The Glomerular Filtration Rate (GFR) at Dialysis Initiation and Mortality in Chronic Kidney Disease (CKD) in East Asian Populations: A Meta-analysis

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Abstract

Objective The impact of dialysis initiation on survival is still somewhat controversial. Given that race or ethnicity has been observed to be a predictor of mortality and the rate of progression of chronic kidney disease, we conducted a meta-analysis to investigate the effect of early vs. late dialysis initiation on mortality in East Asian populations.

Methods All eligible cohort studies of target were selected from the MEDLINE (PubMed), EMBASE, The Cochrane Library and the Clinical Trials Registry databases from inception to October 2014. The data were extracted with all-cause mortality rates as the primary outcome, and pooled adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

Results Ten studies examined the association between early vs. late dialysis initiation and mortality. Compared to late dialysis initiation, patients who received early dialysis initiation had a higher overall mortality risk (adjusted HR, 1.36; 95% CI, 1.0-1.85; p<0.05) in East Asian populations. In a subgroup analysis, baseline characteristic differences (adjusted HR, 2.0; 95% CI, 1.56-2.57; p<0.001), initial dialysis modalities (adjusted HR, 2.12; 95% CI, 1.72-2.62; p<0.001) and follow up duration (adjusted HR, 1.59; 95% CI, 1.19-2.12; p=0.002), demonstrated that the association between early dialysis initiation and mortality were significant.

Conclusion A higher glomerular filtration rate (early) at the initiation of dialysis is associated with a higher all-cause mortality risk in East Asian populations.

Key words: chronic kidney disease (CKD), early dialysis initiation, late dialysis initiation, mortality, glomerular filtration rate (GFR)

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Introduction

End-stage renal disease (ESRD) is not only a devastating medical problem, but also a social and economic issue. The numbers of ESRD patients continue to increase worldwide, as well as in East Asia. According to the ESRD Registry Committee of the Korean Society of Nephrology (KSN), in 2009, the total number of patients with renal replacement therapy (RRT) in Korea was 56,396 and the rate of ESRD cases per million population reached 1,113.6 (1). In Japan, the number of new dialysis patients was 38,055 and the number of dialysis patients per million was 2,431.2 at the end of 2012 (2). The Chinese Society of Blood Purification (CSBP) also showed that in mainland China, at the end of 2008, a total of 102,683 ESRD patients on dialysis and the prevalence was 79.1 patients per million populations, with an annual increasing rate of 52.9% (3). China is not like many Western countries, the lower rate of dialysis patients is mainly due to the lack of sufficient financial and clinical resources, and inequalities in access to health care across regions and populations. In fact, the number of ESRD patients requiring dialysis in China is underestimated in the above figures.
Materials and Methods

Study selection

Two reviewers (X.L. and X.Z.Z.) independently performed an initial eligibility screen of all retrieved titles and abstracts (when available). Studies reporting original data that specifically mentioned the association between the timing of dialysis initiation (assessed by the GFR) and mortality were selected for further review. Full texts were independently assessed by the same two authors. No restrictions were placed on the sample size or study duration. Disagreements between the reviewers were resolved by a third reviewer or by discussion and a consensus.

Data extraction

All data were extracted independently by the two reviews (X.L. and X.Z.Z.) to a predesigned form (Microsoft Office Excel 2007; Microsoft Corp, Redmond, WA, USA). All data extractions were then checked by a third reviewer (J.A.). The following data were extracted from each trial: first author and year, country of origin, study design, sample size, study period, initial dialysis modality [including hemodialysis (HD), peritoneal dialysis (PD), or both], follow-up duration, demographics and baseline characteristics (mean age, proportion of male patients, rate of diabetes, mean BMI, mean serum albumin level, mean hemoglobin), and estimated-GFR [calculated using the Modification of Diet in Renal Disease (MDRD) formula, the Cockcroft-Gault equation, or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation]. Outcomes of interest were all-cause mortality rates and cardio-cerebrovascular mortality, which were calculated as adjusted hazard ratios [HRs; with 95% confidence intervals (CIs)]. Some exact HRs were not directly stated in some studies, in which the results were presented as Kaplan-Meier survival curves, in this situation, we obtained the data from the curves using the Get Data Graph Digitizer2.25 software program and a consensus was achieved between the two reviewers. Five studies did not directly state the HRs of the GFR for cardio-cerebrovascular mortality, but provided the number of cardio-cerebrovascular deaths or the survival curves, from which we obtained the HRs through the curve or directly calculated them.

Assessment of methodological quality

We evaluated the quality of each study using the Newcastle-Ottawa Scale (NOS) (41). The NOS criteria are categorized into three sections: selection, comparability and outcome. Each study is designated a score for each section, based on some queries, with a total score of 9. Scores 0-3,
4-6, and 7-9 indicate an overall study quality of poor, fair, and good, respectively. The quality of the studies was independently assessed by two authors (X.L. and X.Z.Z.). In cases of disagreement, a consensus was reached by discussion.

**Statistical analysis**

Data were analyzed using the STATA software program (version 12.0, StataCorp, College Station, TX, USA). We assessed and quantified statistical heterogeneity for each pooled summary estimate using Q statistic p value and the \( I^2 \) statistic, respectively. The random effects model was used to combine the data if significant heterogeneity existed (p<0.1; \( I^2 >50\% \)). The adjusted HR was used as a measure of the association for all-cause or cardio-cerebrovascular mortality between early and late dialysis initiation. A meta-regression analysis was performed to assess the possible sources of heterogeneity. Publication bias was assessed using Egger’s regression model (42).

**Results**

**Literature search**

The literature search yielded 1,854 articles, of which 76 were reviewed in full text (Fig. 1). After primary and secondary screening, 10 cohort studies fulfilled all criteria for final analysis (9 articles and 1 abstract); their study characteristics are listed in Table 1.

**Trial characteristics**

We identified 10 cohort studies (9, 13, 20-26, 28): three prospective cohort studies (25, 26, 28), and eight retrospective cohort studies (9, 13, 20-24, 27). Of these, 9 studies were published as journal articles (9, 13, 21-26, 28) and 1 study was published as an abstract only (20). The patients of the 10 cohort studies were of East Asian descent. These studies varied in sample size (210-23,551 patients), follow-up duration (1-15 years) and involved patients with various initiating dialysis modalities (HD, PD, or both). Five studies had more men (range 51-65\%), with a mean age ranging from 46 to 67 years. The proportion of patients with diabetes varied from 19-59\%. The GFR was calculated using different equations (the MDRD, CKD-EPI, Cockcroft-Gault equation or urea and creatinine clearance rates). A propensity score (PS) analysis was employed in three cohorts (22, 23, 26) to eliminate baseline differences between the early and late groups. In five cohorts (9, 13, 20, 21, 25), baseline characteristic differences were present between the early and late dialysis initiation groups (the early dialysis
initiation group was older, predominantly male, had a higher incidence of diabetes, lower serum ALB and higher burden of comorbidities than the late dialysis initiation group (Table 2).

Mortality in the early vs. late dialysis initiation groups

Ten studies examined the association between early vs. late dialysis initiation and mortality. Compared to late dialysis initiation, patients who received early dialysis initiation had a higher overall mortality risk (adjusted HR, 1.36; 95% CI, 1.01-1.85; p<0.05) (Fig. 2). However, there was significant heterogeneity (I²=79.5%; p<0.001).

A subgroup analysis was performed according to the differences in the baseline characteristic (including age, diabetes, the proportion of male patients and comorbidity, and serum albumin level), follow-up duration (>10 or <10 years), initial dialysis modalities (HD, PD, or both). In the five cohorts (9, 13, 20, 21, 25) that showed baseline characteristic differences between the groups, early dialysis initiation was associated with a higher mortality risk (adjusted HR, 2.0; 95% CI, 1.56-2.57; p<0.001). Compared with the other five cohorts (22-24, 26, 28) that showed no baseline characteristic differences between early dialysis initiation and mortality (adjusted HR, 0.92; 95% CI, 0.54-1.55; p=0.752). In four cohorts (13, 20, 23, 26) where HD therapy was initiated, the association between early dialysis initiation and mortality was significant (adjusted HR, 2.12; 95% CI, 1.72-2.62; p<0.001) in comparison to, the six cohorts restricted to PD (9, 21-23, 26, 28) therapy as the initial dialysis mortality, for which early dialysis initiation was not associated with mortality (adjusted HR, 1.37; 95% CI, 0.96-1.94; p=0.08). The cohorts (9, 13, 20-22, 25, 26, 28) that had a maximum follow-up of less 10 years showed, a significant association between early dialysis initiation and mortality (adjusted HR, 1.59; 95% CI, 1.19 to 2.12; p=0.002), whereas, the cohorts (23, 24) that had a maximum follow-up of 10 years or longer did not (adjusted HR, 1.23; 95% CI, 0.85 to 1.77; p=0.265) (Table 3).

Table 1. Characteristics of Studies Included in the Meta-analysis.

| Study | Country of origin | Study design | Sample size | Accrual period | Initial dialysis modality | Max follow-up duration (year) | Mean age (y) | Male (%) | DM (%) | MeaneGFR (mL/min/1.73m²) | NOS scale |
|-------|------------------|--------------|-------------|----------------|--------------------------|-------------------------------|--------------|----------|-------|--------------------------|-----------|
| Tang et al. 2007 [28] | HK | PCS | 233 | 2002-2004 | PD | 2 | 58 | 51 | 42 | 9.1 | 6 |
| Shiao et al. 2008 [9] | TW | RCS | 275 | 1997-2005 | PD | 6 | 51 | 45 | 19 | 4.8 | 3 |
| Kim et al. 2009 [21] | Korea | RCS | 210 | 2000-2005 | HD+PD | 7 | 50 | 33 | 47 | 8.5 | 4 |
| Huang et al. 2010 [13] | TW | RCS | 23,551 | 2001-2004 | HD | 1 | 62 | 48 | 50 | 4.7 | 4 |
| Oh et al. 2012 [22] | Korea | RCS | 491 | 2000-2010 | PD | 2 | 49 | 61 | 34 | 8.2 | 5 |
| Chang et al. 2012 [23] | Korea | RCS | 450 | 2000-2009 | HD+PD | 11 | 54 | 54 | 59 | 8.6 | 5 |
| Yamagata et al. 2012 [24] | Japan | RCS | 20,854 | 1989-1990 | HD+PD | 18 | 58 | 65 | 32 | 5.0 | 6 |
| Lee et al. 2014 [26] | Korea | PCS | 854 | 2008-2013 | HD+PD | 5 | 57 | 63 | 57 | 11.2 | 6 |
| Liu et al. 2014 [20] | China | RCS | 5,612 | 2007-2012 | HD | 6 | -- | -- | -- | -- | -- |
| Kim et al. 2014 [25] | Korea | PCS | 495 | 2009-2013 | PD | 2 | 52 | 61 | 44 | 7.8 | 6 |

Table 2. Baseline Characteristics and Outcomes in the Early- and Late Dialysis Initiation Groups in 10 Studies Included in the Meta-analysis.

| Study | GFR category | Mean GFR (mL/min/1.73m²) | Mean age (y) | Male (%) | DM (%) | ALB (g/dL) | All-cause mortality (early vs. late) |
|-------|--------------|--------------------------|--------------|----------|-------|------------|-----------------------------------|
| Tang et al. 2007 [28]* | Elective starter | 9.2 ± 0.9 | 8.9 ± 1.4 | 58 ± 14 | 58 ± 11 | 50 | 54 | 40 | 46 | NR | NR | 0.33 (0.11-0.76) |
| Shiao et al. 2008 [9] | ≥5 | 6.8 ± 2.1 | 3.5 ± 0.9 | 56 ± 19 | 48 ± 16 | 65 | 32 | 38 | 12 | 3.4 ± 0.7 | 3.7 ± 0.6 | 1.81 (1.01-3.22) |
| Kim et al. 2009 [21] | <5 | 8.0 ± 3.0 | 3.4 ± 1.1 | 53 ± 15 | 48 ± 14 | 43 | 21 | 58 | 36 | 3.1 ± 0.7 | 3.1 ± 0.7 | 0.81 (0.39-1.69) |
| Huang et al. 2010 [13] | ≥5 | 26.52 | <3.29 | 7.7 | 2.6 | 65 | 14 | 55 | 14 | 62 | 39 | 69 | 25 | NR | NR | 2.44 (2.11-2.81) |
| Oh et al. 2012 [22]* | ≥7.7 | 10.8 ± 2.5 | 5.5 ± 1.3 | 48 ± 15 | 49 ± 13 | 37 | 61 | 37 | 31 | 3.5 ± 0.5 | 3.6 ± 0.6 | 0.47 (0.16-1.35) |
| Chang et al. 2012 [23]* | ≥7.4 | 11.1 ± 3.9 | 6.1 ± 1.2 | 53 ± 14 | 54 ± 14 | 55 | 54 | 59 | 59 | 3.2 ± 0.6 | 3.3 ± 0.5 | 1.32 (0.87-1.99) |
| Yamagata et al. 2012 [24]* | >10 | 40 | 40 | 63 | 60 | 67 | 65 | 54 | 30 | NR | NR | 0.965 (0.447-2.084) |

*No differences in the baseline characteristics between the early- and late dialysis initiation groups were observed in these studies (the early dialysis initiation group was older, had a higher incidence of diabetes, lower ALB and higher burden of comorbidities than the late dialysis initiation group).

ALB: serum albumin, DM: diabetes mellitus, HD: hemodialysis, HK: Hong Kong, NOS scale: Newcastle-Ottawa Quality Assessment Scale, NR: not reported, PCS: prospective cohort study, PD: peritoneal dialysis, RCS: retrospective cohort study, TW: Taiwan

a Median age.

b Median GFR at the initiation of dialysis.

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Figure 2. A forest plot shows the effect of early vs. late dialysis initiation on all-cause mortality. A meta-analysis was performed using a random-effects model. Data are presented as adjusted hazard ratios with 95% confidence intervals (CIs). Boxes are scaled to the weight of the studies in the overall meta-analysis. The test for heterogeneity is significant ($I^2=79.2\%$ and $p<0.001$ by Q test).

Table 3. Subgroup Meta-analysis.

| Subgroup                          | Number of studies | Total patients | Hazard Ratios | 95% Confidence Intervals | I-square | p for Heterogeneity |
|----------------------------------|-------------------|----------------|---------------|--------------------------|----------|---------------------|
| Baseline characteristic differences |                   |                |               |                          |          |                     |
| Yes                              | 5                 | 30,143         | 2.03          | 1.6 to 2.59              | 59.6%    | 0.042               |
| No                               | 5                 | 22,882         | 0.92          | 0.54 to 1.55             | 65.1%    | 0.022               |
| Dialysis modality                |                   |                |               |                          |          |                     |
| Hemodialysis                     | 4                 | 30,467         | 2.12          | 1.72 to 2.62             | 55.6%    | 0.08                |
| Peritoneal dialysis              | 6                 | 1,887          | 1.06          | 0.62 to 1.83             | 60.1%    | 0.028               |
| Follow-up duration               |                   |                |               |                          |          |                     |
| < 10 years                       | 8                 | 52,333         | 1.61          | 1.2 to 2.14              | 82%      | $<0.001$            |
| >10 years                        | 2                 | 21,304         | 1.23          | 0.85 to 1.77             | 0        | 0.482               |

Baseline characteristic differences (Yes): in these 5 studies the early dialysis initiation group was older, had a greater incidence of diabetes, lower ALB and higher burden of comorbidities than the late dialysis initiation group.

Publication bias and sensitivity analysis

Publication bias was assessed using Egger’s linear regression test and statistical evidence of bias was demonstrated ($\beta=1.50$, 95% CI=-2.06 to -0.94, $p<0.0001$). When we conducted a sensitivity analysis, excluding 3 small sample size studies (9, 28, 21), the finding that early dialysis initiation was associated with mortality was maintained (adjusted HR, 1.65; 95% CI, 1.24-2.2; $p=0.001$; $I^2=73.5\%$). In addition, a sensitivity analysis using the trim and fill method showed negligible differences between the corrected and uncorrected HRs, suggesting the result to be relatively reliable.

Discussion

This systematic review and meta-analysis of 10 unique studies compared early vs. late initiation of dialysis with mortality in East Asian populations and indicated that early dialysis initiation was associated with an increased mortality risk. A subsequent subgroup analysis showed that cohorts with baseline characteristic differences between early and late dialysis and HD therapy, demonstrated that early dialysis initiation resulted in a poor survival. Cardiovascular events are the main cause of death in dialysis patients. Thus we also performed a subgroup analysis of five cohorts (21, 22, 25, 26, 28), which suggested that a
higher GFR at dialysis initiation did not appeared to be associated with cardio-cerebrovascular mortality (HR, 0.54; 95% CI, 0.26-1.14; p=0.108). But three (22, 25, 28) of these five studies were PD patients and all five studies had small sample sizes (the total number of patients was 2,283).

During the past decades, there had been a worldwide trend toward early dialysis initiation. However, according to recent a report from the USRDS, the proportion of early dialysis initiation grew from 19% to 54% between 1996 and 2009, but remained stable between 2009 and 2011 in the United States (43). The decreasing trend of early initiation dialysis patients might be due to recent observational studies, which have consistently suggested that early dialysis initiation might be harmful (7-20). Additionally, the IDEAL study also suggested that early dialysis initiation had no significant benefit on the survival (30), which is the only randomized controlled trial to date to address the timing of chronic dialysis initiation. In this trial, a total of 828 ESRD patients were randomized to the early group (10-14 mL/min/1.73 m²) and late group (5-7 mL/min/1.73 m²) according to the eGFR (MDRD formula); after a median follow-up of 3.6 years, the results showed that there were no significant differences between the two groups regarding the survival, complications, or quality of life. However, we must note that the patients in the IDEAL study, were younger, better nourished, better prepared for ESRD, had fewer requirements for temporary dialysis catheter access, and a greater proportion were started on peritoneal dialysis compared with the typical European dialysis patients. Thus, it was difficult to generalize the results of the IDEAL study to all patients preparing for dialysis. In addition, two recent systemic reviews also indicated that a higher GFR at the initiation of dialysis was associated with an increased risk of death (44, 45). Reflecting the results of these investigations, recent guidelines have recommend delaying dialysis and emphasized the clinical symptoms or signs to guide the initiation of dialysis, rather than only considering the GFR (32-34). In addition, the follow-up times of previous studies may affect the judgment of dialysis initiation; however, a recent study in Japan, which included 25,804 patients (GFR>10 mL/min/1.73 m² as the early dialysis group and 4-6 mL/min/1.73 m² as the late dialysis group), showed that early dialysis initiation had an increased mortality risk in the short-term follow-up (1-5 years), but there was no survival differences between the early and late dialysis initiation groups after unadjusted and multivariable adjusted analyses from the long-term outcome (5-10 years or >10 years) (24). Our findings were similar to this result; when the follow-up duration was less than 10 years, early dialysis initiation indicated a poor prognosis, with a 61% increased mortality risk, but no significant differences were observed when the follow-up duration was more than 10 years.

The baseline characteristics, such as older age, lower ALB, higher incidence of diabetes and higher burden of comorbidities in dialysis initiation, could lead to a poor prognosis. Recently, several studies used the propensity score (PS) matching method to overcome the limitation of non-random allocation to the baseline differences, and the results suggested that before matching, early dialysis had a poor survival. However, after propensity score matching, patients with early and late initiation demonstrated no differences in the survival (23, 26). In line with these observations, a retrospective analysis of 11,685 patients in the French Renal Epidemiology and Information Network Registry showed that each 5 mL/min/1.73 m² increase in the GFR was associated with a 40% increase in the risk of mortality. However, after adjusting for age, ALB, diabetes, and comorbidities, the risk of mortality in early dialysis was greatly attenuated to 9%. This study indicated that age and comorbidity strongly determined the decision to start dialysis and might explain most of the paradoxical inverse associations observed between the GFR and survival (46). Our subgroup analysis was supportive of these findings, whereby early dialysis was associated with a higher mortality risk when restricted to five cohorts that showed baseline differences between the dialysis groups (early dialysis initiation group was older, had a higher incidence of diabetes, lower ALB and higher burden of comorbidities than the late dialysis initiation). However, there was no association between the GFR and mortality in five cohorts wherein no baseline differences were observed between the early and late dialysis initiation. Taken together, existing patient conditions might be more important predictors of the survival than the timing of dialysis initiation.

HD is the major dialysis modality in most East Asia countries (1, 47). Two recent systemic reviews suggested that early dialysis initiation was associated with a higher mortality in HD patients, but lower in PD patients (45, 48). In addition, a study based on the IDEAL trial showed that early- and late-start PD patients showed no differences in mortality (49). Our subgroup analysis was consistent with this result, for which a higher GFR in patients initiating HD therapy was associated with an increased risk of death, whereas in studies restricted to PD populations, the GFR was not associated with mortality. PD had a lower risk of mortality compared to HD, because although HD therapy might have increase central venous catheter exposure, HD could more easily promote transient myocardial ischemia, myocardial stunning, and ventricular arrhythmias (50). Furthermore, HD therapy was associated with an increased risk of residual kidney function loss, which was strongly related to a risk of mortality while receiving dialysis (51). Additionally, diabetes, age, and co-morbidity all significantly modify the effect of dialysis modality on the patient survival (52). Therefore, these factors must be considered when selecting the dialysis modality.

There are several limitations associated with our meta-analysis. The studies included were cohort studies, particularly retrospective cohort studies. This could inevitably lead to various biases, particularly survival bias, which could favor late dialysis initiation. On the other hand, the definitions of early and late dialysis were not standardized and only...
simply defined by the serum creatinine-based eGFR, for which seven of ten studies used the MDRD equation. A study found that patients initiated on dialysis therapy with a higher eGFR were found to represent a lower creatinine production rather than higher creatinine clearance, thus the assumptions of the MDRD for estimating the GFR were invalid in patients with advanced renal failure with high and low creatinine production (53). The 2011 European dialysis guidelines also showed that the MDRD equation should not be used to estimate renal function in patients with stage 5 CKD (54). Another potential limitation of any meta-analysis is the possibility of publication bias, due to the fact that studies obtaining optimistic results are more readily published than studies with unfavorable results. However, sensitivity analyses using the trim and fill method showed the results were reliable. Finally, there was substantial heterogeneity in the effect size estimates across studies. The dialysis modality, baseline characteristic differences and the duration of follow-up might be sources of the heterogeneity.

In conclusion, this meta-analysis suggested that early dialysis initiation for ESRD patients is associated with an increased mortality risk, a higher mortality risk in HD therapy and poor outcomes in the short-term follow-up. Moreover, this systemic review showed that baseline characteristics, such as older age, diabetes, lower ALB and comorbidity, strongly influenced the result of dialysis, suggesting that the decision to initiate dialysis should consider patient’s clinical conditions rather than the GFR alone. Cardio-cerebrovascular mortality between the early and late dialysis initiation groups in this meta-analysis showed no survival differences, however, this could be due to the limited number of studies. This review was based on observational studies with significant heterogeneity, therefore, well designed randomized controlled trials are necessary to confirm these results.

The authors state that they have no Conflict of Interest (COI).

Xin Lin and Xiang-Zhen Zeng contributed equally to this work.

References

1. Jin DC; ESRD Registry Committee, Korean Society of Nephrology. Current status of dialysis therapy in Korea. Korean J Intern Med 26: 123-131, 2011.
2. Nakai S, Hanafusa N, Masakane I, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2012). Ther Apher Dial 18: 535-602, 2014.
3. Zuo L, Wang M; Chinese Association of Blood Purification Management of Chinese Hospital Association. Current burden and probable increasing incidence of ESRD in China. Clin Nephrol 74 Suppl 1: S20-S22, 2010.
4. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. Am J Nephrol 15: 283-289, 1995.
5. McCusker FX, Teehan BP, Thorpe KE, et al. How much peritoneal dialysis is required for the maintenance of a good nutritional state? Canada-USA(CANUSA) Peritoneal Dialysis Study Group.
6. Sesso R, Belasco AG. Late diagnosis of chronic renal failure and mortality on maintenance dialysis. Nephrol Dial Transplant 11: 2417-2420, 1996.
7. Beddhu S, Samore MH, Roberts MS, et al. Impact of timing of initiation of dialysis on mortality. J Am Soc Nephrol 14: 2305-2312, 2003.
8. Kazmi WH, Gilbertson DT, Obrador GT, et al. Effect of comorbidity on the increased mortality associated with early initiation of dialysis. Am J Kidney Dis 46: 887-896, 2005.
9. Shiao CC, Huang JW, Chien KL, et al. Early initiation of dialysis and late implantation of catheters adversely affect outcomes of patients on chronic peritoneal dialysis. Perit Dial Int 28: 73-81, 2008.
10. Sawhney S, Djurdjev O, Simpson K, et al. Survival and dialysis initiation: comparing British Columbia and Scotland registries. Nephrol Dial Transplant 24: 3166-3172, 2009.
11. Stel VS, Dekker FW, Ansell D, et al. Residual renal function at the start of dialysis and clinical outcomes. Nephrol Dial Transplant 24: 3175-3182, 2009.
12. Lassalle M, Labeuwe M, Frimat L, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int 77: 700-707, 2010.
13. Hwang SJ, Yang WC, Lin MY, et al. Impact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients: a national cohort study in Taiwan. Nephrol Dial Transplant 25: 2616-2624, 2010.
14. Wright S, Klausner D, Baird B, et al. Timing of dialysis initiation and survival in ESRD. Clin J Am Soc Nephrol 5: 1828-1835, 2010.
15. Rosansky SJ, Eggers P, Jackson K, et al. Early start of hemodialysis may be harmful. Arch Intern Med 171: 396-403, 2011.
16. Clark WF, Na Y, Rosansky SJ, et al. Association between estimated glomerular filtration rate at initiation of dialysis and mortality. CMAJ 183: 47-53, 2011.
17. Evans M, Tettamanti G, Nyren O, et al. No survival benefit from early-start dialysis in a population-based, inception cohort study of Swedish patients with chronic kidney disease. J Intern Med 269: 289-298, 2011.
18. Bao Y, Dalrymple L, Chertow GM, et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med 172: 1071-1077, 2012.
19. Wilson B, Harwood L, Locking-Cusolito H, et al. Optimal timing of initiation of chronic hemodialysis? Hemodial Int 11: 263-269, 2007.
20. Li Liu, Li Zuo, Yang Luo. Not too late initiation of dialysis could improve survival in hemodialysis patients from Beijing: experience of 6 years’ follow-up. Nephrol Dial Transplant 29 (Suppl 3): iii272-iii286, 2014.
21. Kim SG, Kim NH. The effect of residual renal function at the initiation of dialysis on patient survival. Korean J Intern Med 24: 55-62, 2009.
22. Oh KH, Hwang YH, Cho JH, et al. Outcome of early initiation of peritoneal dialysis in patients with end-stage renal failure. J Korean Med Sci 27: 170-176, 2012.
23. Chang JH, Rim MY, Sung J, et al. Early start of dialysis has no survival benefit in end-stage renal disease patients. J Korean Med Sci 27: 1177-1181, 2012.
24. Yamagata K, Nakai S, Iseki K, Tsukihara Y; Committee of Renal Data Registry of the Japanese Society for Dialysis Therapy. Late dialysis start did not affect long-term outcome in Japanese dialysis patients: long-term prognosis from Japanese Society for Dialysis Therapy Registry. Ther Apher Dial 16: 111-120, 2012.
25. Kim HW, Kim SH, Kim YO, et al. The impact of timing of dialysis initiation on mortality in patients with peritoneal dialysis. Perit Dial Int 35: 703-711, 2015.
26. Lee J, An JN, Hwang JH, et al. Effect of dialysis initiation timing on clinical outcomes: a propensity-score matched analysis of a prospective cohort study in Korea. PLoS ONE 9: e105532, 2014.

27. Korevaar JC, Jansen MA, Dekker FW, et al. When to initiate dialysis: effect of proposed US guidelines on survival. Lancet 358: 1046-1050, 2001.

28. Tang SC, Ho YW, Tang AW, et al. Delaying initiation of dialysis till symptomatic uremia: is it too late? Nephrol Dial Transplant 22: 1926-1932, 2007.

29. Coronel F, Cigarran S, Herrero JA. Early initiation of peritoneal dialysis in diabetic patients. Scand J Urol Nephrol 43: 148-153, 2009.

30. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 363: 609-619, 2010.

31. Watanabe Y, Yamagata K, Nishi S, et al. Japanese society for dialysis therapy clinical guideline for "hemodialysis initiation for maintenance hemodialysis". Ther Apher Dial 19 (Suppl 1): 93-107, 2015.

32. Tattersall J, Dekker F, Heimburger O, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. Nephrol Dial Transplant 26: 2082-2086, 2011.

33. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3: 1-150, 2013.

34. Nesrallah GE, Mustafa RA, Clark WF, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. CMAJ 186: 112-117, 2014.

35. Wong JS, Port FK, Hulbert-Shearon TE, et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int 55: 2515-2523, 1999.

36. Held PJ, Brunner F, Odaka M, et al. Five-year survival for end-stage renal disease patients in the United States, Europe, and Japan, 1982 to 1987. Am J Kidney Dis 15: 451-457, 1990.

37. Yoshino M, Kuhlmann MK, Kotanko P, et al. International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. J Am Soc Nephrol 17: 3510-3519, 2006.

38. Hemmelgarn BR, Chou S, Wiebe N, et al. Differences in use of peritoneal dialysis and survival among East Asian, Indo Asian, and white ESRD patients in Canada. Am J Kidney Dis 48: 964-971, 2006.

39. Conley J, Tonelli M, Quan H, et al. Association between GFR, proteinuria, and adverse outcomes among White, Chinese, and South Asian individuals in Canada. Am J Kidney Dis 59: 390-399, 2012.

40. Derose SF, Rutkowski MP, Crooks PW, et al. Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. Am J Kidney Dis 62: 236-244, 2013.

41. Wells GA, Shea B, O’Conell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Hospital Research Institute [Internet]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

42. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634, 1997.

43. Rosansky SJ, Clark WF. Has the yearly increase in the renal replacement therapy population ended? J Am Soc Nephrol 24: 1367-1370, 2013.

44. Pan Y, Xu XD, Guo LL, et al. Association of early versus late initiation of dialysis with mortality: systematic review and meta-analysis. Nephron Clin Pract 120: c121-c131, 2012.

45. Susantitaphong P, Altamimi S, Ashkar M, et al. GFR at initiation of dialysis and mortality in CKD: a meta-analysis. Am J Kidney Dis 59: 829-840, 2012.

46. Lassalle M, Labeeuw M, Frimat L, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int 77: 700-707, 2010.

47. Nakai S, Masakane J, Shigematsu T, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2007). Ther Apher Dial 13: 457-504, 2009.

48. Cantero-Munoz P, Ruano-Ravina A, Otero-Gonzalez A, et al. Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review. Nephrol Dial Transplant 25: 2414-2421, 2010.

49. Johnson DW, Wong MG, Cooper BA, et al. Effect of timing of dialysis commencement on clinical outcomes of patients with planned initiation of peritoneal dialysis in the ideal trial. Perit Dial Int 32: 595-604, 2012.

50. Rosansky S, Glassock RJ, Clark WF. Early start of dialysis: a critical review. Clin J Am Soc Nephrol 6: 1222-1228, 2011.

51. Moist LM, Port FK, Orzol SM, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol 11: 556-564, 2000.

52. Vonesh EF, Snyder JJ, Foley RN, Collins AJ. Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? Kidney Int Suppl (103): S3-S11, 2006.

53. Bedhu S, Samore MH, Roberts MS, et al. Creatinine production, nutrition, and glomerular filtration rate estimation. J Am Soc Nephrol 14: 1000-1005, 2003.

54. Tattersall J, Dekker F, Heimburger O, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. Nephrol Dial Transplant 26: 2082-2086, 2011.

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