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Physical functioning and mortality in very old patients on dialysis

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ABSTRACT

Background: Old patients with end-stage kidney disease (ESKD) represent an increasing segment of the ESKD population maintained on chronic dialysis treatment. Quality of life (QoL) is notoriously poor in ESKD but relationship between QoL and mortality has not been investigated in the old dialysis population. The objective of this study is to investigate the relationship between QoL and mortality in the old dialysis population.
Methods: Quality of Life was measured by the Rand- QoL Short Form 36 questionnaires in a multicentre, perspective cohort study including 253 very old patients (age ≥ 75 years) on chronic dialysis. Prognostic power of QoL was assessed applying C-statistics.
Results: In multivariate statistical models including a series of demographic and clinical variable physical function and general health maintained an independent relationship with survival ($P \leq 0.01$). In analyses testing the prognostic value of these two SF36 components physical functioning was the component adding the highest explanatory power to standard demographic and clinical risk factors (+5.7%). Furthermore, the same parameter increased by 4.5% the discriminant power by the Harrell's C Index, improved risk reclassification by the 20% ($P = 0.003$) and model calibration by the 83%.
Conclusions: In the very old dialysis population the physical function component of the SF36 is the QoL component holding the highest predictive power for mortality among the eight components of this instrument. As the discrimination power and risk reclassification ability by physical functioning is of degree relevant for clinical practice, such a measure has potential for refining prognosis and informing exercise programs in this population.

1. Introduction

Old patients with end-stage kidney disease (ESKD) constitute a frail population with multiple comorbidities and a high risk of cardiovascular morbidity and mortality (Kurella Tamura et al., 2009). In Europe, between 2001 and 2011 the incidence rate of ESKD in the age stratum 75–84 years has increased from approximately 450 patients per million population (pmp) to approximately 530 patients pmp and in the oldest age stratum (> 85 years) from about 180 pmp to about 280 pmp (Pippias et al., 2016). In 2014 approximately 20% ESKD patients across Europe were older than 75 years (VV.AA, 2016). On the other hand analyses in the USA Renal Data System (USRDS) document a coherent, progressive aging of the dialysis population (Stevens, Viswanathan, & Weiner, 2010). Thus, the ESKD burden of the old population is an issue of major clinical and public health relevance both in Europe and in the USA.

Quality of life (QoL) is notoriously poor in ESKD patients and the problem is of particular concern in older people (Kurella, Covinsky, Collins, & Chertow, 2007) where cognitive and (Murray et al., 2006) physical impairment are quite common (Kurella et al., 2007). QoL is a known predictor of mortality both in community studies (Idler & Benyamini, 1997) and in advanced chronic liver disease (Kanwal et al., 2009) but, to our knowledge, the relationship between HRQoL and mortality has been scarcely investigated in ESKD.

The RAND QoL Short Form 36 (SF-36) represents an efficient, easy to administer, tool for assessing QoL (Ware & Gandek, 1998; Ware & Sherbourne, 1992). SF-36 incorporates eight QoL components which explore both emotional and physical well-being (Ware & Sherbourne, 1992). This instrument has been specifically validated in ESKD patients (Hays, Kallich, Mapes, Coons, & Carter, 1994) and the physical and

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mental components of SF36 associated with the risk of death independently of other risk factors in an international study in middle-age dialysis patients in five European countries (France, Germany, Italy, Spain, and the United Kingdom), Japan and United States (Mapes et al., 2003). However, the relationship between the eight components of SF-36 and mortality has never been investigated in the old ESKD population. Most importantly, no data are available to clarify if assessment of QoL may help to refine prognosis in this population. This issue is of relevance because the identification of the components that better capture the risk of mortality in older people may be useful for profiling interventions in these frail, high risk patients.

With this background in mind we investigated the relationship between the eight QoL components of the SF36 and mortality in a cohort of dialysis patients older than 75 years. The objective of this analysis was to investigate if QoL had a prognostic power for mortality in the very old dialysis population. We specifically focused in this population because very old patients represent the most vulnerable population of patients with chronic diseases [9] and because the incidence rate of ESKD in the very old people has grown at an accelerated rate both in the dialysis population of the United States Renal Data System (USRDS) (Stevens et al., 2010) and in the European Renal Association, European Dialysis and Transplantation (ERA-EDTA) Registry(Kramer et al., 2009) where about 20% of patients are older than 75 years (VV.AA, 2016).

2. Methods

The study protocol had the approval of the ethical committee of our institution. All participants gave their informed consent before enrolment.

2.1. Study design

The PROGREDIRE (Prospective Registry of The Working Group of Epidemiology of Dialysis Region Calabria) study (IRB number 238, April 16th 2009) is a multicentre, perspective cohort study involving 35 dialysis units in two regions in Southern Italy (Calabria and Sicily) (Torino et al., 2014). In order to enrol a cohort representative of dialysis patients in these regions, no inclusion or exclusion criteria were applied, and all patients on regular dialysis at the participant centres were invited to join the cohort.

2.2. Sampling

In this analysis we included 245 haemodialysis patients aged more than 75 years who completed the Rand- QoL Short Form (SF36) questionnaire among the 1189 composing the whole PROGREDIRE cohort,

2.3. Study population

Patients included in the present analysis had been on regular dialysis for a median time of 44 months (inter-quartile range: 18–76) and were being treated with standard bicarbonate dialysis with non-cellulosic membrane filters of various type. A hundred and forty patients were treated with various anti-hypertensive drugs (64 on mono-therapy with ACE inhibitors, calcium channel blockers, α- and β-blockers, vasodilators, diuretics or other drugs, 46 on double therapy, 19 on triple therapy and 11 patients on quadruple or quintuple therapy with various combinations of these drugs). The main demographic, somatometric, clinical and biochemical characteristics of the study population are detailed in Table 1.

2.4. Baseline data

Patient's information was locally collected at baseline by the nephrologist in charge at each participant centre. Demographic, somatometric, clinical and laboratory information were collected by using clinical records.

2.5. Questionnaires

The SF-36 questionnaire (Ware & Gandek, 1998) contains 36 short questions, that can be grouped into 8 components: Physical Function (PF, 10 questions), Role Limitation due to Physical Health (RLPH, 4 questions), Role Limitation due to Emotional Problems (RLEP, 3 questions), Energy/Fatigue (EF, 4 questions), Emotional Well-being (EW, 5 questions), Social Functioning (SF, 2 questions), Pain (P, 2 questions), General Health (GE, 5 questions), and one question about any change in the health status. The validated, Italian version of SF36 (Klersy et al., 2007) was administered to the enrolled patients at baseline. Patients unable to fill the questionnaire in by themselves were helped by a trained nurse.

2.6. Assessment of covariates included in the analysis

Age, gender, current smoking, diabetes, cardiovascular comorbidities, arterial pressure, antihypertensive use, BMI, dialysis vintage were obtained at baseline by using clinical records, as reported above. Laboratory measurements [serum cholesterol, C-Reactive Protein (CRP), albumin, haemoglobin and phosphate] were made using standard methods in the routine clinical laboratory. Blood sampling was performed after an overnight fast and blood was always drown during a mid-week day (brief dialysis interval).

2.7. Study end-point

The main study end-point was all-cause mortality. The follow-up period was 2.2 years (interquartile range: 1.3–3.3 years). Nephrologists at the participating centres recorded each death, contacting the coordinating centre shortly after the event. Each cause of death was assessed by 3 independent physicians. In doubtful cases, diagnosis was attributed by consensus. During the review process, involved physicians used all available medical information, including hospitalization forms and medical records. In case of death occurred at home, family members and/or general practitioners were interviewed to better understand the circumstances which led to death.

2.8. Statistical analysis

Data were expressed as mean ± standard deviation (normally distributed data), median and inter-quartile range (non-normally distributed data) or as per cent frequency (categorical data). Correlates of the 8 components of SF36 were found by using the Spearman's Rho (ρ). Linear regression analysis was applied to investigate the explained variability of physical functioning. Survival analyses were performed by using both univariate and multivariate Cox regression analyses, including as covariates traditional [age, gender, current smoking, diabetes, cardiovascular comorbidities, cholesterol, arterial pressure, antihypertensive use, BMI], inflammatory [CRP, albumin], dialysis-related risk factors [dialysis vintage, haemoglobin, phosphate] for mortality. The prognostic power of the components of SF36 was assessed by the explained variation in mortality (R^2) (Royston & Sauerbrei, 2004); the discrimination power (Harrell's C Index) (Harrell, Lee, & Mark, 1996); risk reclassification (Net Reclassification Index, NRI) (Pencina, D'Agostino, & Steyerberg, 2011) and calibration by the May-Hosmer test (Crowson, Atkinson, & Therneau, 2016). To calculate the cut-off for death predicted probability to be used in NRI calculation, we performed a multivariate logistic regression analysis, including in the model the set of covariates listed above. The distribution of the individual (i.e. patient by patient) predicted probabilities was used to identifythe 33rd and 66th percentile, and these values were chosen as cut-offs for NRI. In each of the prognostic tests listed above we compared a basic model, including Framingham risk factors, inflammatory

Table 1
Main demographic, somatometric and clinical characteristics in the whole study population and in patients according to the vital status.

Characteristics	Study cohort N = 245	Vital status: alive N = 94	Vital status: dead
Age (years)	81 ± 4	81 ± 4	80 ± 4
Gender (males)	137(56)	55(59)	82(54)
BMI (kg/m^2)	24 ± 4	24 ± 4	24 ± 5
Systolic/Diastolic Blood Pressure (mmHg)	135 ± 23/70 ± 11	137 ± 23/71 ± 11	134 ± 24/69 ± 11
Diabetics n. (%)	74(30)	24(26)	50(33)
Dialysis vintage (months)	44(18–76)	41(18–76)	44(18–76)
With cardiovascular comorbidities n. (%)	*153(62)*	*52(55)*	*101(67)*
Coronary Heart Disease[a] n. (%)	53(22)	16(17)	37(25)
Heart Failure n. (%)	38(16)	11(12)	27(18)
Cerebrovascular Disease [b] n. (%)	34(14)	7(7)	27(18)
Peripheral Vascular Disease n. (%)	65(27)	20(21)	45(30)
On anti-hypertensive treatment n. (%)	140(57)	51(43)	89(59)
Cholesterol (mg/dL)	152 ± 41	158 ± 39	148 ± 42
Hemoglobin (g/dL)	11.0 ± 1.5	11.0 ± 1.5	11.0 ± 1.5
Albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.4	3.7 ± 0.4
C-Reactive Protein (mg/L)	6.0(3.0-16.0)	7.2(3.2–18.6)	5.7(3.0–14.5)
Calcium (mg/dL)	9.1 ± 0.9	9.0 ± 0.8	9.2 ± 0.9
Phosphate (mg/dL)	4.7 ± 1.5	4.7 ± 1.3	4.6 ± 1.6
PTH (pg/ml)	190(92–346)	147(86–254)	214(96–377)
SF-36 components			
Physical function	20 (0–50)	35 (17–55)	15 (0–40)
Role Limitation due to Physical Health	0 (0–100)	0 (0–100)	0 (0–100)
Role Limitation due to Emotional Problems	33 (0–100)	33 (0–100)	33 (0–100)
Energy/Fatigue	35 (20–50)	43 (24–50)	30 (15–45)
Emotional Well-being	50 (32–64)	56 (34–72)	44 (30–64)
Social Functioning	50 (37–75)	50 (38–88)	50 (25–75)
Pain	45 (23–78)	45 (23–78)	45 (23–78)
General Health	25 (15–40)	30 (20–46)	25 (10–40)

Data are expressed as mean ± SD. median and inter-quartile range or as percent frequency, as appropriate; BMI: Body Mass Index; PTH: Parathormone.
[a] Past myocardial Infarction or angina, coronary angioplasty or surgery.
[b] Stroke or transient ischemic attack.

and dialysis-related factors, with a full model, including the same variables of the base model and, in turn, each of the eight components of SF36. To assess statistical significance we adopted the two-tailed test, with a $p < 0.05$ considered significant. Statistical analysis was performed by using standard statistical packages (SPSS for Windows, Version 22, Chicago, Illinois, USA; STATA for Windows, Version 13, College Station, Texas, USA).

3. Results

Among a total of 297 patients ≥75 years, 245 haemodialysis patients underwent the SF36 questionnaire. Patients who underwent the questionnaire did not differ from people not included in this analysis for the main demographic, somatometric and clinical characteristics.

The main baseline characteristics of the study population are reported in Table 1. Fifty-six per cent of patients were males; mean age was 81 years. Diabetics were 30% and 62% of patients had cardiovascular co-morbidities.

3.1. Correlation analyses

As expected, the eight components of the SF36 were strongly associated to each other, with ρ values ranging from 0.21 to 0.77 ($P < 0.001$). Six SF-36 components (Physical Function, Role Limitation due to Emotional Problems, Energy/Fatigue, Emotional Wellbeing, Social Functioning, Pain) were directly associated with gender [ρ ranging from 0.15, P = 0.01 (Role Limitation due to Emotional Problems) to 0.24 (Pain), P ≤ 0.02]. Overall, the seven component of the SF-36 explain 44% of the variability in Physical Function. All SF36 components [ρ ranging from = 0.16, (Role Limitation due Physical Health) to 0.29 (Physical Function), P < 0.020.05 (Pain)] but Role Limitation due to Emotional Problems and Pain associated with serum albumin. Physical function and Role Limitation due to Physical Health correlated with background cardiovascular comorbidities [Physical Function: ρ = −0.21, P = 0.001; Role Limitation due to Physical Health: ρ = −0.19, P = 0.03]. Pain (ρ = −0.18, P = 0.006) and General health (ρ = −0.16, P = 0.02) but no other SF36 component were related with dialysis vintage. No association was found between SF-36 components and age or diabetes.

3.2. Survival analysis

During a median follow-up of 2.2 years (interquartile range: 1.3–3.3 years), 151 patients died.

Among SF36 components, physical function, energy/fatigue and general health predicted survival (P ≤ 0.011). In adjusted models, including traditional, inflammatory and dialysis related risk factors, only physical functioning and general health remained significantly associated to the outcome (P ≤ 0.01) (Table 2).

3.3. Prognostic power of the SF36 components

Prognostic analyses were focused on physical functioning and general health, i.e. the two components that were independently related to death risk (see Table 2). Physical functioning added a higher explanatory power (+5.7%, P for the overall fitting < 0.001) to a clinical model formed by established predictors of mortality in dialysis patients (age, gender, current smoking, diabetes, cardiovascular comorbidities, cholesterol, arterial pressure, antihypertensive use, BMI, CRP, albumin, dialysis vintage, phosphate and haemoglobin) as compared to general health (2.0%, P for the overall fitting = 0.01). The gain in discriminating power (Harrell's C Index) was 4.5% for physical functioning, and 3.3% for general health. Physical functioning improved model calibration because the difference between observed and predicted outcomes of the model including physical functioning ($\chi 2 = 0.39$) was less significant - which indicates improvement (Crowson et al., 2016)- than that of the model not including this

Table 2
HR of the eight SF-36 components for all-cause mortality in univariate and multivariate models. Multivariate models are adjusted for traditional [age, gender, current smoking, diabetes, cardiovascular comorbidities, cholesterol, arterial pressure, antihypertensive use, BMI], inflammatory [CRP, albumin], dialysis-related risk factors [dialysis vintage, haemoglobin, phosphate] for mortality. See text for details.

SF-36 component	Univariate analysis HR (95%CI), P	Multivariate analysis HR (95%CI), P
Physical Function	0.87 (0.81–0.93), P < 0.001	0.88 (0.81–0.95), P = 0.001
Role Limitation due to Physical Health	0.99 (0.96–1.03), P = 0.78	1.01 (0.97–1.05), P = 0.72
Role Limitation due to Emotional Problems	1.000 (0.97–1.04), P = 0.99	1.00 (0.96–1.03), P = 0.99
Energy/Fatigue	0.90 (0.83–0.98), P = 0.01	0.92 (0.84–1.00), P = 0.051
Emotional Well-being	0.94 (0.87–1.01), P = 0.08	0.94 (0.87–1.01), P = 0.09
Social Functioning	0.95 (0.90–1.01), P = 0.11	0.95 (0.89–1.01), P = 0.09
Pain	0.99 (0.94–1.05), P = 0.79	1.00 (0.94–1.06), P = 0.96
General Health	0.87 (0.79–0.95), P = 0.003	0.87 (0.79–0.96), P = 0.01

Table 3
Comparison of **e**xplained variation in mortality, Harrell's C Index, AUC, Calibration, NRI, IDI of the base model, the base model + physical functioning, the base model + general health, the base model + physical functioning and general health. See more details in the text.

	Base model	Base model + PF	Base model + GH	Base model + PF and GH
Explained variation in mortality	0.067	0,124	0.097	0,129
Harrell's C Index	0.583	0.628	0.616	0.637
AUC	66.3%	71.5%	70.2%	72.6%
Calibration (May-Hosm test)	X^2 = 2.28	X^2 = 0.39	X^2 = 1.54	X^2 = 0.81
NRI	—	20%	16%	28%
IDI	—	7%	4%	7%

variable ($\chi 2$ = 2.28), corresponding to an estimated difference of 83%. Conversely, the addition of general health improved the overall fitting only by the 32%. Furthermore, physical functioning was also more powerful for correctly reclassifying the risk categories (Net Reclassification Improvement +20%, P = 0.01) than general health (+16%, P = 0.03). The combination of physical activity and general health added a 6.2% discriminant power for mortality, which is a gain of the same order achieved by the physical functioning component alone (+5.7%, see above). The risk reclassification and calibration improvement (28% and 64% respectively) achieved by the combination of these QoL components were again of the same order or lower than that of physical functioning per se (20% and 83%, see above). By the same token, the Integrated Discrimination Index (IDI) of physical functioning (7%, P < 0.001) was higher than that of general health (4%, P = 0.004) and the combination of these two SF36 components did not increase the IDI of physical functioning alone (7%) (Table 3).

4. Discussion

This analysis in very old ESKD patients on haemodialysis focusing on the prognostic power for mortality by the quality of life components of the SF36 questionnaire indicates that physical activity is the component holding the highest predictive power for this outcome.

Measuring QoL in older people is important for the identification of possible areas of intervention aimed at alleviating the multiple comorbidities and disabilities burden of the aged population (Kutner et al., 1992). Furthermore, the identification of the QoL components more strongly related to the risk of death may help to define priority areas for intervention in the scenario characterized by chronic diseases of the old population. Even though QoL has received substantial attention in ESKD (Chen, Al Mawed, & Unruh, 2016), there is no detailed analysis of the relationship between individual components of QoL and mortality in old and very old ESKD patients. The issue is important for at least three reasons. First because risk factors for death in older people differ from those in the middle aged population(De Ruijter et al., 2009) Second, because life priorities and health perception in older people (Tkatch et al., 2017) do not coincide with those in other age-strata. Third, because ESKD is a condition with a peculiar series of risk for mortality (Kalantar-Zadeh, Block, Humphreys, & Kopple, 2003) and because this condition is characterized by disability and poor QoL (Chen et al., 2016).

As previously alluded to, the SF-36 is an instrument well suited for the assessment of QoL in chronic conditions and this instrument has been specifically validated in the ESKD population (Hays et al., 1994; Klersy et al., 2007). This questionnaire is a reduced version of a much broader QoL instrument which was specifically produced for large surveys and for clinical practice and it can be completed in 10 min or less. In the present study in ESKD patients the physical functioning component of SF-36 was the one holding the highest prognostic power in that it added about the 5% discriminant ability to prediction made on a simple model based on demographic and clinical variables. Furthermore, physical function held a robust risk reclassification ability (+21%), i.e. the ability to correctly reclassify high risk patients versus low risk patients as identified by standard risk factors. Besides physical functioning, only the general health component of SF36 was related to mortality but the prognostic power for mortality of this component was inferior to that by physical function and the combination of this component with physical function added just a small additional prognostic value as compare to physical functioning alone. Even though an assessment of QoL in clinical practice at least once a year is formally recommended by the Center for Medicare and Medicaid Services (Chen et al., 2016) QoL is still not measured in clinical practice in most dialysis centres worldwide. Comprehensive assessment of QoL by the SF36 provides relevant information on the psychological and physical dimensions of QoL which cannot be easily surrogated by minimalist approaches to the problem. In this respect our findings indicate that assessment of physical function only may suffice to refine prognosis in ESKD. The physical function component of SF36 demands no more than 2 min to be assessed and therefore it appears ideally suited for application in clinical practice, at least for the scope of refining prognosis in a high risk population like very old patients maintained on chronic dialysis treatment. Furthermore, knowledge of physical function at patient level may be useful for designing physical rehabilitation interventions in this high risk, sedentary population (Manfredini et al., 2017).

Our study has limitations. First, our cohort was relatively small and composed by very old Caucasian dialysis patients. Therefore, findings in the present study should be confirmed in larger cohorts and in other ethnicities. Second, although findings in our study were robust and internally consistent, the lack of a validation cohort reduces generalizability of our results.

5. Conclusion

The physical function component of the SF36 is the QoL component holding the highest predictive and discrimination power for mortality among the eight components of this instrument and the top rank predictor among all risk factors currently applied to model survival in the dialysis population. The prognostic value of this component is of magnitude that it may have potential for refining risk stratification in clinical practice in a high risk population like very old dialysis patients.

Author contributions

CT contributed to acquisition of data, analysis and interpretation of data and preparation of manuscript; FMR and JvS contributed to the preparation of manuscript; VP and MP contributed to study design, RT and AV contributed to acquisition of data; GT contributed to analysis and interpretation of data; FM contributed to study concept and design; CZ contributed to study concept and design and preparation of manuscript. All authors contributed to drafting or revising the article and approved the final version.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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