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Perspective

Association between timing of peritoneal dialysis initiation and mortality in end-stage renal disease

Yuan Peng [a,b], Xiao Yang [a,b], Wei Chen [a,b], Xue-Qing Yu [a,b,*]

[a] *Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510080, China*

[b] *Key Laboratory of Nephrology, National Health Commission and Guangdong Province, Guangzhou, Guangdong 510080, China*

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Abstract

Despite the widespread use of chronic dialysis for end-stage renal disease (ESRD), there is no consensus on the optimal timing of initiating renal replacement therapy. Over the past decade, a worldwide trend toward increasing glomerular filtration rate at the initiation of dialysis has been noted. However, available data indicate that early dialysis has no survival benefit or is harmful. Peritoneal dialysis (PD) is one alternative for ESRD and has potential survival factors different from those of hemodialysis. The association between the timing of PD initiation and survival is unclear. This review examines the effect of the timing of dialysis on clinical outcomes in PD patients.

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Keywords: Peritoneal dialysis (PD); Initiation; Mortality; Glomerular filtration rate (GFR)

Introduction

The prevalence of end-stage renal disease (ESRD) continues to increase worldwide. According to the United States Renal Data System (USRDS), in 2016, the number of incident ESRD cases was 124,675 and the unadjusted incidence rate was 373.4 per million/year.[1] The prevalence of chronic kidney disease (CKD) in China was 10.8%.[2] The results of our epidemiology survey in Guangdong Province of China showed that the prevalence of CKD was 10.1% in urban populations and up to 13.6% in rural areas.[3,4] It is estimated that the prevalence of ESRD in China is approximately 200–250 cases per million population.[5] The increasing incidence of ESRD has a major effect on dialysis needs, including maintenance hemodialysis (HD) and peritoneal dialysis (PD). In the USA, in 2015, the number of patients on HD was 107,198, with 11,744 on PD.[1] In China, at the end of 2017, 510,101 patients were on HD and 86,264 were on PD.[6] Despite the widespread use of dialysis, there remains a lack of consensus about the optimal time at which renal replacement therapy (RRT) should be initiated.

* Corresponding author. Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510080, China.

E-mail address: yuxq@mail.sysu.edu.cn (X.-Q. Yu).

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There is general agreement that dialysis should be started in those with absolute indications such as uremic pericarditis, serositis, encephalopathy, refractory metabolic acidosis, hyperkalemia, and volume overload.[7] Current guidelines regarding when to initiate RRT are based on symptoms or signs of uremia and malnutrition, as well as the glomerular filtration rate (GFR).[8–10] However, the ideal GFR for dialysis initiation in asymptomatic patients has not been completely clarified. Over the past decade, a worldwide trend toward increasing GFR at the initiation of dialysis has been noted. However, available data indicate that early dialysis has no survival benefit or is harmful. PD is a well-accepted dialysis modality for ESRD. As a home-based therapy, PD has many inherent advantages, such as residual renal function (RRF) preservation, hemodynamics maintenance, better quality of life, and cost savings.[11] Even so, the association between early PD therapy initiation and mortality has been a matter of controversy. The following discussion summarizes the effect of the timing of dialysis on clinical outcomes in PD patients.

Timing of dialysis initiation and outcomes in ESRD

As early as the 1980s, studies that examined the role of "early" versus "late" dialysis have consistently shown a better outcome in patients starting dialysis early. A lower GFR at the initiation of dialysis was associated with an increased probability of hospitalization and death.[12–14] On the basis of these data, the clinical practice guidelines at that time had recommended the initiation of dialysis at relatively high levels of renal function. For example, initial National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines in 1997 recommended that dialysis be initiated at a GFR of approximately 10.5 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$.[15] The updated NKF-DOQI guidelines in 2006 emphasized that the benefits and risks should be considered when the estimated GFR (eGFR) is $< 15\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, or even earlier in certain circumstances when patients have coexisting conditions or symptoms and signs of uremia.[16] In addition, the Caring for Australasians with Renal Impairment guidelines suggested that dialysis can be started when GFR is $> 10\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ in those with evidence of uremia or malnutrition and $>6\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ in those without evidence of uremia or malnutrition.[17] The Canadian Society of Nephrology recommended a targeted eGFR of 12 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ for the initiation of dialysis and that dialysis can be deferred in patients without evidence of uremia or malnutrition.[18] Over the past decade, there has been a strong trend towards earlier initiation of dialysis in ESRD. Data from the 2017 USRDS showed the proportion of ESRD patients who started dialysis at eGFR $\geq 10\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ increased from 13.0% in 1996 to 39.0% in 2015. In parallel, the proportion of ESRD patients who started therapy at eGFR $<5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ decreased from 33.7% in 1996 to 14.1% in 2015.[1] There was a similar trend in Canada, where the mean eGFR at dialysis initiation increased from 9.3 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ in 2001 to 10.7 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ in 2009, and the percentage starting early dialysis (eGFR $>10.5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) rose from 29% to 44%.[19] Most of these studied dialysis populations included both PD and HD patients.

However, none of these studies used a rigorous randomized clinical trial design and therefore were subject to bias. In the past decade, it was found that early initiation of dialysis had no effect on better survival or potentially worsened survival. Crews et al[20] conducted an observational cohort study that comprised 652 patients with CKD (eGFR $\leq 60\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) from the Cleveland Clinic Foundation Registry, and the results showed no significant difference in survival between patients with advanced CKD in the early start group (eGFR $\geq 10\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) and those in the late start group (eGFR$<10\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), even accounting for lead time bias and survivor bias. In contrast, a large body of observational studies indicated that late initiation of dialysis was associated with a reduced risk of mortality. One study from British Columbia and Scotland enrolled 7299 patients on dialysis who were classified into 5 groups based on eGFR 0–4.9, 5–9.9, 10–14.9, $\geq 15\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, and unavailable values. During follow-up, patients who started dialysis at an eGFR $<5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ showed better survival compared with other groups and a similar outcome was found in both HD and PD patients.[21] In addition, an observational study from America with 896,546 incident patients suggested that early start dialysis (eGFR $>15\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) presented an increased risk of death compared with a reference group (eGFR 10–15 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), whereas late start dialysis (eGFR $\leq 5\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) was associated with reduced risk of mortality.[22] The results were similar irrespective of the modality of dialysis. Although patients who initiated dialysis early had a greater number of comorbid conditions and older age in some studies,[23,24] the observed association between early dialysis initiation and mortality cannot be completely explained by these factors. The randomized controlled Initiating Dialysis Early and Late (IDEAL)

trial with 828 ESRD patients at 32 centers in Australia and New Zealand demonstrated that planned early initiation of dialysis (GFR 10–14 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) was not associated with an improvement in survival compared with late initiation (GFR 5–7 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) over a median follow-up duration of 3.6 years. There was no significant difference between the groups in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis).[25] Furthermore, the study showed that planned early initiation of dialysis therapy in patients with ESRD had higher costs and was not associated with improved quality of life.[26] However, because PD patients constitute a minority of those on dialysis, results from studies on ESRD may not be generalizable to PD.

Timing of PD initiation and survival in ESRD patients

The Canada–USA investigators reported that each 5 L/1.73 m^2 decrease in weekly creatinine clearance was associated with a 7% increase in the hazard ratio *(HR)* of death and that a higher GFR at PD initiation was associated with an improved nutritional status.[27] A cohort of 8047 incident PD patients treated in Canada showed that contrary to most observational studies assessing HD, early initiation of PD at eGFR >10.5 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ was not associated with increased mortality.[19] Tang et al[28] conducted a prospective study that enrolled 233 patients from Hong Kong with a median follow-up duration of 52 weeks and found that starting dialysis when the symptoms of uremia are apparent is probably too late and that starting early may improve survival rates in PD patients. However, other studies demonstrated that starting dialysis early had no effect on survival or was harmful. Subgroup analysis of the IDEAL trial also demonstrated that there was no significant difference in clinical outcomes between early and late start PD.[25] An observational study of 495 incident PD patients with a median follow-up of 23 months showed that an eGFR <5 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at initiation of PD was a significant risk factor for all-cause mortality, while no significant difference was observed in survival between eGFR >10 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ and eGFR 5–10 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at initiation of PD.[29] A meta-analysis also showed similar results, suggesting that higher GFR at initiation of dialysis was associated with a higher mortality risk in HD patients, whereas there was no association between GFR and mortality in PD patients.[30] We conducted a retrospective study of 2021 incident PD patients with a median follow-up duration of 35.5 (range 2.6–131.4) months and mean eGFR at dialysis initiation of $6.78 \pm 2.74\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. After adjustment for all covariates, there was no significant association between early (eGFR >10 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) and late dialysis (<5 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) with mortality ($HR = 0.81$, 95% confidence interval [*CI*]: 0.58–1.11, $P = 0.181$). Older age and coexisting conditions may explain worse outcomes among patients who had a higher GFR when dialysis was initiated.

Compared to HD, PD has many unique characteristics and potential survival benefits, such as relatively slow reduction of RRF, relatively stable hemodynamics, and relatively desirable clearance of middle molecules, all of which favor survival in PD patients. Many prior observational studies have demonstrated that RRF is a significant predictor of mortality in patients on PD. Sustained RRF contributes significantly to both patient and PD technique survival[31,32] and also has a beneficial effect on other complications such as cardiovascular disease, fluid overload, disorders of bone and mineral metabolism, anemia, inflammation and malnutrition.[13,33] We found that some interrelated factors for PD, such as fluid overload,[34] high glucose dialysate,[35] malnutrition,[36] ratio of high serum triglyceride to high-density lipoprotein cholesterol,[37] and metabolic syndrome,[38] were associated with higher mortality in PD patients. In general, the rate of decline of GFR had a greater effect on mortality than baseline GFR in PD patients. A longitudinal study from the Canadian Organ Replacement Registry showed that baseline GFR and its rate of decline were independent predictors of mortality and technique survival in PD patients. Patients with a low baseline GFR followed by a rapid decline presented the worst survival outcome compared with those with a high baseline GFR followed by a slow decline.[19] Overall, when the risk-benefit balance of early versus late start PD was evaluated, the rate of decline of GFR had to be considered.[39] Early initiation of PD could improve the patient's nutritional status and decrease cardiovascular complications associated with declining renal function, resulting in a decrease in mortality in the early stages of dialysis. Even so, some PD technique-related factors, such as peritonitis, peritoneal protein loss, use of peritoneal membrane fast transporters, and high glucose load, may be associated with mortality in early start PD patients.[40–42]

Latest guidelines and recommendations

The IDEAL study prompted international expert panels to revisit previous guidelines based on prior observational experience with timing of dialysis initiation (Table 1). In 2011, the European Renal Best Practice recommended a specific GFR range at which symptoms can be expected to develop (6–9 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) and that the decision to start dialysis should mainly be based on the complications of kidney failure, rather than on a specific GFR.[8] The Kidney Disease Improving Global Outcomes 2012 recommended timing of dialysis initiation be based primarily on assessment of symptoms or signs attributable to kidney disease.[9] The Canadian Society of Nephrology updated clinical practice guidelines in 2014 and recommended an "intent-to-defer" over an "intent-to-start-early" strategy and placed a high value on quality of life and avoidance of burdens on patients.[43] The updated 2015 Kidney Disease Outcomes Quality Initiative clinical practice guideline for HD adequacy also avoids mention of a specific GFR at which dialysis should be initiated in the absence of signs and symptoms. Additionally, conservative non-dialysis therapy may be an alternative to consider for some older or more infirm individuals. The expert panels also emphasized that patients who reach CKD stage 4 (GFR <30 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), including those with urgent need for maintenance dialysis at the time of initial assessment, should be monitored closely by a nephrologist and educated about kidney failure and options for treatment. Timely nephrology referral can help patients to make a reasonable decision on timing of dialysis initiation as well as dialysis modality to optimize outcomes.[10] Some believe that patients with diabetes should start dialysis earlier than those without diabetes, in an attempt to prevent complications of diabetes or uremia.[21,44] However, no significant difference was detected in a systematic review on survival rate in patients with and without diabetes.[45] RRT should thus be started based on the same criteria in all patients, irrespective of the presence or absence of diabetes. That is to say, patients with diabetes should be monitored closely, and RRT should be started when the symptoms of uremia or other complications develop or a decline in eGFR to less than 6 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ is observed.

A remaining challenge is measurement of GFR. The most commonly used Modification of Diet in Renal Disease (MDRD) Study Group and Chronic Kidney Disease Epidemiology Collaboration equations are 4-variable formulas that use age, gender, and race to account for creatinine production, and therefore, the GFR is constant for a given age, race, gender, and

Table 1
Latest clinical practice guidelines on timing of dialysis initiation in ESRD.

Guideline	Statement
European Renal Best Practice (ERBP) advisory board (2011)[8]	Dialysis should be considered when one or more of the following conditions are observed in patients with GFR <15 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$: symptoms or signs of uremia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status. The majority of patients will be symptomatic and need to commence dialysis with GFR in the range 6–9 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. High-risk patients (e.g., diabetics) and those whose renal function is deteriorating more rapidly than eGFR 4 ml/min per year require particularly close supervision.
KDIGO (2012)[9]	Starting dialysis is recommended when one or more of the following conditions are present: symptoms or signs attributable to kidney failure, such as serositis, pruritus, and acid-base or electrolyte disorders; refractory volume overload or hypertension; progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. These symptoms often but not invariably occur in the GFR range from 5 to 10 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$.
Canadian Society of Nephrology (2014)[43]	For adults (aged >18 years), an "intend-to-defer" strategy for the initiation of dialysis is recommended: patients with an eGFR <15 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ should be under the care of a nephrologist, and dialysis is initiated with the inception of uremic symptoms, fluid overload, refractory hyperkalemia or metabolic acidosis, or other signs or symptoms that could be ameliorated by dialysis, or a decline in eGFR to $\leq$6 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$.
NKF-KDOQI (2015)[10]	The decision for dialysis initiation should be based primarily upon an assessment of signs and/or symptoms of uremia, evidence of malnutrition, and refractory metabolic abnormalities and/or volume overload unmanageable with medical therapy, rather than on a specific level of kidney function in the absence of signs or symptoms.

ESRD: end-stage renal disease; GFR: glomerular filtration rate; eGFR: estimated GFR; KDIGO: Kidney Disease Improving Global Outcomes; NKF-KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

serum creatinine level. It is known that serum creatinine level is a measure of combined creatinine production by muscle and excretion by the kidney; consequently, the eGFR has a significantly negative correlation with muscle mass. Measured with the equations, GFR in patients with malnutrition may be overestimated, while GFR in patients with higher muscle mass may be underestimated. Consequently, these equations are invalid estimates of GFR in advanced CKD patients. A study showed that higher GFR estimated from serum creatinine using the MDRD equation was associated with increased mortality, in contrast with no observed association between higher measured GFR (mean of creatinine and urea clearance, mGFR) and increased mortality.[46] These data suggested that increased mortality with higher MDRD GFR at start of dialysis may be an artifact due to error in estimation of GFR in patients with poor nutritional status. For this reason, traditional criteria based on measures of kidney function (such as eGFR) might have limitations. Compared with eGFR, the mGFR was less likely to be influenced by muscle mass, and in those with more advanced CKD and extremes of nutrition, mGFR might provide more accurate GFR estimation by reflecting real kidney function for initiation of dialysis.[47]

Currently published guidelines unanimously recommend that assessing the timing of dialysis initiation should be based on symptoms or signs of uremia. A study from the USA described the symptom burden and clinical indications prompting the initiation of dialysis therapy among patients with chronic kidney failure and found that patients initiating dialysis therapy due to evidence of volume overload or hypertension had higher risk of subsequent death compared with patients initiating dialysis therapy prompted solely by laboratory evidence of kidney function decline. In contrast, patients who initiated dialysis therapy primarily due to uremic symptom burden did not have an increased risk for death.[48] This study suggested that improved understanding of symptoms may lead to innovation in making the decision for the optimal time of dialysis initiation, and that targeted GFR for the initiation of dialysis may be different according to the symptoms. Moreover, most studies have focused primarily on the association between eGFR or symptoms at initiation of dialysis and outcomes, while there is considerable uncertainty about the optimal time to initiate maintenance dialysis in individual patients. A more recent study investigated the factors influencing timing of initiation of dialysis in clinical practice and the results showed that timing reflected the complex interplay of at least 3 interrelated and dynamic processes, including the management practices of physicians, sources of momentum for initiation of dialysis, and interactions between patients and physicians. However, interactions between patients and physicians were sometimes inconsistent and physician suggestions to initiate dialysis sometimes seemed to conflict with patient priorities. It should be stressed that making the optimal decision of when to start dialysis by improving communication between physicians and patients is essential to reach better clinical outcomes.[49,50]

Summary

Initiating dialysis has major implications on patient outcomes and health care systems. There is a need to identify a threshold before which starting dialysis offers no benefit to the patient but beyond which there may be some adverse effects; however, this is difficult in clinical practice. According to current guidelines, the decision for dialysis initiation should be based primarily on the assessment of clinical signs and/or symptoms rather than on the specific level of kidney function. The balance among benefits, risks, and disadvantages of initiating or not initiating dialysis should be evaluated. In addition, making the optimal decision of when to initiate dialysis by improving communication between physicians and patients is essential to reach better clinical outcomes. Future large-scale randomized controlled trials need to critically identify whether there is any difference in mortality with early versus late initiation of HD and PD. In the meantime, ongoing observational studies will provide novel information on the timing of dialysis initiation.

Conflicts of interest

The authors declare that they have no conflict of interest.

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