



Higher Risk of Hip Fracture Among Patients on Hemodialysis Than on Peritoneal Dialysis: Taiwan National Cohort Study

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Hip fractures occur more frequently in patients with chronic kidney disease (CKD) than in the general population [1], and they are an important complication associated with a high mortality rate, decreased quality of life, and large economic burden [2]. The mechanisms of impaired skeletal strength in patients with ESRD are either osteoporosis or renal bone disease, such as adynamic bone disease [2-4]. Old age, female gender, white race, diabetes, and duration of dialysis are also risk factors for hip fractures in patients with CKD^{5,6}. However, few studies have investigated whether different dialysis modalities are risk factors for hip fractures. In addition, few studies have evaluated long-term mortality rates after hip fractures in patients with end-stage renal disease (ESRD) and on dialysis. We recently evaluated the incidence and outcome of hip fractures in 51,473 patients with ESRD who began dialysis between 1999 and 2005 [7]. The data source was the Taiwan National Health Insurance Research Database, and the patients were followed until death, transplantation, dialysis cessation, or 31 December 2008.

The mean follow-up period was 4.14 ± 2.48 years. During the follow-up, 1903 (3.70%) patients had a hip fracture (incidence rate: 89.21/10,000 patient-years; males: 3%; females: 4.3%). Only 0.6% of those 18-44 years old had a hip fracture; however, 6.1% of those ≥ 65 years old had a hip fracture (incidence rate: 182.27/10,000 patient-years). Patients on hemodialysis (HD) had a higher incidence of hip fractures (92.79/10,000 patient-years) than did those on peritoneal dialysis (PD) (40.86/10,000 patient-years). Patients with a hip fracture tended to have more comorbidities. Many more patients with a hip fracture had a prior hip fracture, osteoporosis, DM, congestive heart failure, cerebrovascular accident, liver cirrhosis, or psychiatric disorders.

The cumulative incidence rates of hip fractures of the patients on HD were 1.1% at one year, 4.6% at five years, and 6.3% at nine years, and in those on PD were 0.6% at one year, 2% at five years, and 2.8% at nine years. Female gender, old age, being on HD, and having baseline comorbidities were independent risk factors for a hip fracture. Patients on HD had a 31% higher incidence of hip fracture than those on PD (HR: 1.31; 95% CI: 1.01-1.70). Patients ≥ 65 years old had more than 13 times the risk of a hip fracture than did those 18-44 years old (HR: 13.65; 95% CI: 10.12-18.40). The overall in-hospital mortality rate was 3.2%. The cumulative survival rates after a hip fracture were 74.6% at one year and 50.6% at three years.

FROM THE EDITORIAL OFFICE

Dear All,

In this issue, we are delighted to have Dr. CC Chien from Taiwan to discuss the issue of hip fracture in dialysis patients. In addition, two groups from Korea will share their clinical experience: Researchers lead by Dr. SH Han will discuss the implications of hyponatremia in peritoneal dialysis patients, and Dr YK Kim's group will share their experience in deciding the appropriate time to initiate peritoneal dialysis.

The ISPD Asia-Pacific Chapter meeting 2015 is coming this September. We look forward to seeing you at Daegu, Korea!

Dr. Cheuk-Chun SZETO
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Our current data demonstrated three important points about Asian patients with ESRD and on dialysis: (1) old age was still the most significant factor for hip fracture, (2) HD was associated with a higher incidence of hip fractures, and (3) the in-hospital mortality rate of hip fractures was 3.2%. Our findings are consistent with 2 recent studies [8,9] which reported that being on HD has a higher risk for hip fracture than dose being on PD. This may be explained by the baseline characteristics with younger and less comorbid conditions in patients on PD than HD patients. Second, hemodynamic instability and orthostatic hypotension [10], which easily induce falling and a resultant hip fracture, often occur in patients on HD. Third, patients on PD preserve residual renal function (RRF) longer than do those on HD. Naylor et al [11] reported that an increasing risk of fracture was associated with a declining glomerular filtration rate. Thus, baseline characteristics, a stable hemodynamic status, and preserved RRF may protect against falling and bone fracture. In conclusion, being on HD has a higher risk for hip fracture than dose being on PD. Old age is a significant factor for hip fracture among Asian ESRD patients on dialysis.

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Clinical Implications of Hyponatremia in Peritoneal Dialysis Patients

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Hyponatremia, which is among the most common electrolyte disorders, is believed to be an important risk factor for adverse outcomes in patients with serious medical conditions such as advanced heart failure, liver cirrhosis, and chronic kidney disease (CKD) [1–5]. Patients with CKD are more likely to develop hyponatremia compared to healthy individuals, because the ability of their kidneys to maintain water homeostasis becomes increasingly impaired commensurate with a progressive decline in kidney function [5]. Although partially ameliorated by dialysis treatment, patients with end-stage renal disease frequently suffer from electrolyte disturbances [6]. Recent reports have identified hyponatremia as a modifiable factor strongly associated with increased mortality in hemodialysis patients [7–9]. It is notable that hemodialysis is only intermittently provided, such that serum electrolyte levels may fluctuate between dialysis sessions. In contrast, these levels remain relatively stable in peritoneal dialysis (PD) patients. To date, few studies have addressed the incidence of hyponatremia and the relationship between serum sodium levels and risk of death in PD patients.

With this background in mind, we recently evaluated the incidence of hyponatremia and its clinical impact on mortality in a large prospective cohort of incident PD patients recruited from two Korean medical centers [10]. A total of 441 incident PD patients were included; the mean follow-up duration was 43.2 months. Time-averaged serum sodium (TA-Na) levels, calculated as averages of the means of measurements taken every 3 months, were determined to assess the effect of hyponatremia on mortality.

Our study clearly showed that hyponatremia is common among PD patients, with an incidence of 13.2% when defined as < 135 mEq/L. A more-severe form (< 130 mEq/L) was also observed in 11 patients (2.5%). During follow-up, 115 (26.1%) and 21 (4.8%) patients developed hyponatremia according to the < 135 mEq/L and 130 mEq/L thresholds, respectively. Our data accords with previous studies indicating that hyponatremia can occur despite patients being on PD [11,12]. This finding merits attention because it might have been expected that hyponatremia would be less common in PD patients, given the continuous nature of the treatment.

In our study, we also provide important evidence that hyponatremia is significantly associated with an increased risk of mortality in PD patients. Even after adjusting for demographic, clinical, laboratory, and dialysis-specific covariates, this increased risk remained significant and consistent. Indeed, all-cause mortality risk was 21% lower for every 1 mEq/L increase in TA-Na [hazard ratio (HR), 0.79; 95% confidence interval (CI), 0.73–0.86; $p < 0.001$]. A similar association was observed for infection-related death (HR, 0.77 per 1 mEq/L higher TA-Na; 95% CI, 0.70–0.85; $p < 0.001$) although the mechanisms

underlying this association remain unknown. Furthermore, when patients were categorized into tertiles according to TA-Na level, patients in the lowest tertile (< 137 mEq/L) conferred a 3.35- and 3.18-fold increased risk of all-cause and infection-related mortality, respectively, compared to those in the highest tertile (≥ 139 mEq/L). In keeping with previous observational studies (5,7–9), our robust finding supports evidence that hyponatremia portends a poor prognosis in PD patients.

The underlying mechanisms for the higher risk of mortality in advanced CKD patients with lower serum sodium levels are complex and largely presumptive. One potential explanation involves neurohormonal activation, such as the non-osmotic release of vasopressin [13], activation of the renin-angiotensin system [14], and increased catecholamine production [15]. On the other hand, hyponatremia might exhibit a bystander effect because it is associated with other key adverse features specifically related to CKD. For example, reduced residual renal function may limit free water clearance, thereby resulting in hyponatremia, and protein-energy wasting status may affect the sodium level by depleting intracellular potassium and solutes [16]. Thus, it is still uncertain whether hyponatremia itself can contribute to mortality or merely represents a surrogate marker for other unknown risk factors in chronic maintenance dialysis patients. To date, no studies have investigated whether correcting hyponatremia improves patient survival. Nevertheless, our findings convey a message that hyponatremia should not be ignored even in dialysis patients, and further that physicians should be more meticulous in clinical practice with respect to correcting both this electrolyte imbalance and the disease that underlies it.

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Timing of Dialysis Initiation and Mortality in Peritoneal Dialysis

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Initiating dialysis at the optimal time is one of the most important prognostic factors in patients with end-stage renal disease (ESRD). Current guidelines on when to initiate renal replacement therapy are based on symptoms or signs of uremia and malnutrition, as well as the glomerular filtration rate (GFR) [1,2]. Most of these guidelines are primarily based on clinical evidence of uremia and malnutrition. The ideal GFR level for dialysis initiation in asymptomatic patients has not been fully clarified.

Recently, a randomized controlled trial, the Initiating Dialysis Early and Late (IDEAL) study, demonstrated that a planned early dialysis initiation (eGFR 10-14 ml/min/1.73m²) was not associated with improvement in survival or clinical outcomes compared with late dialysis initiation (eGFR 5-7 ml/min/1.73m²) [3].

PD has different potential survival factors from HD, such as residual renal function, peritonitis, peritoneal protein loss, peritoneal membrane transport status and high glucose load. Furthermore, because residual renal function is an important determinant of mortality and is better preserved in patients on PD than those on HD, the impact of timing of dialysis initiation on survival may be different from that in HD.

The association of timing of PD initiation with survival is controversial. Some observational studies demonstrated that early PD initiation had a survival advantage [4], whereas other observational studies demonstrated that early PD initiation is associated with increased mortality [5] or equivalent mortality compared with late PD initiation [6]. Subgroup analysis of the IDEAL study showed that early PD initiation was associated with clinical outcomes comparable to those in late PD initiation [7]. This discrepancy may be due to differences in the study design or the populations of the studies.

We focused on PD patients with very late dialysis initiation, defined as an eGFR < 5 ml/min/1.73m² at the time of PD initiation. Although the European Best Practice Guideline (EBPG) recommends that dialysis should be initiated before GFR falls before 6 ml/min/1.73m², wide variation in the timing of dialysis initiation exists in different countries and periods. In actual clinical practice, 14-60% of patients with ESRD initiate dialysis at an eGFR less than 5 ml/min/1.73m². The impact of very late dialysis initiation on mortality is not well established. Because loss of residual renal function is a risk factor for mortality in PD patients, the impact of very late dialysis initiation on mortality may be different from late dialysis initiation or early dialysis initiation.

We recently analyzed the impact of timing of PD initiation on mortality. A total of 495 incident patients with PD were included from the Clinical Research Center (CRC) registry for ESRD, a prospective cohort study

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on dialysis in Korea. Patients were categorized into three groups according to eGFR at the initiation of PD using the Modification of Diet in Renal Disease equation. Group A was defined as eGFR < 5 ml/min/1.73m², group B as eGFR 5-10 ml/min/1.73m², and group C as eGFR > 10 ml/min/1.73m². The number of patients in group A was 109, group B was 279, and group C was 107.

The median follow-up period was 23 months. Multivariate Cox regression analysis showed that group A had a significantly higher risk of all-cause mortality compared with group B (HR 4.13, 95% CI, 1.55-11.03, P = 0.005) after adjustment for age, gender, cause of ESRD, serum albumin level, diabetes mellitus, and cardiovascular diseases. There was no significant difference in mortality between group C and group B (HR 1.50, 95% CI, 0.59-3.80, P = 0.398) after adjustment for clinical variables.

These findings suggest that very late PD initiation (eGFR < 5 ml/min/1.73m² at the initiation of PD) was independently associated with increased mortality, while early PD initiation (eGFR > 10 ml/min/1.73m² at the initiation of PD) had equivalent survival with patients who initiated PD with an eGFR 5-10 ml/min/1.73m².

Our results are inconsistent with previous studies that included mainly HD populations, which reported that late start of dialysis has a survival benefit. The reason for increased mortality in group A (eGFR < 5 ml/min/1.73m² at the initiation of PD) compared with group B (eGFR 5-10 ml/min/1.73m² at the initiation of PD) in our study is unclear. However, some plausible explanations may be possible.

Our study included only PD patients. From large, registry-based studies, PD has been reported to have an early survival advantage over HD [8]. The early survival advantage in PD patients compared with HD patients may be attributable, in part, to better preservation of residual renal function [9]. Furthermore, the effect of the loss of GFR on mortality may be higher in patients initiating PD compared to patients initiating HD [10]. Therefore, the very low residual renal function in very late PD initiation may have more of an influence on mortality than that in very late initiation of HD.

Another interesting finding of our study was the absence of a significant difference in mortality between group C (eGFR > 10 ml/min/1.73m² at the initiation of PD) and group B (eGFR 5-10 ml/min/1.73m² at the initiation of PD). These findings are consistent with the subgroup analysis of the IDEAL study [7], which supports the idea that the initiation of PD may be delayed until eGFR 5-10 ml/min/1.73m² with careful clinical management unless patients with CKD stage V have traditional clinical indications for the initiation of dialysis.

Our results may be limited by survival bias, lead-time bias or selection bias. However, we newly demonstrated that the impact of timing of dialysis initiation on mortality in PD patients may be different from HD patients. We hope that our study would be helpful for deciding the timing of dialysis initiation to patients with ESRD considering PD as a renal replacement therapy.

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