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Brief Communication

Title:

PATIENT-REPORTED OUTCOME MEASURES AND THEIR UTILITY IN THE MANAGEMENT OF PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE

Short running title:

Patient Reported Outcome Measures in Chronic Kidney Disease

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Abstract

Symptom and quality of life (QOL) measures in patients with advanced chronic kidney disease (CKD) are recognised indicators of patient-centred care and represent important research, quality and clinical measures. This study examined relationships between symptom burden, QOL and functional status and associations of symptoms and mortality risk.

A multisite longitudinal cohort analysis was undertaken in CKD stage 4/5 (no dialysis, ND) and dialysis patients. Patients completed symptom and QOL measures (Palliative Care Outcome Symptom Score (POS-S renal) [1], World Health Organisation QOL, WHOQOL-BREF) [2] and Karnofsky Performance scale [3]. Clinical and demographic data were recorded.

Participants recruited were 112 dialysis and 40 ND patients. High symptom burden was present and correlated with lower QOL, QOL subdomains and reduced performance status. Comparing groups found a small significant difference in physical QOL suggesting dialysis treatment burden. Further analysis was restricted comparing 102 dialysis and 31 CKD stage 4 (CKD4) patients. Dialysis patients had above target adequacies, but poorer appetite, nausea, vomiting and difficulty sleeping compared with CKD4 patients. Overall, the most prevalent symptoms were also the most severe, specifically pain, dyspnea, weakness, difficulty sleeping. Cox Proportional Hazards regression showed severe pain, nausea, vomiting, poor mobility, itch and skin changes were significantly associated with shorter survival in dialysis patients. Severe symptom score was associated with mortality risk (HR 1.1, 95%CI(1.03,1.17) compared with no increased risk with comorbidity score or age.

Patients with advanced CKD had significant symptom burden correlated with poorer QOL. Symptoms may also be useful in considering clinical outcomes, specifically mortality.

Background

Patient-reported outcome measures (PROMs), which record patients' experiences and are defined as any aspect of patient health directly reported by patients (without interpretation by a clinician or anyone else), and include symptoms, quality of life (QOL) [4]. PROMs are a mechanism to support patient-centred care, shared decision making and have a role in quality improvement activities [5]. Despite assessments of patient wellbeing being fundamental in clinical care, few Australian registries currently include PROMs [4]. As a result, current care of patients including those with chronic kidney disease (CKD) has been described as "often falling short of meeting patients' needs" from a patient reported perspective [6].

There is increasing recognition of PROMs in clinical research. This is particularly important for patients with advanced CKD given their symptom and treatment burden [7]. Patients with advanced CKD (glomerular filtration rate (GFR) < 17ml/min) not receiving dialysis have described symptom burden and impairment of QOL similar to patients with terminal malignancy [8]. Patients with end stage kidney disease (ESKD), regardless of whether they receive renal replacement or conservative care have significant symptom burden, which is currently under recognised by renal clinicians [9,10]. More broadly, clinical approaches which integrate symptom assessment with validated instruments can improve identification of distressing symptoms and may lead to enhanced comfort and better outcomes in patients with both malignant and non-malignant chronic diseases [11].

Risk of death for dialysis patients is significantly increased compared with an aged matched general population [12]. A variety of prognostic assessment tools to assist in identifying dialysis patients with limited life expectancy exist, yet none have incorporated PROMs. Prognostic tools have included biochemical markers such as dialysis adequacy and calcium-phosphate metabolism as well as clinical parameters such as cardiac, nutritional and functional status, comorbidity burden, and the ‘surprise’ question of, “would you be surprised if this patient died in the next 12 months?” [13-15]. PROMs may be a useful addition to renal prognostic assessment and assist clinicians and patients in discussions around commencing or continuing dialysis for certain patients. There is international prospective cohort evidence suggesting higher symptom burden is associated with poorer health related QOL which is correlated with higher mortality in dialysis patients [16]. The generalisability of these results to an Australian population is unknown. This study aimed to identify and examine the relationship of symptoms and QOL scores and relationships between symptom scores and mortality in patients with advanced CKD.

Methods

This longitudinal follow up study was undertaken in consecutive CKD stage 4 and 5 patients attending general nephrology clinics and dialysis patients attending 2 metropolitan and 3 regional satellite dialysis units in Victoria, Australia. Consenting, English speakers and patients on maintenance dialysis (> 3 months) or CKD patients (GFR < 30ml/min; stage 4/5) not on dialysis were included. Data collected comprised clinical and demographic details (age, gender, comorbidity score, dialysis adequacy), a "once-off" survey of symptoms and QOL (Patient Outcome Symptom Scale (POS-S) Renal [1], World Health Organisation QOL (WHOQOL)-BREF) [2] and assessment of Australian Modified Karnofsky Performance status (AKPS) [3] (see appendix A). Low risk ethics approval was obtained.

Phase 1 undertook analyses of differences between groups (Wilcoxon rank-sum test given the non-parametric distribution of the measures) and relationships between variables (Spearman's rank correlation coefficient) performed on outcomes. Phase 2 assessed survival differences in relation to symptoms using follow-up data over 12 months from date of PROM completion. Patient deaths were identified from medical records. Univariate Cox Proportional Hazards were fitted to estimate hazard of death with Schoenfeld residual test to ensure no violation of the proportional hazards assumption. STATA 15.0 was used for analysis.

Results

Between June and September 2014, 112 dialysis patients and 31 CKD stage 4 and 9 CKD stage 5 participated (response rate 40%). N= 67 in-centre haemodialysis, 10 home or nocturnal haemodialysis and 35 peritoneal dialysis patients. Participants had high overall symptom burden which correlated significantly with lower total QOL, reduced performance status and satisfaction with health (Table 1). Total POS-S renal score was strongly correlated with total QOL scores and subdomains and there was no difference between groups with poor QOL scores (Table 1). There was a significant difference in the physical domain of health related QOL, with dialysis patients scoring lower than ND patients (Table 1).

Given small numbers and heterogeneity in samples, home and nocturnal haemodialysis (n=10) and CKD stage 5 (n=9) were excluded from subsequent analysis. Comparisons were made between 102 dialysis and 31 CKD stage 4 (CKD4) patients as control, assuming CKD4 patients have few symptoms associated with renal failure. Dialysis patients were similar age (median 70 years vs 71), gender (67% vs 74% male) with fewer comorbidities compared with CKD4 (median Charlson comorbidity index 4 vs 5). The most prevalent symptoms reported were most severe in both groups, specifically pain, dyspnea, weakness and difficulty sleeping (Table 2). Dialysis patients had higher total symptom burden with median POS-S renal score 14(IQR 9, 22) compared with CKD4 9(IQR 5, 19) p =0.05. Dialysis patients had above target adequacy measures (urea reduction ratio 65%, Kt/V 1.2), but poorer appetite (53% vs 32%, p=0.04), nausea (42% vs 19%, p=0.02), vomiting (24% vs 6%, p=0.05) and difficulty sleeping (80% vs 53%, p=0.05) compared with CKD4 (Table 2).

Phase 2 assessed the relationship of severe POS-S renal responses (defined as 3=severe, 4=overwhelming) to mortality within a maximum follow up of 12 months from date of survey completion (average time 254 days/8.5 months). During this period there were 9 deaths, only in the dialysis group. Cox regression showed pain, nausea, vomiting, poor mobility and itch were significantly associated with shorter survival ($p< 0.05$, Table 3). Overall one point increase in total POS-S renal score was associated with 10% increase in mortality risk; 1.1 95% CI (1.03, 1.17) (Table 3) compared with no statistically increased risk with Charlson comorbidity score (hazard ratio for a one point increase: 1.3, 95% CI (0.9,1.8) and age (hazard ratio for a one year increase: 1.07, 95% CI 0.98,1.15).

Discussion

This research shows Victorian patients with advanced CKD, (including dialysis, patients managed conservatively without dialysis or pre-dialysis) have significant symptom burden; associated with reduced self-reported QOL. Overall, there was no significant difference between dialysis and ND groups in terms of total symptom scores, QOL or health satisfaction which is consistent with previous research [17]. Total POS-S renal score was strongly correlated with overall QOL and subdomains of QOL suggesting symptoms pervasively affect all QOL health domains. The most prevalent symptoms in both dialysis and ND groups were also most severe; consistent with previous research of patients with ESKD managed conservatively [18]. There was an unexpected, small but significant difference in physical domains of health related QOL scores, with dialysis patients scoring lower than ND patients, suggesting treatment burden with dialysis.

This research found specific symptoms such as pain, nausea, vomiting, poor mobility and itch were associated with shorter survival in dialysis patients. These severe symptom scores were associated with increased risk of death over 12 months compared with age or comorbidity score. These results are considered in context of a small data set and 12 month follow up period. Other studies have suggested comorbidity scores have limited ability to discriminate mortality risk for patients commencing dialysis, related to dataset limitations including the timeframe analysed, misclassification bias or comorbidity under-reporting or recording [19].

It is likely comorbidities play a role in overall mortality outcomes. An Australian comparison of elderly patients with ESKD managed conservatively compared with dialysis found survival benefit of dialysis disappeared for patients with 2 or more comorbidities, (at least one being congestive cardiac failure or ischaemic heart disease) and age over 75 years [20]. Large registry datasets have shown certain comorbidities should be more heavily weighted for mortality risk in elderly dialysis patients such as heart failure, peripheral vascular disease, diabetes and active malignancy [21]. Moreover, the underlying aetiology of associations between symptoms, comorbidities and prognosis is multifactorial, potentially related to additional variables such as mobility, frailty and nutritional status. In dialysis patients, functional status and QOL scores are independent predictors of mortality and comorbidities are all likely contributing factors [22]. Future, larger and longer term studies could consider the impact of frailty, specific comorbidities, nutritional and biochemical profile on symptom score severity and may assist understanding these complex and interrelating relationships.

Prognostic utility of symptom scores has been described more broadly with pain, breathlessness and fatigue representing a final common pathway for both malignant and non-malignant advanced disease prior to death [23]. This study suggests the association of certain symptoms and prognosis is present earlier than the final days of life. When comparing patients who electively commence dialysis or wait until symptomatic as “late starters;” the presence of uraemic symptoms contributes to malnutrition and increased 1 year mortality risk [24]. It is possible that “uraemic symptoms” such as nausea, vomiting and itch contribute to both malnutrition and are associated with biochemical complications of ESKD and therefore would herald limited prognosis. Symptoms are useful clinical triggers for having discussions surrounding prognosis and QOL; in addition to addressing patient concerns or symptoms themselves. Schmidt postulated subtle clinical deterioration is commonly due to comorbid illnesses in long-term haemodialysis patients and when detected, should initiate discussions regarding burden and benefit of continuing dialysis [25] and consideration of additional supportive services.

Other authors have demonstrated composite measures of QOL have prognostic utility in dialysis patients. The Dialysis Outcomes and Practice Patterns Study (DOPPS), a multinational prospective observational project, demonstrated health-related QOL scores, including physical, psychosocial and kidney disease components, were strongly associated with higher risk of death and hospitalisation; independent of demographic and comorbid factors [16]. However, underlying mechanisms and factors contributing to associations between symptom burden, functional status, health-related QOL and long-term prognosis remain less well understood.

There is increasing literature demonstrating impaired health related QOL in dialysis patients and symptoms are important contributors to this outcome. There are at least 23 validated symptom assessment tools available; however, the association of using these tools with improved clinical outcomes is currently lacking [26]. Moreover, patient-related factors that cause symptom burden and impaired QOL remain complex and incompletely understood [22]. Given the variety of different PROMs available, there have been uncertainties determining which PROM is most useful for healthcare systems, patients and clinicians representing a possible reason for limited uptake in clinical trials [4]. Despite current uncertainty, it is likely that identifying and addressing symptoms provides therapeutic benefit in a patient-centred approach to care.

This study was limited by response bias and small numbers. Given limited sample size a multivariate regression was not possible to determine whether symptoms play an independent role in predicting outcomes compared with confounders such as nutritional, biochemical or frailty status. We suggest that even with these limitations, the strong association between symptom burden and mortality in our study offers the possibility of a novel approach to consider symptoms as a predictor of death, especially when life expectancy is less than one year. These results could be further investigated in a larger multicentre study using a detailed analysis of known prognostic factors for patients on dialysis including cognition, frailty and comorbidities in seeking to understand the complex relationship between CKD, dialysis effect and symptoms and QOL.

Conclusion

PROMs are increasingly important assessment tools to improve understanding of patient experiences and quality of care. This is the first Australian study to examine the relationship between symptom burden, QOL and mortality outcomes. As increasing numbers of often elderly and medically complex people are considered for dialysis, consideration of symptom burden and QOL should be integrated as part of routine clinical care. This study has highlighted a role for symptom identification as part of clinical assessment for patients with advanced CKD including those managed conservatively, on dialysis or pre-dialysis. The presence of symptoms could have broader clinical implications and may be a useful trigger to review discussions exploring treatment goals, earlier advance care planning and supportive or palliative care referral alongside more traditional medical management approaches of renal disease.

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Conflicts of Interest

None of the authors have conflicts of interest to declare with respect to this research.

References

1. The Palliative care outcome scale. [Webpage in the internet cited on 1.4.2015]. Available from https://pos-pal.org/maix/pos-s-in-english.php.

2. Skevington SM, Lotfy M, O'Connell KA, WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the field trial. A report from the WHOQOL group. *Qual Life Res.* 2004;**13**(2):299-310.

3. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australian-Modified Karnofsky Performance scale: a revised scale for contemporary palliative care clinical practice. *BMC Pall Care*. 2005;**4**(7):1-10.

4. Williams K, Sansoni J, Morris D, Grootemaat P & Thompson C, Patient-reported outcome measures: Literature review. Sydney: ACSQHC; 2016.

5. Food and Drug Administration Guidance for industry – Patient-reported outcome measures: use in medical product development to support labelling claims. U.S. Department of Health and Human Services, Food and Drug Administration. *Fed Reg.* 2009;**74**(235): 6512-6513.

6. Kurella Tamura M. Introduction to Patient-Reported Outcomes Perspectives Series. *Clin J Am Soc Nephrol*. 2017;**12**(11): 1881.

7. Ju A, Tong A. Considerations and Challenges in Selecting Patient-Reported Outcome Measures for Clinical Trials in Nephrology. *Clin J Am Soc Nephrol*. 2017;**12**(11): 1882-1884.

8. Saini T, Murtagh FE, PJ Dupont, McKinnon PM, Hatfield P, Saunders Y. Comparative pilot study of symptoms and quality of life in cancer patients and

patients with end stage renal disease. *Pall Med.* 2006; **20**:631-636.

9. Raj R, Ahuja KDK, Frandsen M, Jose M. Symptoms and their recognition in adult haemodialysis patients: interactions with quality of life. *Nephrol.* 2017;**22**(3): 228-233

10. Weisbord SD, Fried LF, Mor MK et al. Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol*. 2007; **2**(5): 960–7.

11. Kelley A, Morrison S. Palliative Care for the seriously ill. *N Engl J Med*. 2015;**373**:747-55.

12. United States Renal Data System. Excerpts from USRDS 2009 Annual Data Report. U.S. Department of Health and Human Services. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *Am J Kidney Dis*. 2010;**55**(Suppl 1):S1.

13. Alvin H. Moss AH, Ganjoo J, Sharma S. et al. Utility of the "Surprise" Question to Identify Dialysis Patients with High Mortality. *Clin J Am Soc Nephrol*. 2008;**3**(5):1379-1384.

14. Duranton F, Duny Y, et al. Early changes in body weight and blood pressure are associated with mortality in incident dialysis patients. *Clin Kidney J*. 2016;**9**(2):287-294.

15. Stevens LA, Djurdjev O, Cardew S, Cameron EC & Levin A. Calcium, Phosphate, and Parathyroid Hormone Levels in Combination and as a Function of Dialysis Duration Predict Mortality: Evidence for the Complexity of the Association between Mineral Metabolism and Outcomes. *J Am Soc Nephrol*. 2004;**15**:770–779.

16. Mapes DL, Lopes AA, Satayathum S et al. Health-related quality of life as a predictor

or mortality and hospitalization: The Dialysis Outcomes and Practice Patters Study (DOPPS). *Kidney Int.* 2003;**64**(1):339-349.

17. Yong DSP, et al, Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care. *Pall Med*. 2009;**23**:111–119.

18. Brennan F, Collett G, Josland EA, Brown MA. The symptoms of patients with CKD stage 5 managed without dialysis. *Prog in Pall Care*. 2015;**23**(5):267-73.

19. Gomez, AT, Kilberd BA, Royston JP, Alfaadhel T, Soroka SD, Hemmelgam BR, Tennakore KK. Comorbidity burden at dialysis initiation and mortality: A cohort study. Can *J Kidney Health Dis*. 2015; **2**(34):1-9.

20. Brown MA, Collett GK, Josland EA, Foote C, Li Q, Brennan FP. CKD in Elderly Patients Managed without Dialysis: Survival, Symptoms, and Quality of Life. *CJASN*. 2015;**10**:260-8.

21. Couchoud, C, Labeeuw M, Moranne O, Allot V, Esnault V, Frimat L, Strengel B. A clinical score to predict 6 month prognosis in elderly patients starting dialysis for end-stage renal disease. *Nephrol Dial Transplant,* 2009. **24**:1553-1561.

22. AK Khaled, Unruh ML, Weisbord SD. Symptom Burden, Depression, and Quality of Life in Chronic and End-Stage Kidney Disease. *Clin J Am Soc Nephrol.* 2009;**4**: 1057–1064.

23. Solano JP, Gomes B Higginson IJ. A Comparison of Symptom Prevalence in Far Advanced Cancer, AIDS, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal Disease. *J Pain Symptom Manage.* 2006. **31**(1):58-69.

24. Tang S, Ho YW, Tang AW et al. Delaying initiation of diaysis till symptomatic uraemia – is it too late? NDT. 2007;**22**(7):1926-1932.

25. Schmidt RJ, Moss AH. Dying on Dialysis: The case for a dignified withdrawal. *Clin J Am Soc Nephrol.* 2014;**9**(1):174-180.

26. Flythe JE, Powell JD, Poulton C et al. Patient-Reported Outcome Instruments for physical symptoms among patients receiving maintenance dialysis: A systematic Review. *Am J Kidney Dis*. 2015; **66**(6):1033-1043.

Table 1. Symptom Burden, Performance Status, Health Satisfaction and Quality of Life

Outcome	**No dialysis (n = 40)**		**Dialysis (n = 112)**		**Correlation of QOL with total POS-S renal symptom score)**
	Median POS-S Renal (IQR)	No (%) poor QOL p	Median POS-S renal (IQR)	No (%) poor QOL p	
Total POS-S Renal Symptom Score	10 (5,18.5)*		13 (9,22)*		
Karnofsky score	70 (50, 90)		60 (50, 70)		-0.465***
Satisfaction with health	3 (2, 4)		3 (2, 4)		-0.587***
Total QOL^	4 (3, 4)	4 (11%)	4 (3, 4)	15 (13%)	-0.528***
Physical QOL	14 (11, 15.5)**	10 (32%)	13 (10, 15)**	24 (42%)	-0.769***
Psychological QOL	14 (13, 16)	4 (13%)	15 (13, 16)	19 (15%)	-0.573***
Social QOL	13 (12, 15.5)	6 (19%)	15 (12, 16)	17 (16%)	-0.283***
Environmental QOL	15 (13, 17)	5 (16%)	16 (14, 17)	9 (9%)	-0.525***

*p<0.1, **p<0.05, wilcoxon rank-sum test comparing differences of total POS S scores between groups (no dialysis and dialysis)

***p<0.001 spearman's rank correlation coefficient

^Overall QOL scores: 1=very poor, 2 = poor, 3 = neither good nor poor, 4 = good, 5 very good.

p Poor subdomain QOL scores: defined as number of patients with less than half of total domain score

Table 2. POS-S Renal Symptom Profile

	CKD IV (n = 31)	Dialysis (n = 102)	chi ^{2} p	CKD IV (n = 31)	Dialysis (n = 102)	chi ^{2} p
Symptom	**Number (%) of patients with symptom present**			**Number (%) of patients with severe^ symptom present**		
Pain	18 (58%)	77 (75%)	0.06	4 (13%)	13 (13%)	0.98
Dyspnea	18 (58%)	67 (66%)	0.44	5 (16%)	15 (15%)	0.85
Weakness	21 (68%)	90 (88%)	0.01	7 (23%)	21 (21%)	0.81
Difficulty sleeping	16 (52%)	82 (80%)	0.01	9 (23%)	25 (25%)	0.83
Poor mobility	16 (52%)	71 (70%)	0.06	1 (3%)	16 (16%)	0.07
Drowsiness	16(52%)	65 (64%)	0.23	3 (10%)	10 (10%)	0.98
Feeling anxious	20 (65%)	58 (57%)	0.45	3 (10%)	8 (8%)	0.75
Feeling depressed	17 (55%)	48 (46%)	0.45	4 (13%)	6 (6%)	0.19
Restless legs	15 (48%)	52 (51%)	0.08	2 (6%)	13 (13%)	0.33
Itching	14 (45%)	66 (65%)	0.05	3 (10%)	17 (17%)	0.34
Constipation	15 (48%)	57 (56%)	0.45	5 (16%)	8 (8%)	0.17
Diarrhea	13 (42%)	65 (64%)	0.03	1 (3%)	14 (14%)	0.11
Poor appetite	10 (32%)	54 (53%)	0.04	1 (3%)	15 (15%)	0.09
Mouth problems	8 (29%)	37 (36%)	0.46	0 (0%)	7 (7%)	0.13
Skin Problems	10 (32%)	27 (26%)	0.53	2 (7%)	6 (6%)	0.91
Nausea	6 (19%)	43 (42%)	0.02	2 (6%)	6 (6%)	0.91
Vomiting	2 (6%)	24 (24%)	0.04	1 (3%)	3 (3%)	0.93

^severe defined as either POS S renal score 3= severe or 4= overwhelming

Table 3. Symptom Profile and associated mortality risk

Symptom	**Dialysis Patients Number (%) and Severity (scored 3 or more on POS S renal)^ n = 102**	**HR**	**CI (95%)**	**p value**
Total POS-S renal score		1.1	1.0 – 1.2	0.004*
Pain	13 (13%)	5.9	1.6 – 22.3	0.014*
Shortness of breath	15 (15%)	2.9	0.7 – 11.6	0.161
Weakness	21 (21%)	2.0	0.4 – 7.8	0.366
Nausea	6 (6%)	8.5	2.1 - 34.3	0.010*
Vomiting	3 (3%)	9.9	2.0 - 47	0.024*
Poor appetite	15 (15%)	2.9	0.7 - 11.7	0.158
Constipation	8 (8%)	3.1	0.6 – 15.1	0.204
Mouth problems	7 (7%)	3.9	0.8 – 18.9	0.137
Drowsiness	10 (10%)	2.6	0.54 - 12.5	0.278
Poor mobility	16 (16%)	4.6	1.2 – 17.2	0.033*
Itching	17 (17%)	4.0	1.1-15.0	0.050**
Difficult sleeping	25 (25%)	2.5	0.7- 9.2	0.190
Restless legs	13 (13%)	3.2	0.8 – 12.7	0.133
Feeling depressed	6 (6%)	2.0	0.2 – 15.8	0.558
Diarrhoea	14 (14%)	1.6	0.3 – 7.9	0.556
Skin Changes	6 (6%)	5.1	1.0 – 24.3	0.086

*p < 0.05, ** p< 0.1

Note: no patients died with a score of severe anxiety so this symptom was excluded