REVIEW

Outcome Research, Nutrition, and Reverse Epidemiology in Maintenance Dialysis Patients

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High morbidity and mortality of maintenance dialysis patients have led to an increase in interest in outcome research in an attempt to identify causes for this adverse outcome. It has been proposed that a substantial amount of this risk can be explained by protein energy malnutrition, chronic inflammation, or concurrent combination of both, known as malnutrition-inflammation complex syndrome (MICS). Elements of overnutrition, such as increased weight or high serum cholesterol levels, which are deleterious in the general population, paradoxically are protective in dialysis patients. Conversely, a low body mass index and low serum levels of cholesterol, creatinine, and possibly homocysteine are risk factors for poor outcome in dialysis-dependent populations. These reverse or paradoxical relationships between nutritional markers and outcome are referred to as *reverse epidemiology*. The MICS appears to be a main contributor to the reverse epidemiology and poor outcome. Mortality is the most definitive and objective clinical outcome, whereas hospitalization and quality of life (QoL) are additional relevant but somewhat less objective outcome measures in dialysis populations. A systematic classification of outcome measures and their related epidemiologic and statistical assessment tools in dialysis patients are reviewed. The effect of MICS on outcome can be examined by epidemiologic studies that are based on large samples of dialysis patients, use multivariate techniques, and, as long as they follow strict methodologic requirements, provide an invaluable economical alternative to expensive clinical trials.

IN THE UNITED STATES, there currently are more than 250,000 individuals with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (MHD) or chronic peritoneal dialysis (CPD).[1] The number of maintenance dialysis patients will surpass one half million by the year 2010.[1] These patients experience lower quality of life (QoL), greater morbidity, higher hospitalization rates, and increased mortality as compared with the general population.[1,2] The annual mortality rate among dialysis patients in the United States continues to remain unacceptably high (ie, approximately 20%) despite many recent improvements in dialysis treatment.[1] ESRD patients continue to consume a considerable portion of the Medicare budget, and yet they have unacceptably poor outcomes.[3] In recent years, there has been increasing attention on outcome research in maintenance dialysis patients. The goal of much of this research has been to identify and define the scope and impact of risk factors of poor outcome in dialysis patients.

In highly industrialized, affluent countries, protein-energy malnutrition is an uncommon

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Table 1. Pertinent Outcome Measures in Maintenance Dialysis Patients

Outcome Measure	Epidemiological Types and Related Assessment Tools	Statistical Tools
Mortality	All-cause mortality	Survival analysis (Cox regression)
	Cause specific (cardiovascular, etc)	Logistic regression
	Standardized mortality ratio	
Hospitalization	Hospitalization frequency	Poisson regression
	Hospitalization days	Correlation analyses
	Time to first hospital admission	Cox regression (time to hospitalization)
	Standardized hospitalization ratio	
Quality of life	SF36 (and KDQOL)	Correlation analyses
	Others: Karnofsky score	Logistic regression
Others	Access events	Cox regression (time to event)
	EPO hyporesponsiveness	Correlation, logistic regression

Abbreviations: SF36, short-form quality of life questionnaire with 36 questions; KDQOL, kidney disease-related quality of life; EPO, recombinant human erythropoietin.

cause of poor outcome in the general population, whereas overnutrition is associated with a greater risk of cardiovascular disease. In contrast, in dialysis patients, undernutrition is one of the most common risk factors for adverse cardiovascular events.[4,5] These reverse or paradoxical relationships between conventional cardiovascular risk factors and outcome are referred to as *reverse epidemiology*[6–8] or *risk factor paradox*.[9] Indeed some indicators of overnutrition, such as an increased body mass index (BMI) and hypercholesterolemia, actually predict improved outcome in maintenance dialysis patients.[4,10] The elements of protein-energy malnutrition and inflammation, independent of each other or combined together in the form of malnutrition-inflammation complex syndrome (MICS)[11,12] (also known as malnutrition-inflammation atherosclerosis (MIA)[13]), seem to be the main contributors to the reverse epidemiology phenomenon in dialysis patients.[7] Advances in statistical and epidemiologic methods, the availability of robust multivariate techniques that adjust for confounding and case-mix factors, and databases from large dialysis patient populations, including the United States Renal Data System (USRDS),[1] Fresenius Medical Care,[14] and DaVita, Inc,[12] have contributed to advances in the field of outcome research. Epidemiologic studies are much more economical than expensive clinical trials. However, they are subject to significant sources of bias at both the study population selection and the analytical phase and require strict methodologic surveillance and sound expertise.

The findings from large population-based studies suggest that elements of MICS have an important contribution to poor clinical outcome in dialysis patients.[11] The possibility of using nutritional or anti-inflammatory intervention or both to improve clinical outcome in dialysis patients once again has become the focus of attention, especially after a multicenter clinical trial known as the HEMO Study failed to show an improved outcome by increasing dialysis dose or using high-flux hemodialysis membranes.[15] A basic knowledge about pertinent outcome measures in the dialysis population is relevant for nephrologists and dietitians engaged in the field of dialysis and nutritional support (Table 1).

Mortality

Mortality is the most definitive and objective outcome for both clinical trials and epidemiologic (observational) studies.[16] The occurrence of death regardless of its etiology and type of surrounding circumstances (ie, all-cause mortality) is used commonly to evaluate death rates among maintenance dialysis patients.[1] Nevertheless, this outcome measure includes occasional rare deaths that may not be directly related to ESRD or dialysis treatment, such as homicide or motor-vehicle accidents. Despite such potential limitations, mortality remains the most objective and meaningful outcome in dialysis patients.[16] There is a high burden of cardiovascular disease and mortality in dialysis patients, accounting for more than 50% of deaths in these individuals.[13,17] Hence, mortality of dialysis patients, currently about 20% per year in the United States, is not only much higher than that of the general population, but the proportion of deaths from car-

diovascular diseases also is much higher in this group.[1,13,18]

Because of the heterogeneity of clinical and demographic characteristics of maintenance dialysis patients, standardized mortality rates (SMR) are used to adjust for the confounding effects of gender, age, race, and diabetes mellitus, and together are known as *case-mix* features.[1,19] More inclusive statistical models may use an even more expanded number of case-mix variables, such as dialysis vintage and insurance status. However, it is important to appreciate that addition of more covariates in the statistical model increases the chance of missing significant associations when they do exist, which is known as overadjustment or overmatching; this may lead to the elimination of significant associations, especially when such covariates have significant correlations among each other. For example, one might wish to study the impact of food intake on mortality in dialysis patients with a low protein-energy intake, hypoalbuminemia, and increased serum C-reactive protein (CRP) that per se might be secondarily caused by inadequate diet intake. In these circumstances, serum CRP would be expected to covary with nutritional intake. Using such secondary markers as serum CRP as a covariate in multivariate statistical models to study the simultaneous impact of food intake and inflammation on mortality will diminish the true epidemiological effect of food intake on mortality.

Furthermore, epidemiologic analyses of cross-sectional data are associated inherently with several types of errors.[20,21] The selection at one given point in time of a study population that includes both incident (newly started on dialysis), who may or may not survive over time, and prevalent (already on dialysis) patients, who managed to survive over time, may lead to a significant degree of heterogeneity in selection known as *survival bias*.[16] Finally, it is important to appreciate some fundamental aspects of different statistical models (eg, a mortality odds ratio based on logistic regression analyses does not control for the duration of time to death, whereas survival models such as the Cox proportional hazard analyses do so).[22]

Hospitalization

Dialysis patients have a much higher rate of hospitalization as compared with the general population, on average 10 to 15 days per year for each maintenance dialysis patient in the United States.[1] Hospitalization rates are commonly used outcome measures.[1,23] However, hospitalization is a less objective outcome measure when compared with mortality, because the decision to admit, retain, or discharge a patient in the hospital can be affected by subjective and nonstandardized factors, such as regional insurance or health care policies.[16] Moreover, many hospital admissions for both MHD and CPD patients are related to their dialysis access (ateriovenous shunts or catheters), which may or may not be a direct consequence of protein-energy malnutrition, inflammation, or MICS. However, it has been suggested that dialysis patients with the MICS are more prone to develop access failure events.[24]

In most outcome studies, the hospitalization frequency (eg, total number of hospital admissions), the total number of hospitalization days, or both are calculated for a given period of time.[1] Simple or multivariate analyses can be used to evaluate the effect of measures of protein-energy malnutrition on hospitalization rates and to estimate correlation coefficients.[25] Alternatively, Poisson regression models can be used to estimate the hospitalization rate ratios for different nutritional measures.[25] Finally, for dialysis populations with infrequent hospitalization, time to first hospitalization within a predetermined interval can be analyzed with survival-like models (Table 1).

Quality of Life

Monitoring a patient's functional status and the subjective sense of well-being, together known as QoL measurements, is of particular importance in ESRD patients because the physical and emotional debility experienced by maintenance dialysis patients caused by malnutrition or inflammation can be severe.[26–28] The QoL measurements have become an important outcome measure and are heavily relied on not only by physicians and scientists but also by the US Food and Drug Administration and other health policy authorities as a key outcome. Although QoL measures are subjective, studies repeatedly have shown that these measures are both reproducible and reliable predictors of prospective mortality and hospitalizations in maintenance dialysis patients.[29]

Table 2. Reverse Epidemiology of Cardiovascular (CV) Risk Factors in Dialysis Patients: The Effect of CV Risk Factors in Maintenance Dialysis Patients Is the Opposite of the General Population

Risk Factors of Cardiovascular Disease	Direction of the Associations Between Risk Factors and Outcomes	
	General Population	Maintenance Dialysis Patients
Body mass index (BMI)	High BMI and obesity are generally deleterious.	High BMI, or weight for height, and moderate obesity are protective. Underweight is deleterious.[57]
Serum cholesterol	Hypercholesterolemia, high LDL, and low HDL are deleterious.	Hypercholesterolemia (and maybe high LDL) is protective. Low serum cholesterol is deleterious.[50]
Blood pressure (BP)	Hypertension and even borderline high BP are deleterious.	Pre-dialysis low BP may indicate a deleterious state.[58]
Serum creatinine	A mild to moderate increase in serum creatinine is an independent risk factor of CVD.	An increased predialysis serum creatinine level is associated with a better survival.[14]
Total plasma homocysteine	A high level is a risk factor for increased CVD in the general population and likely in dialysis patients.	Several recent studies have found that a low level is associated with increased risk of cadiovascular disease and mortality.[51]
Serum iron	A high serum iron level is associated with hemochromatosis and poor outcome.	A low iron and transferrin saturation level has been recently found to be associated with higher mortality and hospitalization in dialysis patients.[59]
Intact parathyroid hormone (PTH)	In general, a high intact PTH level is considered to be associated with adverse outcome.	Dialysis patients with lower intact PTH may have a worse long-term survival.[60]
Advanced glycation endproducts (AGEs)	Patients with higher AGE levels, such as diabetic patients, have a poor outcome.	A recent report indicates a paradoxically reverse association between lower AGE levels and higher mortality in dialysis patients.[61]
Energy (calorie) and/or protein intake	A high energy and food intake may be associated with risk of obesity and increased mortality.	Increased protein intake is associated with better survival.[62]

Abbreviations: CVD, cardiovascular disease; MD, maintenance dialysis; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

A number of instruments have been used to assess sense of well-being and functional and health status in rather broad categories, whereas some others have a more limited focus. Some of these tools have been validated and even modified for dialysis patients.[28,29] The Karnofsky score is based on a simple questionnaire and assesses the functional status.[30] The Short Form Health Survey with 36 questions (SF36) is one of the most commonly used instruments for QoL evaluation in dialysis patients.[28] It is used both as a stand-alone measure of QoL and as a core component of several major assessment tools, including the Kidney Disease Quality of Life (KDQOL) survey instrument (Rand Corporation, Santa Monica, CA).[31] Such self-administered QoL scores as the SF36 or KDQOL are strong predictors of prospective mortality and hospitalization in dialysis patients.[29,32]

Other Pertinent Outcome Measures

Renal death recently has been introduced in clinical trials addressing chronic kidney disease.[33–35] Renal death measurement (ie, counting the number of patients who died [whatever the cause] or started maintenance dialysis therapy during the course of observational or interventional trials) has been accepted as a robust hard-point criterion. It is easy to ascertain, even if not present in the final trial publication.[36] Limitations include interference between the treatment tested and the decision to start dialysis: for example, modulating protein intake will impact on serum urea nitrogen, and, hence, the need to start dialysis. However, from a patient's point of view, if a treatment allows him to postpone the start of dialysis whatever the reason, this is what he will primarily be interested in. The nature (infection,

occlusion, stenosis) and frequency of dialysis access complications and the survival of different dialysis access modalities (fistula, graft, and tunneled catheter) may have some association with the nutritional and inflammatory processes in dialysis patients and, hence, can be analyzed as an outcome.[37,38] The degree of refractoriness of anemia in dialysis patients is another suggested outcome that may be attributable to MICS.[23,38,39] The ESRD-associated anemia is a multifactorial disorder that can be managed relatively successfully by recombinant human erythropoietin (EPO) and iron therapy. The EPO and iron requirement to maintain the recommended hemoglobin concentration (110 to 120 g/L) may increase when inflammation, protein-energy malnutrition, or both are present.[11,40]

Malnutrition-Inflammation Complex Syndrome and Reverse Epidemiology

Recent studies suggest that protein-energy malnutrition and inflammation, together known as MICS, are associated with a decreased QoL and increased hospitalization and mortality, especially from cardiovascular disease, in maintenance dialysis patients.[41] Hypoalbuminemia and increased serum CRP are strong predictors of poor clinical outcome in these individuals.[42,43] Hypoalbuminemia, which seems to relate to MICS, when compared with such traditional risk factors as obesity, hypercholesterolemia, and hypertension, has the most striking and consistent associations with poor outcome in dialysis patients.[44] On the other hand, as discussed above, certain markers that predict a low likelihood of cardiovascular events and an improved survival in the general population, such as decreased body mass index (BMI)[45–48] or lower serum cholesterol levels,[49,50] are risk factors for increased death rates in dialysis patients.[8] Increased body weight, hypercholesterolemia, and hypertension paradoxically seem to be protective features that are associated with a greater survival among dialysis patients, hence referred to as reverse epidemiology.[8] A similar protective role has been described for high serum creatinine and even plasma homocysteine levels[51] in dialysis patients (Table 2).

The etiology of this inverse association in dialysis patients is not clear. Several possible causes are hypothesized, including survival bias and time discrepancy between competitive risk factors (undernutrition versus overnutrition). However, the presence of the MICS in dialysis patients offers the most plausible explanation for the existence of reverse epidemiology (Fig 1). The reverse epidemiology may be caused or at least accentuated by the MICS in several ways. First, patients who are underweight or who have a low serum cholesterol, creatinine, or homocysteine may be suffering from MICS and its poor outcome. Thus, MICS may both cause these alterations and also be associated with increased mortality either caused by the illnesses that engender MICS or the atherosclerotic cardiovascular diseases that seems to be promoted by MICS.[7,41,52] Second, the previously mentioned paradoxical factors may indicate a state of undernutrition, which may predispose to infection or other inflammatory processes. Finally, it has been argued that when individuals are malnourished, they are more susceptible to the ravages of inflammatory diseases and are predisposed to inflammation-induced cachexia[53,54] (Fig 2). A recent study showed that a decreased appetite or anorexia in maintenance dialysis patients is associated with increased levels of proinflammatory cytokines and inflammatory markers.[55] Hence, any condition that potentially attenuates the magnitude of protein-energy malnutrition or inflammation should be favorable to dialysis patients.

There is also a puzzling inverse relationship

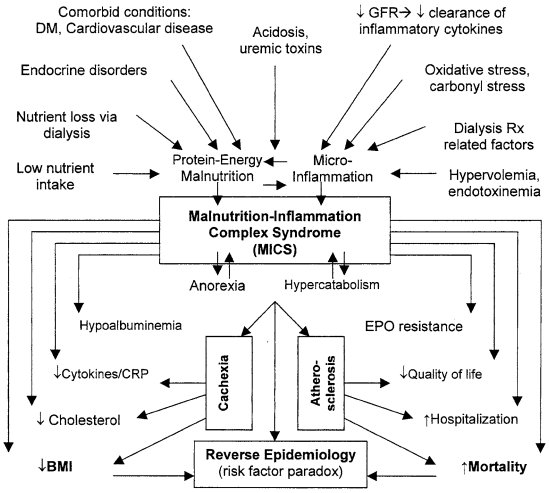

Figure 1. Schematic representation of the causes and consequences of malnutrition-inflammation complex syndrome (MICS). GFR, glomerular filtration rate; DM, diabetes mellitus; Rx, treatment; EPO, erythropoietin; CRP, C-reactive protein; BMI, body mass index.

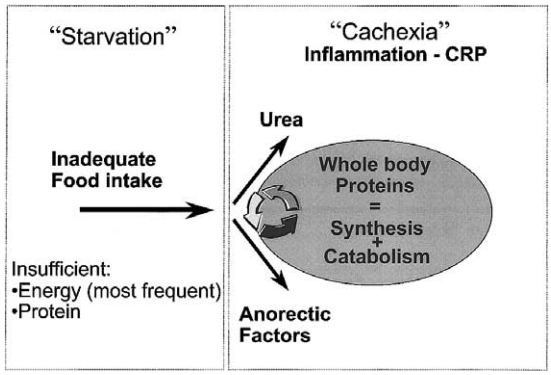

Figure 2. Anorexia versus. cachexia and the role of protein-energy malnutrition and inflammation in their development. CRF, chronic renal failure; CRP, C-reactive protein.

between a low, rather than a high, blood pressure and poor outcome in the dialysis population; this might also be accounted for by nutritional status, inflammation, or both. Iseki et al[56] showed a significant association between a low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of 1,243 hemodialysis patients who were followed for up to 5 years. The death rate was inversely correlated with diastolic blood pressure, which per se was correlated positively with serum albumin and negatively with age. Hence, hypotension may in some cases be a manifestation of MICS in dialysis patients.

Future Steps for Dialysis Outcome Research

Using the previously mentioned outcome measures, possible predictors of poor outcome such as elements of MICS and their contribution to the phenomenon of reverse epidemiology can be explored in observational studies. More robust and inclusive multivariate techniques, such as time-varying models for longitudinal data and more strict methodologic surveillance, should be considered in designing, conducting, and analyzing epidemiologic studies with large sample sizes and adjusting for the effect of such confounders as case-mix features. Clinical trials eventually will be required to verify findings of the epidemiologic studies pertaining to MICS and reverse epidemiology, to compare the effect of various interventions on modifiable risk factors that are detected in epidemiologic studies, and to ascertain whether an improvement of poor outcome in maintenance dialysis patients can be achieved by nutritional or inflammatory interventions or both. Designing low-priced randomized clinical trials with adequately large sample size and optimal statistical power to evaluate the effect of nutritional or anti-inflammatory interventions in dialysis patients is the challenge but a needed endeavor.

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