing interest in HRQoL has led to the creation of several interpretative instruments, notably the EQ-5D, which was proposed in 1991 by the EuroQol group and has since been widely used. It has the advantage of being brief and simple without the loss of proprieties which usually characterizes more complex instruments (Brooks et al. 1996; Kind et al. 1998; Johnson et al. 1998).

Numerous studies in the literature have demonstrated adequate ways of measuring perceived quality of life to estimate variations in the risk of death and hospitalization, though most of them have been in reference to populations characterized by the presence of specific pathologies. The prognostic value of HRQoL on survival has been widely observed in cancer patients (Blazeby et al. 2001; Coates et al. 1992, 1997; Dancey et al. 1997; De Aguiar et al. 2013; Efficace et al. 2004; Grupta et al. 2007; Luoma et al. 2003; Meyer et al. 2009; Montazeri et al. 2001; Park et al. 2006, 2008; Ruckdeschel and Piantadosi 1994). The most commonly used instruments in this case have been the SF-36 and a validated questionnaire for oncologic patients, the EORTC QLQ-C30 (*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire*). These tools both distinguish between physical QoL and psychological QoL and, in most cases, association between the HRQoL and the occurrence of negative health events has only been significant for the physical component (Chang et al. 1998; Karvonen-Gutierrez et al. 2005; Saquib et al. 2011; Shimozuma et al. 2000; Vigano et al. 2004). Research on adults with HIV (Mathews and May 2007) has instead used the EQ-5D and shown that high values on the EQ-VAS (Visual Analog Scale) are associated with a lower mortality risk and both the EQ-VAS and the EQ-5D indexes are significantly inversely associated with hospitalization rates. Longer survival in the presence of a high self-perceived quality of life measured by the EQ-5D index is confirmed in a study on PAD (*Peripherical Artery Disease*) patients (Issa et al. 2010). As the authors point out, these results suggest that the EQ-5D could be used in clinical practice to identify high risk subjects who might benefit from intensification of specific medical treatments. A low self-perceived QoL has been associated with a significantly greater number of hospitalizations in the prediction of short-term outcomes after: coronary artery bypass graft surgery (Curtis et al. 2002; Rumsfeld et al. 1999), in patients with life-threatening ventricular arrhythmias (Steinberg et al. 2008), heart failure (Alla et al. 2002; Di Giulio 2014; Heidenreich et al. 2006; Parissis et al. 2009; Rodrıguez-Artalejo et al. 2005; Soto et al. 2004), coronary diseases (Lenzen et al. 2007; Spertus et al. 2002), diabetes (Li et al. 2009; McEwen et al. 2009; Clarke et al. 2007), arthritis (Ethgen et al. 2002; Singh et al. 2004), lung obstructive diseases (Fan et al. 2002; Gudmundsson et al. 2005; Sprenkle et al. 2004), asthma (Eisner et al. 2002), cystic fibrosis (Abbott et al. 2009) and in hemodialysis (Kalantar-Zadeh et al. 2001; Mapes et al.

2003; McClellan et al. 1991). Further research on heart failure patients (O'Loughlin et al. 2010) has analyzed the predictability of the HRQoL, finding that it is not constant but tends to decrease over time. While the predictability of the HRQoL has been widely analysed in groups characterized by specific pathologies, it has not been sufficiently studied in a general population. One of the few papers on this was recently published by Ul-Haq et al. (2014), who found that the physical component of the SF-12 associated with all-causes mortality in a longitudinal study on a general Scottish population. They analyzed an adult population, whilst we are interested in assessing the prognostic value of the HRQoL in the elderly.

A study which did focus on a generic elderly population (over 65 years) confirmed the prognostic value of quality-of-life scores on 3-year mortality in Taiwan (Tsai et al. 2007). Two other studies on an elderly generic population (Bilotta et al. 2011; Dominick et al. 2002) found the same results for several types of negative health events as outcomes, but the follow-up length was in both cases quite short: 12 months.

The distinctive element of this research is the follow-up length. In an earlier study using the same data as this research, a significant relation between the HRQoL measured by the EQ-5D and both death and hospitalization risks was found for 2 years following data collection (Cavrini et al. 2012). With the present research we aim to verify whether such a relation remains valid over time and the analyses have been performed using various follow-up times over a period of 8 years. Some studies (Domingo-Salvany et al. 2002; Flensborg-Madsen et al. 2011; Griva et al. 2013; Riise et al. 2014; Zuluaga et al. 2010) have already observed a significant association between HRQoL and the risk of death using follow-ups in respective lengths of 6–7, 13, 11, 10 and 7 years, but they refer to specific sub-populations of patients (graft failure in kidney transplantation, chronic obstructive pulmonary disease, lung cancer and heart failure), while to our knowledge the prognostic value of HRQoL on long-term mortality and hospitalization in the elderly has not yet been explored. Being able to demonstrate that the predictive capability of HRQoL maintains its strength over time would be useful for identifying strategies in medical and health planning.

In the following section (Sect. 2) the study design and data collection will be outlined, in particular the EQ-5D questionnaire. Then the methodology used will be presented, which is the Cox regression model for survival analyses and the zero-inflated negative binomial regression for forecasting the number of hospitalizations. All the estimated models will be described in the results section and then discussed in the last part of the paper.

2 Materials and Methods

2.1 Study Design and Population

To evaluate the health status of a cohort of elderly people, socio-demographic and clinical variables were collected in the 'Pianoro Study' (Cavrini et al. 2005), organized by the University of Bologna and the local Health Authority. In November 2003, a postal questionnaire was sent to 9692 people aged 65 years or over (born before 31 December 1938) who were residents of the selected municipalities: Pianoro, Sasso Marconi and Zola Predosa, three small towns with a similar dimension in the hinterland of Bologna, in northern Italy. The target population selection was based on Health Authority registries.

Occupants of Residential Facilities were excluded because the target was a general elderly population without severe health problems at baseline. The questionnaire included a letter presenting the aims of the study and an informed written consent. The study protocol was approved by the Health Authority's Ethical Committee. The response rate was 54.2 %, a total of 5256 people.

Data collected on this sample showed that the capability of the EQ-5D measures to predict negative health events in the 2 years after the questionnaire assessment was good, as presented in the paper mentioned above (Cavrini et al. 2012). In the present paper we have extended the data on Health Authority registered deaths and first hospitalizations from 2 to 8 years in order to analyze the relationships between the HRQoL and the selected health outcomes over a long-term period and assess whether the predictive capability present in the first 2 years after assessment retains its strength over time.

2.2 Comparison Between Respondents and Non-respondents to the Questionnaire

Individuals selected for the study who did not fill in the questionnaire and those who did respond were compared with the log-rank test in order to highlight any differences in terms of survival. Although risk of death and first hospitalization increased faster for non-respondents over time, there was no evidence of significant statistical differences at the beginning of the study between the two groups in terms of first hospitalization risk, and there was negligible difference in survival risk. As a further guarantee of the absence of a selection bias, the Kruskal–Wallis test showed no significant difference in the median number of hospitalizations between respondents and non-respondents at the beginning of follow-up.

2.3 Outcome Variables

The events analyzed as outcome variables are date of death, date of first hospitalization and number of hospitalizations excluding outpatients between November, 1, 2003 (date of EQ-5D assessment) and October, 31, 2011. They were added to the Health Authority registries dataset with a semi-deterministic record linkage based on a combination of name, surname and date of birth.

2.4 Independent Variables

All regressors were collected through a postal questionnaire sent to selected individuals at the beginning of the study.

The instrument used to measure the HRQoL was the EQ-5D, an internationally validated questionnaire proposed in 1991 by the EuroQol group. The first part has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety or depression, each one containing a scale with three levels of severity (no problem, moderate problems, extreme problems) which create 243 unique health states (Torrance 1986; Dolan 1997). It can also be converted into a single summary index (EQ-5D index) by applying scores from a set of general population preference weights. Since weights are not computed for the Italian population and the single dimensions have been observed to provide more interesting information if considered directly (Gutacker et al. 2012), the EQ-5D index which was used in previous research on the same data (Cavrini et al. 2012) has been replaced with single dimensions in this work. According to previous research (Cavrini et al. 2004), the responses collected from the EQ-5D dimensions can be reclassified into 'classes of problems' variable, distinguishing between people with: 'no problem', 'moderate problems in only one dimension', 'moderate problems in two dimensions or more', and 'at least one extreme problem in one dimension'.

The second part of the questionnaire is a Visual Analogue Scale (VAS) on which an individual assesses their current health state using a value (the EQ-VAS score) between zero (worst health status) and 100 (best health status).

We used the EQ-5D in different models according to the following classifications: (1) EQ-5D classes of problems, (2) EQ-5D single dimensions, (3) EQ-VAS score as HRQoL measures.

The socio-demographic variables we considered were: (1) Age (recoded in classes: 65–69, 70–74, 75–79, 80–84 and 85 years or more), (2) Gender, (3) Marital status (originally coded: never married, separated, divorced, married, widowed; but then separated and divorced were combined in a single category), (4) Tertiary level education (Yes/No), (5) Living alone (Yes/No), (6) Current working activity (Yes/No).

The original classification of the variable 'educational level' previewed the categories: none, primary school, middle school, high school or tertiary education. However, as it showed a violation of the proportional hazard hypothesis required by the modelling approach used in the multivariate analysis, educational level was dichotomized into 'tertiary level education' (Yes/No).

In order to adjust for lifestyles, we considered: (1) Smoking status (smoker, ex-smoker, never smoked), (2) Physical activity measured by the classes of PASE score (inactive, moderately active, active, intensively active), and (3) Alcohol consumption status (high, moderate or no consumption). Physical activity was measured through the Physical Activities Scale for the Elderly (PASE), which includes different typologies of physical activity such as walking, running, swimming and others, the indication of weekly time spent on each one and whether the respondents execute domestic activities such as domestic work, care-giving, gardening or others (Washburn et al. 1993; Dinger et al. 2004). Information collected through this questionnaire was weighted and combined into a score which has greater values for greater physical activity. Four classes were then defined according to the quartiles of the distribution.

Height and weight were collected, converted into Body Mass Index (BMI) and finally expressed using the WHO classification which distinguishes between underweight ($BMI < 18.5$), normal weight ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$) and obese ($BMI \geq 30$). Then, each respondent was asked to indicate any current diagnosis of diabetes, hypertension and hypercholesterolemia. Family history of heart failure was recorded if a family member had experienced an event before 60 years of age. Every previous cardio-vascular event or pathology was collected and the co-morbidity variable counted the number of cardio-vascular pathologies (zero, one or at least two). The number of fractures and falls in the previous 3 years were registered, but the variable indicating the number of fractures in the previous 3 years has not been included in the multivariate models since it showed a violation of the proportional hazard hypothesis in the preliminary analysis. The ADL and IADL scores were obtained through two internationally validated questionnaires: the Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADL). These scales enable the classification of individuals with problems in performing some specific activities as 'not independent' rather than 'independent' (Katz and Akpom 1976; Lawton and Brody 1969). Finally, when the analysis concerned mortality, we decided to adjust the multivariate models with the number of hospitalizations which occurred during follow-up, recoded in: one, two or at least three hospitalizations.

Table 1 Descriptive statistics of the sample socio-demographic characteristics

Variable	Category	% of all cases (N = 5256)
Gender	Male	45.2
	Female	54.8
Classes of age	65–69	29.8
	70–74	25.7
	75–79	20.7
	80–84	14.0
	85 or more	9.8
Classes of pase score	Inactive	35.8
	Moderately active	14.5
	Active	25.5
	Intensively active	24.2
Working activity	Yes	9.2
	Not	88.0
	Unknown	*2.8*
Marital status	Married	64.0
	Widowed	29.4
	Separated/divorced	1.9
	Never married	4.3
	Unknown	*0.4*
Living alone	Yes	20.2
	No	78.1
	Unknown	*1.7*
Tertiary level education	Yes	2.9
	No	96.3
	Unknown	*0.8*

The italics indicate the missing values

The inclusion of this variable was an important proxy for evaluating deterioration in the physical condition of respondents which arose after data collection.

Health variables analysed are therefore: (1) Presence of diabetes (Yes/No), (2) Presence of hypertension (Yes/No), (3) Presence of hypercholesterolemia (Yes/No), (4) Co-morbidity of cardio-vascular diseases (none, one, two or more), (5) Autonomous according to the ADL score (Yes/No), (6) Autonomous according to the IADL score (Yes/No), (7) Falls in the previous 3 years (Yes/No), (8) Family history of heart failure (Yes/No), and (9) Number of hospitalizations from the beginning of follow-up (one, two or at least three) for the analysis of mortality only.

Descriptive analyses of the sample according to the listed characteristics are shown in Tables 1 and 2.

2.5 Statistical Analysis

As we had three different outcomes (mortality, first hospitalization and number of hospitalizations) we applied different analytic approaches.

Table 2 Descriptive statistics of the sample medical and life-style characteristics

Variable	Category	% of all cases (N = 5256)
ADL	Autonomous	68.9
	Not autonomous	27.9
	Unknown	*3.2*
IADL	Autonomous	58.4
	Not autonomous	37.9
	Unknown	*3.7*
Pathologies	Diabetes	11.1
	Hypercholesterolemia	19.7
	Hypertension	27.6
	Family history of heart failure	12.4
Comorbilities	None	75.1
	One	16.6
	Two or more	8.3
BMI classes	Underweight	2.0
	Normal weight	37.6
	Overweight	41.8
	Obese	13.2
	Unknown	*5.4*
Smoking habits	Smoker	9.5
	Ex-smoker	31.3
	Never smoked	56.2
	Unknown	*3.0*
Alcohol consumption	High	3.0
	Moderate	52.9
	No consumption	41.7
	Unknown	*2.4*
Falls in the previous 3 years	Yes	19.7
	No	80.3
EQ-5D classes of problems	No problem	17.0
	Moderate problems in only one dimension	19.8
	Moderate problems in two or more dimensions	36.4
	Extreme problems in at least one dimension	13.3
	Unknown	*13.5*
EQ-VAS score	Mean value (±SD)	63.93 (±20.42)
	Median value	70
	Unknown	*6.8*

The italics indicate the missing values

For mortality we applied survival analysis and in particular the Cox proportional hazard regression model, with Breslow's correction for the tied times. We calculated survival time from November 1, 2003 to the endpoint of the study, censoring after eight different lengths of time: the smallest equal to the first year after the EQ-5D assessment, and the longest equal to 8 years after the same date (eight different models). We also specified different models based on different quantities of interest in the EQ-5D: classes of problems, single dimensions and the EQ-VAS score. The endpoints for the survival analysis were any death occurrence. Before applying a multivariate survival model, a preliminary univariate analysis was performed. The proportional hazard assumption was evaluated by the $\ln(-\ln(S(t)))$ function plot based on the Kaplan–Meier survival estimator. The association between each variable and the outcome (date of death or first hospitalization) was tested with the log-rank and Wilcoxon tests. After the model estimation, Schoenfeld residuals were plotted for each independent variable to control for the presence of a trend, and tested in order to underline the cases of violation of the proportional hazard assumption required by the Cox regression model. The Cox–Snell residuals were then plotted for the evaluation of the goodness of fit of the whole model. When the proportional hazard assumption violation concerned one of the measures of the HRQoL, the model was redefined to include interaction with one or more covariates and time, and in these cases the Schoenfeld and Cox–Snell residuals were related to the first version of the model (without the interaction), because those related to the final version of the model were not available. Finally, in order to make a comparison between models with different lengths of time and EQ-5D measures, the Akaike Information Criterion (AIC) was calculated.

As far as hospitalization is concerned we had two outcomes: the time between the questionnaire assessment and the occurrence of first hospitalization, and the number of hospitalizations.

For first hospitalization, we again used the Cox proportional hazard regression model. We calculated survival time the same way as was done for the analysis of mortality and again we censored after eight different lengths of time and performed different models for each year and typology of EQ-5D measure (for classes of problems, single dimensions and the EQ-VAS score). In this case the endpoints were any first hospitalization and the models take into account the presence of censored data corresponding to any death occurrence. Before applying the multivariate analysis, we performed the same preliminary univariate analyses as for mortality. Similarly, after the model estimation we tested the proportional hazard assumption through the Schoenfeld residuals and then we used the Cox–Snell residuals and the AIC to assess the goodness of fit of the models.

Finally, the zero-inflated negative binomial regression model (ZINB) was applied in order to estimate the number of hospitalizations which occurred in the 8 years of follow-up. It was compared with a Poisson regression model, which presented a worse goodness of fit due to the overdispersion of the data. The zero-inflated variation was suggested by the relevant presence of zero values (28 % of the total) and resulted appropriate when evaluated by the Vuong test for non-nested models. The likelihood ratio test and the residual plot of the estimated versus observed values of the models confirmed the choice. Since the follow-up could be different for individuals who had died before the end of the study, an exposure time variable was defined and used in the analysis. The ZINB model goodness of fit was evaluated through the Akaike information criterion and McFadden R-squared. As preliminary univariate analysis we tested the association between the number of hospitalizations and each independent variable through the Kruskal–Wallis test.

Predictors of the multivariate models were selected using a stepwise procedure, taking into account the association with the outcome being significantly different from zero when the associated P value was less than 0.05. In the analysis on mortality the variables which did not result significant were: living alone, falls in the previous 3 years, hypercholesterolemia and alcohol consumption, while in the analysis on first hospitalization these variables were significant: BMI, living alone, hypercholesterolemia, alcohol consumption, marital status, working activity and hypertension. Finally, the number of hospitalizations covariates which did not result significant were: living alone, education, autonomy according to IADL and autonomy according to ADL. However, if a predictor seemed to be relevant, it was kept in the model even if the value had not been found to be statistically significant at the Wald test. The listed variables were considered to be important in analysing mortality and hospitalization risk, since they are directly or indirectly related to health. The primary interest of this research is the assessment of the relationship between the HRQoL and negative health events, so that other variables collected through the questionnaire were only included in the multivariate models to adjust the results. We therefore considered it more prudent to keep these factors in the models as control variables regardless of the results of the univariate analysis.

Statistical analysis was performed using STATA 12.0.

3 Results

Deaths and first hospitalizations which occurred during the follow-up were respectively 1500 and 3801. Tables 3 and 4 show the temporal repartition of these events in the course of the follow-up, distinguishing for follow-up length.

Of the sample, 72.3 % presented at least one hospitalization, whilst 27.7 % were never hospitalized during the follow-up.

The mean number of hospitalizations was 2.31 (±2.87), with a minimum of zero hospitalizations, a maximum of 33 hospitalizations and a median number of one hospitalization.

3.1 The Capability of the EQ-5D to Predict Mortality

From the univariate analysis, all the considered variables were found to be significantly associated with respondent survival in at least one of the follow-up periods considered, with the exceptions of family history of heart failure and living alone.

In the multivariate analysis, the classes of problems variable was dichotomized, since the intermediate categories did not present any association with the outcome in preliminary analysis. After the transformation it was observed that 8 years after the beginning of the study the category ‘extreme problems in at least one dimension’ was associated with an 11 % higher risk of mortality in respect to those having no problem or moderate problems

Table 3 Number of deaths per follow-up length

Follow-up length	Time period	Number of deaths	Cumulative number of deaths
1 year	01/11/2003–31/10/2004	140	140
2 years	01/11/2004–31/10/2005	209	349
3 years	01/11/2005–31/10/2006	188	537
4 years	01/11/2006–31/10/2007	189	726
5 years	01/11/2007–31/10/2008	179	905
6 years	01/11/2008–31/10/2009	184	1089
7 years	01/11/2009–31/10/2010	195	1284
8 years	01/11/2010–31/10/2011	216	1500
Total		1500	

Table 4 Number of first hospitalizations per follow-up length

Follow-up length	Time period	Number of hospitalizations	Cumulative number of hospitalization
1 year	01/11/2003–31/10/2004	1010	1010
2 years	01/11/2004–31/10/2005	724	1734
3 years	01/11/2005–31/10/2006	513	2247
4 years	01/11/2006–31/10/2007	442	2689
5 years	01/11/2007–31/10/2008	329	3018
6 years	01/11/2008–31/10/2009	311	3329
7 years	01/11/2009–31/10/2010	255	3584
8 years	01/11/2010–31/10/2011	217	3801
Total		3801	

at the beginning of the study. Significantly higher values of mortality risk associated with this variable also resulted across all the other time periods, with the exception of the shortest (Table 5).

We then performed a multivariate analysis with the EQ-5D single dimensions, but it did not highlight the presence of significant associations with the outcome (data not shown).

Finally we used the EQ-VAS score, which resulted in being significantly negatively associated with the risk of death, though the predictive value of the EQ-VAS score tends to be weaker as the follow-up length increases. It indicates that the variable is time-dependant and does not respect an important hypothesis of the Cox model, the proportional hazard assumption. For this reason, an interaction between the EQ-VAS score and time have been included in the models. Although it resulted as only significant in the follow-up periods of 2 and 3 years, it has been retained in all models in order to make them comparable. In the first year after data collection, for a unit increase in the index value, the risk of the occurrence of events decreased by 3.6 %, while after seven and 8 years it decreased respectively by 1 and 0.9 % (Table 6). In the intermediate follow-up periods, the values were comprised in this range, with the exception of the analysis at 6 years when the hazard ratio associated with the EQ-VAS score was not strictly significant but the related *P* value was close to the threshold of 0.05 (being equal to 0.067).

Results of all models analysing mortality were adjusted for: gender, age, autonomy according to the ADL score, autonomy according to the IADL score, physical activity measured by PASE, marital status, living alone, tertiary level education, BMI, working activity, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, co-morbidity, falls in the previous 3 years and number of hospitalizations from the beginning of follow-up.

Models with the EQ-5D dimensions contained 3856 units while the model with EQ-VAS contained 4101 units, as the presence of missing values for some different variables, even in the EQ-5D items, led to the exclusion of some units.

The proportional hazard assumption required for the use of the Cox model was tested using the Schoenfeld residuals (*rho* coefficients and residual plots), which revealed negligible problems for some variables. Since the objective of the study was to observe the relationships between negative health events and the EQ-5D measures as indicators of the HRQoL, interactions with time were included in the model only when the violation concerned the EQ-5D measures, which is the case with the EQ-VAS score. The Cox–Snell

Table 5 Hazard ratios of EQ-5D classes of problems on mortality risk by follow-up length

Follow-up length	Extreme problems in at least one dimension
1 year	
HR	1.18 [0.97; 1.44]
P value	*0.099*
2 years	
HR	1.16 [1.03; 1.31]
P value	***0.012***
3 years	
HR	1.13 [1.03; 1.24]
P value	***0.011***
4 years	
HR	1.14 [1.06; 1.24]
P value	***0.001***
5 years	
HR	1.12 [1.04; 1.20]
P value	***0.002***
6 years	
HR	1.09 [1.02; 1.16]
P value	***0.007***
7 years	
HR	1.10 [1.04; 1.17]
P value	***0.001***
8 years	
HR	1.11 [1.05; 1.17]
P value	***0.000***

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant

residuals were then used to evaluate the goodness of fit. As they were not available for time-dependent models, in these cases the Cox–Snell residual plots were only checked in the previously estimated version of the models which did not include interaction with time. In all sets of models estimated, the Cox–Snell residuals tended to ameliorate with increase in follow-up length. A deviation in the right tail of the Cox–Snell residual distribution was observed for short follow-up periods, but it was probably due to the small number of events which occurred. Finally, models were compared with the AIC values, which suggested a better goodness of fit for models with the EQ-5D dimensions than with the EQ-VAS score.

3.2 The Capability of the EQ-5D to Predict First Hospitalization

From the univariate analysis, family history of heart failure, BMI, alcohol consumption and living alone resulted not associated with first hospitalization risk at any of the follow-up times considered.

In the multivariate analysis, 8 years after the beginning of the study, those who had indicated 'moderate problems in at least two dimensions' at baseline resulted having a 52 % higher risk of first hospitalization in respect to having no problem, when considering a significant interaction with time. This indicates that the force of such an association tended to decrease slightly over time. The classes of problems variable was in fact

Table 6 Hazard ratios of EQ-VAS score on mortality risk by follow-up length

Follow-up time	EQ-VAS score	Interaction between EQ-VAS score and time
1 year		
HR	0.964 [0.939; 0.991]	1.00010 [0.99999; 1.00022]
P value	***0.008***	*0.088*
2 years		
HR	0.976 [0.960; 0.992]	1.00005 [1.00001; 1.00008]
P value	***0.003***	***0.008***
3 years		
HR	0.983 [0.971; 0.995]	1.00002 [1.00000; 1.00004]
P value	***0.007***	***0.025***
4 years		
HR	0.989 [0.979; 0.999]	1.00001 [1.00000; 1.00002]
P value	***0.029***	*0.124*
5 years		
HR	0.990 [0.981; 0.999]	1.00001 [1.00000; 1.00001]
P value	***0.024***	*0.160*
6 years		
HR	0.993 [0.985; 1.001]	1.00000 [0.99999; 1.00001]
P value	*0.067*	*0.730*
7 years		
HR	0.991 [0.984; 0.998]	1.00000 [1.00000; 1.00001]
P value	***0.014***	*0.528*
8 years		
HR	0.990 [0.983; 0.996]	1.00000 [1.00000; 1.00001]
P value	***0.003***	*0.302*

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant

observed to be time-dependent and for this reason the models included an interaction between the categories of this covariate and time. Extreme problems in at least one dimension at baseline were associated with a 64 % higher risk. Similar results were also found for follow-up with different time lengths. Since the presence of only one moderate problem at baseline did not result as a significant predictor of first hospitalization, the column related to this category has been excluded from the table, because of limits of space (Table 7).

Considering then the single dimensions on a separate basis, it was observed that having moderate problems in usual activities and pain/discomfort at baseline were significantly associated with a higher first hospitalization rate in respect to having no problems. The hazard ratio values estimated in the 8 years follow-up were respectively equal to 1.21 and 1.48 for moderate and extreme problems in usual activities and equal to 1.13 and 1.31 for moderate and extreme problems in pain/discomfort. For the mobility dimension, only the category 'moderate problems' at baseline was significantly associated with an increment in the risk of first hospitalization (HR 1.18), while moderate problems in self-care at baseline had a hazard ratio which was significant >1, but only for a short period of follow-up (12 months). Data are shown in Table 8 (results for the anxiety or depression dimension

Table 7 Hazard ratios of EQ-5D classes of problems on first hospitalization risk by follow-up length

Follow-up length	Moderate problems in ≥2 dimensions	Extreme problems in ≥1 dimension	Interaction between moderate problems in ≥2 dimensions and time	Interaction between extreme problems in ≥1 dimension and time
1 year				
HR	2.13 [1.47; 3.10]	2.66 [1.67; 4.23]	0.99890 [0.99728; 1.00053]	0.99855 [0.99646; 1.00064]
P value	***0.000***	***0.000***	*0.186*	*0.173*
2 years				
HR	2.01 [1.54; 2.63]	2.45 [1.74; 3.44]	0.99927 [0.99867; 0.99986]	0.99905 [0.99824; 0.99985]
P value	***0.000***	***0.000***	***0.016***	***0.020***
3 years				
HR	1.72 [1.38; 2.16]	2.02 [1.51; 2.71]	0.99960 [0.99925; 0.99995]	0.99947 [0.99899; 0.99995]
P value	***0.000***	***0.000***	***0.026***	***0.032***
4 years				
HR	1.72 [1.41; 2.10]	2.01 [1.55; 2.61]	0.99964 [0.99940; 0.99987]	0.99951 [0.99917; 0.99984]
P value	***0.000***	***0.000***	***0.002***	***0.004***
5 years				
HR	1.62 [1.35; 1.94]	1.84 [1.44; 2.35]	0.99974 [0.99957; 0.99992]	0.99968 [0.99942; 0.99993]
P value	***0.000***	***0.000***	***0.005***	***0.014***
6 years				
HR	1.59 [1.34; 1.88]	1.71 [1.36; 2.15]	0.99979 [0.99965; 0.99993]	0.99985 [0.99965; 1.00005]
P value	***0.000***	***0.000***	***0.003***	*0.147*
7 years				
HR	1.56 [1.32; 1.83]	1.69 [1.35; 2.10]	0.99982 [0.99971; 0.99994]	0.99987 [0.99970; 1.00004]
P value	***0.000***	***0.000***	***0.003***	*0.140*
8 years				
HR	1.52 [1.30; 1.78]	1.64 [1.33; 2.03]	0.99987 [0.99977; 0.99996]	0.99992 [0.99977; 1.00007]
P value	***0.000***	***0.000***	***0.008***	*0.292*

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant

have been omitted as they were not significantly associated with first hospitalization risk in any follow-up period considered).

Using the EQ-VAS score, a significant negative association with the outcome for all the follow-up periods analyzed was observed (Table 9). The force of such an association tended to decrease over time, indicating that the EQ-VAS score variable is time-dependent, and for this reason an interaction between EQ-VAS score and time was created and included in all models. The interaction HR was not significant when analysing the first 12 months after data collection, but the interaction HRs were always significantly greater than 1 for longer periods. For an increase in the EQ-VAS index value, the risk of first hospitalization decreased by 1.7 % in the analysis at 12 months and 1 % in the analysis at 8 years. Values resulting for the intermediate follow-up periods were comprised in this range.

All the results of models regarding first hospitalization are adjusted for: gender, age, autonomy according to the ADL score, autonomy according to the IADL score, physical activity measured by PASE, marital status, living alone, tertiary level education, BMI, working activity, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, co-morbidity and a family history of heart failure. Models with the EQ-5D dimensions contained 3855 units while the model with EQ-VAS contained 4100 units, as

Table 8 Hazard ratios of EQ-5D dimensions on first hospitalization risk by follow-up length

Follow-up length	Mobility		Self-care		Usual activities		Pain/discomfort	
	Moderate problems	Extreme problems	Moderate problems	Extreme problems	Moderate problems	Extreme problems	Moderate problems	Extreme problems
1 year								
HR	1.08 [0.88; 1.34]	1.68 [0.81; 3.49]	1.36 [1.06; 1.75]	0.70 [0.38; 1.28]	1.36 [1.07; 1.73]	1.69 [1.12; 2.57]	1.32 [1.08; 1.60]	1.55 [1.11; 2.16]
P value	*0.463*	*0.166*	***0.017***	*0.244*	***0.011***	***0.013***	***0.007***	***0.010***
2 years								
HR	1.17 [1.00; 1.38]	1.58 [0.86; 2.90]	1.09 [0.89; 1.34]	0.65 [0.40; 1.06]	1.29 [1.07; 1.54]	1.64 [1.17; 2.29]	1.23 [1.06; 1.42]	1.50 [1.15; 1.94]
P value	*0.053*	*0.140*	*0.387*	*0.085*	***0.007***	***0.004***	***0.006***	***0.002***
3 years								
HR	1.20 [1.04; 1.38]	1.54 [0.88; 2.68]	1.05 [0.88; 1.26]	0.66 [0.42; 1.03]	1.26 [1.07; 1.48]	1.61 [1.19; 2.18]	1.17 [1.03; 1.33]	1.34 [1.06; 1.69]
P value	***0.013***	*0.128*	*0.608*	*0.065*	***0.005***	***0.002***	***0.013***	***0.014***
4 years								
HR	1.19 [1.04; 1.35]	1.58 [0.94; 2.64]	1.08 [0.92; 1.28]	0.74 [0.49; 1.12]	1.22 [1.05; 1.42]	1.46 [1.09; 1.95]	1.18 [1.05; 1.32]	1.34 [1.08; 1.66]
P value	***0.010***	*0.082*	*0.346*	*0.160*	***0.008***	***0.011***	***0.004***	***0.008***
5 years								
HR	1.18 [1.04; 1.33]	1.51 [0.92; 2.49]	1.06 [0.90; 1.24]	0.77 [0.52; 1.14]	1.25 [1.09; 1.44]	1.52 [1.15; 2.00]	1.13 [1.02; 1.25]	1.23 [1.00; 1.52]
P value	***0.009***	*0.102*	*0.496*	*0.196*	***0.002***	***0.003***	***0.024***	***0.046***
6 years								
HR	1.18 [1.05; 1.33]	1.56 [0.97; 2.51]	1.04 [0.89; 1.22]	0.77 [0.53; 1.13]	1.21 [1.06; 1.38]	1.50 [1.15; 1.96]	1.12 [1.01; 1.23]	1.24 [1.02; 1.51]
P value	***0.005***	*0.069*	*0.620*	*0.183*	***0.006***	***0.003***	***0.031***	***0.035***
7 years								
HR	1.18 [1.05; 1.32]	1.47 [0.91; 2.36]	1.01 [0.87; 1.18]	0.80 [0.55; 1.16]	1.23 [1.08; 1.40]	1.50 [1.15; 1.95]	1.12 [1.01; 1.23]	1.29 [1.07; 1.56]
P value	***0.005***	*0.114*	*0.892*	*0.245*	***0.002***	***0.003***	***0.024***	***0.009***
8 years								
HR	1.18 [1.05; 1.31]	1.43 [0.89; 2.30]	0.99 [0.86; 1.15]	0.79 [0.54; 1.14]	1.21 [1.07; 1.37]	1.48 [1.14; 1.92]	1.13 [1.03; 1.24]	1.31 [1.09; 1.58]
P value	***0.004***	*0.136*	*0.933*	*0.208*	***0.003***	***0.003***	***0.010***	***0.004***

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant

Table 9 Hazard ratios [95 % CI] of EQ-VAS score on first hospitalization risk by follow-up length

Follow-up length	EQ-VAS score	Interaction between EQ-VAS score and time
1 year		
HR	0.983 [0.977; 0.990]	1.000025 [0.999991; 1.000059]
P value	***0.000***	*0.150*
2 years		
HR	0.985 [0.979; 0.990]	1.000020 [1.000006; 1.000033]
P value	***0.000***	***0.003***
3 years		
HR	0.986 [0.981; 0.990]	1.000014 [1.000006; 1.000022]
P value	***0.000***	***0.001***
4 years		
HR	0.987 [0.983; 0.991]	1.000008 [1.000003; 1.000013]
P value	***0.000***	***0.004***
5 years		
HR	0.988 [0.985; 0.992]	1.000006 [1.000002; 1.000010]
P value	***0.000***	***0.008***
6 years		
HR	0.989 [0.985; 0.992]	1.000005 [1.000001; 1.000008]
P value	***0.000***	***0.007***
7 years		
HR	0.989 [0.985; 0.992]	1.000005 [1.000002; 1.000007]
P value	***0.000***	***0.001***
8 years		
HR	0.990 [0.986; 0.993]	1.000003 [1.000001; 1.000006]
P value	***0.000***	***0.007***

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant

the presence of missing values for some different variables, even in the EQ-5D items, led to the exclusion of some units.

As we had done for the analysis on mortality, we tested the proportional hazard assumption required for the use of the Cox model through the Schoenfeld residuals, which again revealed negligible problems for some variables. However, also in this case interactions with time were included in the model only when the violation concerned the EQ-5D measures, that is for the EQ-5D classes of problems variable and for the EQ-VAS score. The Cox–Snell tended to ameliorate with the increase in follow-up length. Similar to the analysis on mortality, when compared through the AIC values, the models showed themselves to fit better when the EQ-5D classes of problems or dimensions were used (rather than the EQ-VAS score).

3.3 The Capability of the EQ-5D to Predict the Number of Hospitalizations

Comparing the median number of hospitalizations through the Kruskal–Wallis test as a preliminary analysis, the association was not significant for: having a working activity, alcohol consumption, fractures in the previous 3 years and hypercholesterolemia.

In the multivariate models, moderate problems in two or more dimensions of the EQ-5D and extreme problems in at least one dimension at baseline were significantly associated with a larger number of hospitalizations at the end of the follow-up (14 and 26 % respectively) than having no problem.

A significantly higher number of hospitalizations was also found using the single dimensions: moderate problems in mobility and usual activities (IRR = 1.11 and IRR = 1.24 respectively) and extreme problems in pain/discomfort (IRR = 1.32).

Finally, for a unit increase in the EQ-VAS score, the number of hospitalizations was significantly associated with a drop of 0.5 %, while the probability of zero hospitalizations increased (coef. = 0.048).

All the results of the zero-inflated negative binomial models are shown in Table 10. The Poisson partition in the multivariate models was adjusted for: gender, age, co-morbidities, BMI, autonomy according to the ADL score, autonomy according to the IADL score, physical activity measured by PASE, living alone, tertiary level education, smoking habits,

Table 10 Incidence rate ratios [95 % CI] based on three multivariate zero-inflated Poisson regression models of HRQoL measured by EQ-5D and EQ-VAS with number of hospitalizations in 8 years

	Number of hospitalizations		Probability of zero hospitalizations	
	IRR [95 % CI]	*P* value	Coef. [95 % CI]	*P* value
Classes of problems				
Moderate problems in only one dimension	1.03 [0.91; 1.16]	*0.610*	−0.05 [−0.84; 0.74]	*0.897*
Moderate problems in two or more dimensions	1.14 [1.02; 1.27]	***0.024***	−1.35 [−2.79; 0.08]	*0.064*
Extreme problems in at least one dimension	1.26 [1.09; 1.46]	***0.002***	−1.61 [−4.76; 1.54]	*0.316*
Mobility				
Moderate problems	1.11 [1.01; 1.22]	***0.035***	–	
Extreme problems	1.27 [0.83; 1.93]	*0.274*	–	
Self-care				
Moderate problems	0.87 [0.76; 1.00]	***0.047***	–	
Extreme problems	0.79 [0.57; 1.09]	*0.151*	–	
Usual activities				
Moderate problems	1.24 [1.10; 1.38]	***0.000***	–	
Extreme problems	1.25 [0.99; 1.58]	*0.064*	–	
Pain/discomfort				
Moderate problems	1.06 [0.97; 1.16]	*0.202*	−0.83 [−1.58; −0.09]	***0.029***
Extreme problems	1.32 [1.11; 1.58]	***0.002***	−2.22 [−7.85; 3.41]	*0.439*
Anxiety or depression				
Moderate problems	0.98 [0.91; 1.06]	*0.575*	–	
Extreme problems	0.98 [0.84; 1.14]	*0.782*	–	
EQ-VAS	0.995 [0.993; 0.997]	***0.000***	0.048 [0.018; 0.078]	***0.002***

Italics indicate the *P*-value, Bolditalics indicate that the *P*-value is statistically significant diabetes, hypertension and hypercholesterolemia. The binomial partition depended on the same regressors excluding co-morbidities, living alone, hypercholesterolemia and autonomy according to the ADL score and including autonomy according to the IADL score. Models with the EQ-5D dimensions contained 4021 units while the model with EQ-VAS contained 4296 units.

The likelihood-ratio test suggested a better goodness of fit of the negative binomial model than the Poisson model ($P < 0.001$), while the Vuong test suggested that the zero-inflated partition was a significant improvement ($P < 0.01$) to the classical negative binomial model. McFadden R^2 values confirmed the goodness of fit of the models, which were always very small ($R^2 < 0.027$).

4 Discussion

The aim of the study was to assess the capability of the EQ-5D instrument to independently predict mortality and first hospitalization risks in an elderly population in the north of Italy.

Previous analysis on the same data revealed an association between the HRQoL measured by the EQ-5D questionnaire and the occurrence of negative health events in the 2 years following data collection (Cavrini et al. 2012). In the present work, analysis extended the follow-up to 8 years to determine whether such a relationship remains valid over longer periods of time, which would enable the EQ-5D measures to be more applicable in policy-making processes for medical planning. In order to take into account that a deterioration in the health status of individuals may have arisen after data collection we matched information collected through the questionnaire at the beginning of the study with hospitalization data.

Similar studies have shown that a number of instruments measuring the HRQoL can be used as significant predictors of death and hospitalization, but overall they have only referred to populations specifically characterized by the presence of pathologies such as different typologies of cancer, cardio-vascular diseases, history of heart failure and others. As well as focusing on particular populations, the majority of the quoted studies in literature used specific instruments for the assessment of HRQoL rather than the EQ-5D. The choice of studying a generic elderly population is one of the unique features of the present work, as is the extended length of follow-up.

Survival analysis regarding mortality has confirmed that in the long term the risk of death is greater for those who report severe problems in at least one of the five EQ-5D dimensions, while it lessens as the self-perceived health status measured by the EQ-VAS increases. Nevertheless, no strong association was observed with the single dimension EQ-5D.

As far as first hospitalization risk is concerned, the association with the HRQoL is significant when analysing the EQ-VAS (which is an independent predictor of a low risk of death). Moreover, the single dimensions were significantly associated with the outcome (although not all were independent predictors except ‘usual activities’ and ‘pain/discomfort’, which were significantly associated with a greater risk). Finally, the categories ‘moderate problems in at least two dimensions’ and ‘severe problems in at least one dimension’ of the classes of problems (associated with a greater risk) were also significant predictors of first hospitalization risk. Nevertheless, for both EQ-VAS score and classes of problems EQ-5D there is evidence of a decline in the predictive capability of the HRQoL over time, which is a finding already observed by O’Loughlin et al. (2010).

The number of hospitalizations in the 8 years after data collection presents the same significant associations found in the survival analysis on first hospitalization, even though it mainly concerns the estimation of the number of hospitalizations rather than the probability of having zero hospitalizations. In fact, the variables ‘moderate problems in at least two dimensions’, ‘extreme problems in at least one dimension’, ‘moderate problems in mobility and usual activity’, ‘extreme problems in pain/discomfort’ and lower values of the EQ-VAS score, were all significantly associated with a higher number of hospitalizations. Only moderate problems in pain/discomfort and lower values of the EQ-VAS score were significantly associated with a lower probability of zero hospitalizations.

Limitations of the study firstly involve the presence of missing values concerning the overall EQ-5D. In fact, 13.5 % did not fill in or complete the questionnaire. The self-reporting of subjects in data collection (on height and weight, medical diagnosis, etc.) could lead to the presence of some bias. A further element for future research may also be a longitudinal study design with repeated measures of the covariates, which would adjust for changes in socio-economic characteristics, medical history or health status of individuals that may occur over time.

However, despite the weaknesses of this study, it has been shown that the EQ-5D measures are important independent predictors of mortality and overall hospitalization in an elderly population, with the only exception being the EQ-5D single dimensions which did not consistently predict mortality. The EQ-5D measures could be used to identify the individuals who are most at risk of poor health outcomes, and preventive interventions targeted at these groups may improve health outcomes and decrease health care expenditure.

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Appendix: Pianoro Study Group

Dipartimento di Medicina Interna, Cardioangiologia, Epatologia – University of Bologna

Steering Committee: Marco Zoli (Chief), Giampaolo Bianchi, Donatella Magalotti, Antonio Muscari

Medical Staff: Annalisa Berzigotti, Nicola Castaldini, Grazia Maria Costa, Susanna Dapporto, Gianmarco Drago, Claudia Giannoni, Cosimo Ludovico, Fausta Montesi, Francesco Nicolino, Stefano Ramilli, Dario Sbano, Paola Zappoli

Technical Staff: Raffaela Chianese, Franca Ferri, Giorgia Passerini

Dipartimento di Istologia, Embriologia e Biologia Applicata – University of Bologna

Physical Training Staff: Pasqualino Maietta, Claudio Tentoni, Erika Nerozzi, Carlo Ravaioli, Paola Masi, Irene Negrini

Azienda USL Bologna

Epidemiological staff: Marilina Colombo, Paolo Pandolfi, Barbara Pacelli

Laboratory staff: Amedeo Ligabue, Loretta Dini, Annalisa Zacchini

General Practitioners: Alberto Melli, John Sonnino, Antonio Ajuti, Stefano Bacci, Luca Bruni, Gemma Chiarini, Giampaolo Corradini, Fulvia Nucci, Elisabetta Ongaro, Elisabetta Scandellari, Serena Selva

Municipality of Pianoro

Simonetta Saliera (Mayor), Gianalberto Cavazza, Antonella Grazia, Maria Pia Mezzini, Daniela Mignogna, Emanuela Torchi

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