Pre-dialysis clinic attendance improves quality of life among hemodialysis patients
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Abstract

Background: Although previous research has demonstrated that referral to pre-dialysis clinics is associated with favourable objective outcomes, the benefit of a pre-dialysis clinic from the perspective of patient-perceived subjective outcomes, such as quality of life (QOL), is less well defined.

Methods: A retrospective incident cohort study was conducted to determine if pre-dialysis clinic attendance was a predictor of better QOL scores measured within the first six months of hemodialysis (HD) initiation. Inclusion criteria were HD initiation from January 1 1998 to January 1 2000, diagnosis of chronic renal failure, and completion of the QOL questionnaire within six months of HD initiation. Patients receiving HD for less than four weeks were excluded. An incident cohort of 120 dialysis patients was identified, including 74 patients who attended at least one pre-dialysis clinic and 46 patients who did not. QOL was measured using the SF 36-Item Health Survey. Independent variables included age, sex, diabetes, pre-dialysis clinic attendance and length of attendance, history of ischemic heart disease, stroke, peripheral vascular disease, heart failure, malignancy, and chronic lung disease, residual creatinine clearance at dialysis initiation, and kt/v, albumin and hemoglobin at the time of QOL assessment. Bivariate and multivariate linear regression analyses were used to identify predictors of QOL scores.

Results: Multivariate analysis suggested that pre-dialysis clinic attendance was an independent predictor of higher QOL scores in four of eight health domains (physical function, p < 0.01; emotional role limitation, p = 0.01; social function, p = 0.01; and general health, p = 0.03), even after statistical adjustment for age, sex, residual renal function, kt/v, albumin, and co-morbid disease. Pre-dialysis clinic attendance was also an independent predictor of the physical component summary score (p = 0.03).

Conclusions: We conclude that pre-dialysis clinic attendance favourably influences patient-perceived quality of life within six months of dialysis initiation.
Background

The National Institutes of Health have recommended that patients with chronic progressive renal insufficiency be referred to a multidisciplinary pre-dialysis team in order to minimize patient morbidity and ensure a smooth transition to dialysis therapy. [1] Referral to a pre-dialysis clinic is associated with many desirable outcomes including longer dialysis-free time intervals, [2] enhanced employment opportunities, [3] better patient education, [4,5] and greater participation in the selection of dialysis modality. [4,5] Patients referred to a multi-disciplinary pre-dialysis program also demonstrate better metabolic profiles, are less likely to require central venous catheter insertion, and require fewer in-hospital emergency dialysis starts and hospital admission days compared to patients who receive standard care. [6,7]

However, research exploring the benefits of pre-dialysis care from a patient-oriented perspective using self-reported quality of life measurements is limited. In a single Brazilian study, quality of life was compared between patients diagnosed with chronic renal failure less than one month before dialysis initiation (n = 53) and those patients diagnosed more than six months before starting dialysis (n = 60) using the Kidney Disease Questionnaire (KDQ). [8] Compared to patients diagnosed earlier, quality of life scores were significantly worse in the late-diagnosis group—a finding that was particularly evident among elderly patients. However, statistical adjustment for covariates other than age and time of diagnosis was not performed. As well, only 28% of patients were over age 60, suggesting that the association between early diagnosis and improved quality of life may have been underestimated. Further study using a more representative sample reflecting the demographics of an aging Canadian population is therefore warranted.

The present study hypothesized that attendance at a pre-dialysis clinic is an independent predictor of improved quality of life scores measured within the first six months of dialysis initiation in an incident cohort of chronic hemodialysis patients. Quality of life, measured using the SF 36-item Health Survey, was compared between patients who attended a pre-dialysis clinic and those who did not, adjusted for clinical and biochemical covariates.

Methods

Patient population

Kingston General Hospital is a tertiary care university teaching centre in Southeastern Ontario, Canada, providing pre-dialysis, hemodialysis, peritoneal dialysis and transplantation programs. The hospital is the only centre offering nephrology consultation in this region, serving a population of about 450,000 people. Referral patterns are therefore very centralized. Patients receive hemodialysis at either Kingston General Hospital or one of several affiliated satellite units that offer both self-care and full nursing care services.

Patients with renal failure are referred by primary care physicians to a nephrologist for initial assessment. The care of patients diagnosed with chronic and progressive renal failure who do not require imminent dialysis initiation is subsequently transferred by the nephrologist to the pre-dialysis clinic. Direct referral to the pre-dialysis clinic by a primary care physician is not permitted. The pre-dialysis clinic is scheduled weekly and staffed by nurse clinicians, dieticians, social workers, pharmacists, and nephrologists. The nephrologists at the hospital operate a group practice and staff the pre-dialysis clinic according to a rotating schedule.

The medical records of all patients beginning chronic hemodialysis at Kingston General Hospital or affiliated satellite dialysis units were reviewed by the primary investigator for study eligibility. Study inclusion criteria were first hemodialysis initiation from January 1 1998 to January 1 2000, history of chronic irreversible renal failure, and completion of the QOL survey within six months of dialysis initiation. Exclusion criteria included receipt of dialysis for less than four weeks and previous kidney transplantation. Reasons for non-completion of the SF-36 questionnaire within six months of dialysis initiation included death (16 patients from the pre-dialysis group and nine patients from the non-pre-dialysis group) and transfer to peritoneal dialysis (two patients from the non-pre-dialysis group). Five patients were excluded due to a significant number of missing data points. An incident cohort of 120 adult hemodialysis patients satisfying the above inclusion and exclusion criteria was identified, of whom 74 patients had attended the pre-dialysis clinic on at least one occasion, while 46 patients began dialysis without previous pre-dialysis clinic attendance.

Independent variables

Possible predictors of outcome included age (at dialysis initiation), sex, diabetes (yes/no), pre-dialysis clinic attendance (yes/no), length of pre-dialysis clinic attendance, date of QOL assessment, history of ischemic heart disease, congestive heart failure, peripheral vascular disease, stroke, malignancy, and chronic lung disease, Kt/V (measured within three months of QOL assessment), residual creatinine clearance (at dialysis initiation), albumin and hemoglobin levels (measured within one month of QOL assessment). Positive diabetic status included a history of either Type I or II diabetes. Patients were classified as having attended the pre-dialysis clinic if they presented on at least one occasion. Length of pre-dialysis clinic attendance was measured from the date of first attendance to date of dialysis initiation. The date at which
the QOL assessment was performed was included as an independent variable (calculated from the date of dialysis initiation to QOL assessment) in order to account for any possible confounding effect due to the different times at which the Health Survey was administered. \(Kt/V\) was estimated based on a single-pool model using the urea reduction ratio method. Residual creatinine clearance at the time of dialysis initiation was estimated using the Gault-Cockroft method and the serum creatinine level at the start of dialysis initiation. History of co-morbid disease was extracted from medical records using local chart review and the Canadian Organ Replacement Registry (a national dialysis database). Angina was defined as any previous or present history of ischemic symptoms (possibly but not necessarily requiring anti-anginal therapy) or any past history of coronary artery angioplasty or bypass surgery. Congestive heart failure was defined as any previous or present history of dyspnea, orthopnea or paroxysmal nocturnal dyspnea due to cardiac etiologies and not solely attributable to renal failure and volume expansion alone. Echocardiographic documentation of systolic dysfunction was not required. Peripheral vascular disease was defined as either a typical history of exertional leg discomfort or previous history of vascular angioplasty or bypass surgery. Stroke was defined clinically and did not require radiographic confirmation. Patients were primarily of Caucasian race, reflecting the demographics of the south-eastern Ontario region. Race was therefore not included as an independent variable.

**Dependent variables**

QOL was assessed using the SF 36-Item Health Survey. \([9,10]\) This health survey is routinely administered every three months to all dialysis patients at Kingston General Hospital as standard care in order to monitor patient well-being. The survey is a well-validated self-report questionnaire that assesses QOL in eight domains: physical function (phy), physical role limitation (rlp), emotional role limitation (rel), social function (soc), body pain (pai), emotional well being (ewb), energy (eng), and general health (gh). The maximum score in each domain is 100 – higher scores being desirable and indicative of better well-being or less pain. Changes in score of 5 units have been shown to be clinically relevant. \([9]\) Additionally, the final multivariate model was used to explore the association between selected independent predictors of outcome and two composite scores that summarize physical and emotional QOL. Composite physical (pRaw) and emotional (eRaw) scores were calculated based on an aggregation of the eight separate domain scores using standard published equations (where each of the domain scores is standardized using age-stratified Canadian national means and standard deviations). \([11,12]\)

**Statistical analysis**

The distribution of independent and dependent variables was examined using univariate analyses. Comparison of continuous and categorical independent variables was performed between patients who attended the pre-dialysis clinic and those who did not using t-test, Mann-Whitney, and chi-square analyses as appropriate (Tables 1 and 2; see Additional file Table 1 and Additional file Table 2). QOL scores were compared between patients who attended the pre-dialysis clinic and those who did not using t-test and Mann-Whitney analyses as appropriate (Table 3; see Additional file Table 3). The association between independent variables and QOL scores in each of the eight health domains was examined using bivariate linear regression analysis (Table 4; see Additional file Table 4). Based on the results of bivariate analyses, clinically relevant and statistically significant independent variables were selected for multivariate linear regression analysis (Table 5; see Additional file Table 5). The final model was examined for adherence to linear model assumptions. In the situation where linear model assumptions were compromised due to the non-parametric distribution of outcome variables, non-parametric bivariate and multivariate analyses were also performed using Spearman correlation and logistic regression analyses respectively. As such, non-parametric analyses were used to examine physical and emotional role limitation scores due to the non-parametric distribution of these two dependent variables. The non-parametric distribution of these two domains is attributed to the relatively small number of questions devoted to these two domains in the SF 36-item Health Survey and is therefore not unexpected. Recognizing that earlier research using the health survey has traditionally reported results using parametric analyses despite the non-parametric distribution of the data, the present paper will present both parametric and non-parametric results in order to conform to previous methodologies and permit comparisons.

Analyses were performed using the SAS statistical analysis package for personal computers (version 6.12, Cary, NC). The study protocol was approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

**Results**

The distribution of categorical independent variables within the entire cohort and according to pre-dialysis clinic attendance is presented in Table 1 (see Additional file Table 1). Overall, 55.8% of patients were male, while diabetes was identified in 43.6% of patients. Almost 40% of patients had a history of ischemic heart disease. The distribution of categorical independent variables was compared between the group of patients who attended the
were the only predictors of better emotional role limitation, social function, and general health scores were statistically higher among patients who attended the pre-dialysis clinic compared to patients who did not (Table 3; see Additional file Table 3).

Results of a series of bivariate linear regression analyses examining the association between each independent variable and each of the eight QOL domains are presented in Table 4 (see Additional file Table A.4). A positive parameter estimate denotes a positive correlation between independent variable and QOL score, while a negative parameter estimate indicates an inverse relationship. Youn

ger age, male gender, pre-dialysis clinic attendance, longer attendance at the pre-dialysis clinic, higher residual creatinine clearance at dialysis initiation, absence of ischemic heart disease, stroke, and peripheral vascular disease, and higher albumin level were associated with significantly higher physical function score. Higher scores in the physical role limitation domain were associated with younger age, pre-dialysis clinic attendance, and higher albumin level. Because physical role limitation scores did not follow a normal distribution, the bivariate analysis was re-examined using a nonparametric Spearman correlation analysis. Using a nonparametric analysis, pre-dialysis clinic attendance still predicted higher QOL score. Younger age (p=0.02), pre-dialysis clinic attendance (p=0.03), absence of ischemic heart disease (p=0.04) and stroke (p=0.03), and higher albumin level (p=0.03) were associated with higher physical role limitation scores. Linear regression analysis suggested that higher emotional role limitation score was predicted by longer pre-dialysis clinic attendance. Due to the non-parametric distribution of the emotional role limitation score, a non-parametric analysis was also preformed, which demonstrated that pre-dialysis clinic attendance and longer pre-dialysis clinic attendance were the only predictors of better emotional role limitation score (p=0.04 and p=0.01 respectively). Significant predictors of better social function were pre-dialysis clinic attendance, absence of lung disease, and higher albumin level. Male gender, absence of ischemic heart disease, peripheral vascular disease and malignancy, and higher albumin level were significant predictors of higher pain scores (where higher score is indicative of less pain). Better emotional well-being was associated with male gender alone. Younger age, higher residual creatinine clearance at dialysis initiation, absence of peripheral vascular disease and lung disease, and higher albumin level predicted better energy level. Male gender, pre-dialysis clinic attendance, absence of ischemic heart disease, peripheral vascular disease and lung disease, and higher albumin level were significant predictors of higher general health scores.

A total of nine independent variables were selected for inclusion in the final multivariate analysis: pre-dialysis clinic attendance, residual creatinine clearance, Kt/V, age, albumin, sex, ischemic heart disease, peripheral vascular disease, and diabetes (Table 5; see Additional file Table 5). Age, sex, pre-dialysis clinic attendance, ischemic heart disease, peripheral vascular disease, and albumin were included as covariates because of their significant associations with QOL scores in bivariate analyses. Despite the absence of statistically significant associations with QOL scores, diabetes and Kt/V were included as covariates in the final multivariate model because of their perceived clinical relevance. Since residual renal function at dialysis initiation was significantly higher among patients attending the pre-dialysis clinic compared to those who did not, residual creatinine clearance was also included in the final model in order to permit statistical adjustment. The final multivariate model suggested that pre-dialysis clinic attendance was an independent predictor of four of eight health domains: higher physical function, emotional role limitation, social function, and general health scores. Physical function score was predicted by pre-dialysis clinic attendance, younger age, and absence of ischemic heart disease and peripheral vascular disease, while emotional role limitation and social function scores were predicted by pre-dialysis clinic attendance alone. Male gender and absence of peripheral vascular disease were independent predictors of higher pain scores (reflecting less pain). Higher emotional well-being score was predicted by male gender. Pre-dialysis clinic attendance, male gender, and absence of peripheral vascular disease were independent predictors of higher general health score. Because of the non-parametric distribution of the physical and emotional role limitation scores, repeat analyses were performed for these two QOL domains using multivariate logistic regression analyses. The conclusions of logistic and linear regression analyses were identical.

Multivariate analysis using the final model suggested that pre-dialysis clinic attendance, younger age, and absence of
ischemic heart disease and peripheral vascular disease were independent predictors of the composite physical health score (Table 5; see Additional file Table 5). Pre-dialysis clinic attendance was not an independent predictor of the mental health composite score.

Adjusted r-squared values (Table 5; Additional file Table 5) indicate the extent to which the variability of each health survey domain score can be explained by the final multivariate model. The final model accounts for 42% and 28% of the physical function score and composite physical score variability respectively, suggesting that the model is most effective in predicting physical function scores.

Discussion

Although previous research has suggested that pre-dialysis clinic attendance is associated with better objective outcomes compared to standard care, research examining the benefits of pre-dialysis care with respect to patient-oriented outcomes such as QOL is limited. The results of the present study suggest that attendance at a predialysis clinic is an independent predictor of improved quality of life measured within the first six months of dialysis initiation in an incident cohort of chronic hemodialysis patients. The benefits of pre-dialysis clinic attendance are therefore not limited to objective measures of patient health such as decreased hospitalization and better biochemical profiles at the time of dialysis initiation. Rather, these results suggest that the benefits of pre-dialysis clinic attendance can be extended to include more subjective measures of patient health.

The evaluation of medical therapies using patient-oriented outcomes has acquired a larger research profile in recent years. Nonetheless, to our knowledge, only one study has formally evaluated the benefits of pre-dialysis clinic attendance using patient-administered QOL questionnaires. [8] The present study confirms the conclusions of Sesso et al, who suggested that pre-dialysis clinic attendance improved QOL as measured by the Kidney Disease Questionnaire. However, only 28% of patients were over age 60 in the Brazilian study. Recognizing that the benefits of pre-dialysis clinic attendance were particularly pronounced among elderly patients, the value of pre-dialysis clinic attendance may have been underestimated by this earlier study. The mean age of 62.7 years in the present cohort is a closer representation of North American dialysis populations. The study is also benefited by a publicly funded and universally accessible Canadian healthcare system in which the importance of confounding variables such as socioeconomic status has been minimized. Furthermore, whereas the results of the Brazilian study were adjusted for age and time of diagnosis, differences in residual renal function and other covariates were not included. The present study has controlled for several covariates including age, sex, ischemic heart disease, peripheral vascular disease, diabetes, albumin, residual renal function, and Kt/V.

Interestingly, pre-dialysis clinic attendance was associated with improved QOL scores in a wide range of domains that included both physical and emotional outcomes. Attendance was an independent predictor of better QOL score in four of eight domains: higher physical function, emotional role limitation, social function, and general health. Indeed, pre-dialysis clinic attendance was the only independent predictor of QOL score in the case of emotional role limitation and social function. Importantly, the difference in QOL scores between patients who did and patients who did not attend the pre-dialysis clinic is not only statistically significant but clinically significant as well. Previous research has suggested that a difference in SF-36 scores of five or more points is considered clinically relevant. [9,11]

The means by which a pre-dialysis clinic leads to better physical and emotional QOL is likely multi-factorial, resulting from opportunities for patient education, dietary counseling, modality selection, dialysis access creation, and management of co-morbid illnesses. The importance of early pre-dialysis correction of anemia using erythropoietin has also been emphasized in recent years. Several studies have suggested that earlier initiation of erythropoietin may improve patient morbidity and mortality by retarding or preventing the development of cardiomyopathy secondary to anemia. [13]

The association between several covariates and QOL score seems intuitive in many cases. For example, in addition to pre-dialysis clinic attendance, younger age and absence of ischemic heart disease and peripheral vascular disease were independent predictors of better physical function score. Absence of peripheral vascular disease was also an independent predictor of better pain and general health scores. Although bivariate analysis suggested that higher serum albumin level predicted better QOL in many domains (including physical function, physical role limitation, social function, pain, energy, and general health), a statistically independent relationship between serum albumin and QOL was not demonstrated by multivariate analysis.

Both pre-dialysis clinic attendance and increasing length of time attending the pre-dialysis clinic were predictors of better physical function and emotional role limitation scores in univariate analysis, but not multivariate analysis, thus suggesting statistical redundancy between these two covariates. The absence of an independent association between length of pre-dialysis clinic attendance (and pre-
sumably severity of chronic renal failure) and QOL outcome parallels the conclusions of Harris and colleagues, who found that, in a cohort of 360 non-dialysis patients with chronic renal failure, functional status was correlated with socioeconomic status and comorbid illness, but not severity of renal function. [14]

Interestingly, multivariate analysis suggested that male gender was an independent predictor of better pain, emotional well-being, and general health scores. Although a significant association between male gender and QOL scores may seem doubtful, this finding has in fact been demonstrated previously in non-dialysis populations in which males consistently score slightly higher than females in all QOL domains. [12]

QOL scores in the present study are comparable to earlier reports and underscore the fact that QOL is severely compromised among dialysis populations. [15,16] In a prospective Dutch study involving 13 dialysis centres, QOL measured three months after dialysis initiation using the SF-36 questionnaire was significantly impaired compared to a general non-dialysis population, particularly with respect to physical role limitation and general health status. [15] Mean physical role limitation and general health scores for hemodialysis patients corresponded to the lowest 8% and 12% of the reference group respectively. Independent predictors of poor quality of life included a higher number of co-morbid illnesses, lower hemoglobin level, and lower residual renal function. Pre-dialysis attendance was not included as a covariate.

Compared to more objective measures of patient well-being, the importance of QOL, not only as an outcome, but also as a predictor of patient morbidity and mortality, is probably under-estimated. For example, DeOreo has demonstrated that dialysis patients with a physical component summary score below the cohort median were twice as likely to die and 1.5 times more likely to be hospitalized compared to patients with scores above the median. These findings suggest that patient-reported QOL is as much a significant predictor of mortality as more well-established markers of patient care such as normalized protein catabolic rate and Kt/V. [17] Patient morbidity and mortality is significant even prior to dialysis initiation. [14,18] Therefore, interventions that can potentially improve QOL should be pursued early and aggressively during the pre-dialysis phase of chronic renal insufficiency. The present study suggests that pre-dialysis care can improve QOL measured six months after dialysis initiation, while the conclusions of DeOreo argue that such improvement could lead to lower patient mortality.

The inability of the present study to identify any predictors of the mental health composite score may be due to small sample size causing a Type II statistical error. However, other researchers have demonstrated that, while hemodialysis patients report low physical scores, mental and emotional scores are less affected, suggesting that the absence of any statistically significant predictors of poor mental health composite score in the present study may be valid. [15,16]

Surprisingly, diabetes did not predict QOL scores, even in bivariate analysis. This also could be due to effect of small sample size. Alternatively, failure to identify an association between diabetes and QOL scores may be due to short follow-up time in which the more long-term complications of diabetes could not be realized. Furthermore, the results of studies that have reported an association between diabetes and functional status are possibly limited by the use of cross-sectional study designs and prevalent cohort populations. [19] In a prospective cohort of dialysis patients over age 60, Kutner and colleagues showed that diabetic nephropathy was not an independent predictor of survival when controlled for functional status in multivariate analysis. [16]

Kt/V was not a predictor of QOL outcomes in this study or previous investigations. [15] Some investigators have suggested that the absence of an association between Kt/V and QOL may be due to the effect of residual renal function and the possibility that clearance achieved by native kidneys is superior to that obtained by dialysis. [15] However, residual creatinine clearance was not a predictor of QOL outcomes in the present study. The absence of a statistically significant association between Kt/V and QOL scores could also be attributed to short follow-up time in which QOL assessments were performed soon after dialysis initiation. Alternatively, since Kt/V values were confined to a relatively narrow range in which the majority of patients achieved adequate dialysis dosing, a Type II statistical error simply due to lack of variability of the independent variable may account for the absence of any statistically significant association.

The present study is limited by the retrospective design in which the possibility of selection bias cannot be definitively excluded. Indeed, previous research has demonstrated that referral of patients by primary care physicians to nephrology programs is influenced, either consciously or unconsciously, by patient-related factors including age, gender, diabetes, and other co-morbid illnesses. [20,21] Consequently, referral bias is currently a feature of primary care practice and is likely unavoidable regardless of study design. Not surprisingly, the existence of referral bias in the present study is suggested by the lower residual renal function at the time of dialysis initiation seen in patients who did not attend the pre-dialysis clinic compared to those patients who did attend the clinic. Patient self-se-
lection is also a consideration. For example, it is possible that non-compliant patients are less willing to attend the pre-dialysis clinic, and as such, the poorer QOL scores reported by patients who did not attend the pre-dialysis clinic may be related to issues of self-selection and compliance rather than pre-dialysis clinic attendance itself. However, other than residual renal function, no statistically significant demographic or clinical differences between those patients who did attend the pre-dialysis clinic and those who did not were identified in the present study. Notwithstanding the possibilities of referral and self-selection biases, the decision to examine an incident population restricted to new dialysis patients has avoided the other biases associated with earlier investigations using cross-sectional study designs and prevalent populations. [19]

The retrospective study design also causes difficulty in isolating the independent influences of confounding covariates. For example, pre-dialysis clinic attendance and early dialysis initiation are separate yet potentially confounding variables, both of which are likely related to improved QOL scores. In the absence of randomized prospective studies, the effect of each covariate is difficult to examine independently since patients referred to a pre-dialysis clinic are probably less likely to require emergent dialysis initiation due to more regular follow-up. Consequently, it can be argued that the benefits of pre-dialysis clinic attendance may be the result of either selection biases (related to patient age and co-morbid illness) or confounding variables (such as timing of dialysis initiation and residual renal function) rather than pre-dialysis clinic interventions in and of themselves. However, a comparison of continuous and categorical independent variables between patients who did and did not attend the pre-dialysis clinic failed to demonstrate any statistically significant difference between the two groups apart from residual creatinine clearance at the time of dialysis initiation (which was therefore included as a covariate in multivariate analysis).

The results of the present study support the NIH recommendation suggesting that patients with chronic progressive renal insufficiency should be referred to a pre-dialysis team in order to minimize patient morbidity and mortality. While previous research has demonstrated that pre-dialysis clinic attendance is associated with favourable objective outcomes (including better biochemical profiles and decreased hospitalization at the time of dialysis initiation), the results of the present study suggest that the benefits of a pre-dialysis program can be extended to include more subjective measures of health status. The importance of this finding is underscored by earlier research demonstrating that QOL scores are themselves independent predictors of patient mortality. However, it remains unclear to what extent the benefits of pre-dialysis clinic attendance are sustainable over time. Longitudinal studies evaluating the effects of pre-dialysis care with respect to prospective repeated-measure QOL assessments and objective outcomes are therefore required.

Competing interests
None declared.

Authors’ contributions
Authors 1 (CW) and 2 (RP) designed the study and carried out data entry. Authors 3 (ML) and 4 (DH) performed the statistical analyses. Author 4 (DH) drafted the manuscript. All authors read and approved the final manuscript.

Additional material

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