Executive Summary

Clinical implication and prognostic factor of the dialysis therapy in elderly patients with chronic kidney disease

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▢ Background

According to the 2017 Korea National Health and Nutrition Examination Survey, the prevalence of moderate to severe chronic kidney disease (CKD) is 16% for those aged ≥70 years and increases with age. In the 2020 Periodic Report by the Korean Society of Nephrology, the percentage of patients with CKD who were aged ≥65 years drastically increased from 2.1% in 1990 to 17.4% in 2000, 36% in 2010, and 54.6% in 2020. While clinical practice guidelines for CKD have been developed in major countries in the last decade, few guidelines are available for CKD the elderly or end-stage kidney disease. The only guideline with recommendations for the elderly is the one developed by the European Renal Association in 2017. The guideline provides recommendations regarding when to begin dialysis for elderly patients with CKD of stage 3b or higher, how to assess renal function, prognostic prediction models, how to assess nutritional status, and when to perform dialysis for frail elderly patients. However, the guideline lacks clinical evidence, and there is a

continued need to develop clinical practice guidelines based on clinical evidence collected over time. A clinical practice guideline for CKD in elderly patients is yet to be established in Korea. This study aimed to systematically review scientific evidence that can form the basis of a domestic clinical practice guideline. This study will serve as basic research to the quality of life of elderly patients with CKD and support evidence-based decision-making.

▢ Objectives

This study aimed to present objective evidence that can support the decision-making related to dialysis for elderly patients with CKD through a systematic literature review.

The purpose of this study is to present objective evidence to help rational decision-making in deciding whether to receive dialysis treatment in actual clinical practice by analyzing treatment effects and prognostic factors related to dialysis treatment for elderly patients with CKD. The purpose of this study is 1) to identify the therapeutic effect related to dialysis treatment through comparative analysis of clinical effects between dialysis treatment and conservative management in elderly CKD patients, and 2) comparative analysis of clinical effects between hemodialysis and peritoneal dialysis in elderly chronic kidney disease patients, and 3) to prepare a scientific basis by analyzing the effects of prior planning of dialysis treatment on survival and independent prognostic factors in elderly patients with CKD.

▢ Methods

A systematic review was performed to examine whether dialysis is more effective than conservative care, whether peritoneal dialysis is more effective than hemodialysis, and the effect of unplanned dialysis on the survival of elderly patients with CKD. Studies were searched in three international databases (Ovid-Medline, Ovid-EMBASE, Cochrane Central Register of Controlled Trials) and three domestic databases (KoreaMed, KMbase, KISS)

and were hand-searched additionally. The search was not restricted by publication date and language. Two researchers independently reviewed each study and mutually agreed upon a final selection of studies. RoBANS 2.0 and QUIPS were used to assess the risk of bias in the finally selected studies.

A meta-analysis, which is a type of quantitative analysis, was performed if evidence synthesis was possible. In case the synthesis was not possible, a qualitative review was performed. A meta-analysis was performed using a random-effects model and the generic inverse variance model to present the effect of a variable on survival in terms of hazard ratios (HRs) or odds ratios (ORs) and their 95% confidence intervals. Heterogeneity between studies was visualized on a forest plot and then assessed using the Cochrane Q statistic ($P<0.10$) and I^2 statistics (≥50%) (Higgins et al., 2008). Subgroup analyses pre-defined age cut-offs for the elderly, country of research, research facility, study design, and the risk of bias were performed. In order to perform the sensitivity analysis, we analyzed studies that included only the elderly or studies that included advanced aged subjects (over 80 years old) or subjects with diabetes. If possible (≥10 studies selected), the risk of publication bias was analyzed using a funnel plot and statistical tests (Higgins et al., 2008). Statistical tests were performed using RevMan 5.4. A significance level of 5% was used to analyze the difference between the effect of planned dialysis and that of unplanned dialysis.

▢ Results

1. Systematic reviews on intervention

1) How do the safety and effectiveness of dialysis for elderly patients with CKD compare with those of conservative care?

A systematic review was performed to compare the safety and effectiveness of dialysis for elderly patients with CKD to those of conservative care.

Two studies examined the elderly aged ≥60 years, 5 examined those aged ≥65 years, 6 examined those aged ≥70 years, 7 examined those aged ≥75

years, and 80 examined those aged ≥80 years. The method of dialysis was hemodialysis in 3 studies, peritoneal dialysis in 1 study, and both in 17 studies.

1-, 2-, and 3-year survival rates were investigated in 14 studies that reported on overall survival rates. The 1-, 2-, and 3-year survival rates in the dialysis group were 85% (interquartile range (IQR) 70~96%), 73% (IQR 53~89%), and 58% (IQR 39~90%), respectively. The 1-, 2-, and 3-year survival rates in the conservative care group were 69% (IQR 29~83%), 43% (IQR 15~62%), and 25% (IQR 5~41%), respectively. The median survival time was 38 months (IQR 36~51 months) for the dialysis group and 20 months (IQR 14~27 months) for the conservative care group. The conservative care group had lower survival rates than the dialysis group at all time points and had lower survival time.

In a meta-analysis of mortality, the unadjusted HR of mortality for dialysis relative to conservative care was 0.43 (95% confidence interval (CI) 0.37-0.50, I^2=43%). In a subgroup analysis by the HRs of mortality, dialysis had significantly low mortality with low heterogeneity across the studies (HR 0.42, 95% CI 0.34~0.53, I^2=53%). The adjusted HR for dialysis was 0.44 (95% CI 0.32~0.60, I^2=82%). In a subgroup analysis by follow-up period, mortality was significantly low if the follow-up period was less than 3 years with low heterogeneity across the studies (HR 0.55, 95% CI 0.44~0.69, I^2=0%). In subgroup analyses by age cut-off, dialysis modality, publication year, center type (single/multi center), and 'comparability' from the RoBANS, the HR for mortality in the dialysis group relative to the conservative care group was less than 1 and was statistically significant. I^2 was 26% if the age cut-off was ≥70 years and 0% if patients received both hemodialysis and peritoneal dialysis; thus, these factors reduce the heterogeneity between the studies.

Seven studies reported on the quality of life using different assessment tools and reporting formats. A meta-analysis of the EQ-5D, SF-12 physical component score (PCS), and SF-12 mental component score (MCS), which are

quality-of-life assessment tools, showed a standard mean difference (SMD) of 0.28 (95% CI 0.09~0.47, I^2=25%) for SF-12 MCS. The dialysis group scored significantly high in the "symptom or problem list" and "effects of kidney disease" domains of the Kidney Disease Quality of Life (KDQoL), which is a disease-specific quality of life assessment tool. The conservative care group scored significantly low in the "burden of kidney disease" domain of the KDQoL.

Seven studies reported on the hospital days. Since the studies varied in their definitions of outcome variables and reporting formats, a meta-analysis was conducted on 3 studies for which synthesis was possible. No significant difference in the hospital days was found between the dialysis and conservative care groups (mean difference (MD) −0.03, 95% CI −0.95~0.89).

Three studies reported on hospitalization rates. Since the studies varied in their outcome variables and reporting formats, quantitative synthesis could not be performed. The hospitalization rate was significantly higher in the dialysis group during 6 months, but there was no difference between the two groups in the number of hospitalizations or the annual hospitalization rate per capita.

Three studies reported on disease-specific mortalities. A meta-analysis was performed after categorizing mortalities into infection-, cardiovascular disease-, and treatment termination-related mortalities. No significant differences were found for all four mortality categories.

One study reported on treatment satisfaction measured using the Renal Treatment Satisfaction Questionnaire (RTSQ). Satisfaction scores were 30.5, 31 and 32 for conservative care, hemodialysis groups and peritoneal dialysis, respectively; the peritoneal dialysis group had the highest satisfaction score, indicating that peritoneal dialysis achieves the highest treatment satisfaction.

2) How is the clinical safety and effectiveness of peritoneal dialysis compared to hemodialysis in elderly patients with CKD?

Thirty eight studies were selected for a systematic review conducted to

investigate the effects of peritoneal dialysis and hemodialysis on elderly patients with CKD. Seventeen studies included elderly patients only, and 21 included elderly and adult patients.

The median 1-, 3-, and 5-year survival rates and their IQRs in the peritoneal dialysis and hemodialysis groups were 78.8% (IQR 67.6~85.9%) and 77.2% (IQR 75.1~88.7%) for 1-year survival, 45.6% (IQR 36.3~60.0%) and 48.2% (IQR 45.1~57.9%) for 3-year survival, and 26.2% (IQR 20.7~41.9%) and 27.5% (IQR 25.7~37.0%) for 5-year survival, respectively. The median survival time (MST) was 30.7 months (IQR 23.0~33.9 months) for the peritoneal dialysis group and 32.5 months (IQR 27.3~39.3 months) for the hemodialysis group.

In a meta-analysis of mortality, the unadjusted and adjusted HRs of mortality for peritoneal dialysis relative to hemodialysis was 1.13 (n=14, 95% CI 1.05~1.22, I^2=33%) and 1.15 (n=20, 95% CI1.11~1.20, I^2=81%), respectively, indicating higher mortality for peritoneal dialysis. In a subgroup analysis by age cut-off for the elderly, diabetes, publication year, country of research, number of participating institutions, and "comparability" in the RoBANS, the HR of mortality for peritoneal dialysis relative to hemodialysis was greater than 1 and was statistically significant. I^2 for adjusted HRs was 53% for studies not including diabetic patients and 0% for those with a low risk of bias in the comparability domain of the RoBANS.

In case of disease-specific mortality, the relative risk (RR) of the peritoneal dialysis group compared to the hemodialysis group for cardiovascular disease was 1.63 (n=4, 95% CI 1.35~1.97, I^2=0%), and for infection 2.09 (n=4, 95% CI 1.38~3.17, I^2=0%). For cancer, the RR of the peritoneal dialysis group compared to the hemodialysis group was 0.91 (n=3, 95% CI 0.52~1.60, I^2=0%), which was not statistically significant.

As a result of meta-analysis of RR for hospitalization in the peritoneal dialysis group compared to the hemodialysis group, there was no statistically significant difference between the two groups (n=2, RR=1.09, 95% CI 1.00~1.19, I^2=23%).

No significant differences were found between peritoneal dialysis and hemodialysis in the studies reporting on the quality of life, indicators of improvement in daily life, nutritional status, and treatment satisfaction. No study reported on sarcopenia and the number of visits to an emergency room.

2. Systematic review on prognosis

1) Significant prognostic factors of survival in elderly patients with CKD on unplanned dialysis

Three observational studies (n=823) were reviewed to investigate the significant prognostic factors of survival in elderly patients with CKD on unplanned dialysis. One study was conducted on the elderly aged ≥65 years, and 2 on both adults and the elderly. The factors significantly affecting the survival of patients on unplanned dialysis in the three studies were age, blood potassium levels, dialysis type, and undergoing AVF surgery following the dialysis The risk of death was significantly lower with increasing age (n=2) or in the older age group (n=1) (HR 0.11, 95% CI 0.03~0.38). Mortality significantly decreased as blood potassium levels increased for patients with hypokalemia (HR 0.678, 95% CI 0.487~0.970, p=0.032) and was significantly low in patients who received AVF surgery after unplanned dialysis (HR 0.11, 95% CI 0.03~0.38). Results according to the modality of dialysis were not consistent between the two studies. One study reported a higher risk of death for unplanned hemodialysis compared to unplanned peritoneal dialysis (HR 2.220, 95% CI 1.298~2.790, p=0.004), and no difference was reported in the other study.

No study examined patients of advanced age. One study on the diabetic elderly (Zang, 2020) identified blood albumin and potassium levels and receiving unplanned hemodialysis rather than unplanned peritoneal dialysis as prognostic factors significantly affecting survival. As blood albumin (HR 0.926, 95% CI 0.861~1.000, p=0.049) and potassium levels (HR 0.258, 95% CI 0.126~0.538, p<0.001) increased, mortality significantly decreased. Mortality was

significantly higher among patients who were on unplanned hemodialysis than those on unplanned peritoneal dialysis (HR 2.813, 95% CI 1.092~7.330, p=0.033)

2) How does mortality compare between planned dialysis and unplanned dialysis in elderly patients with CKD?

Twelve observational studies (n=13,268) were reviewed to investigate the difference between the effect of unplanned dialysis and that of planned dialysis on elderly patients with CKD. Nine studies were on elderly patients (≥60 years), and 3 on elderly and adult patients. Of these, 2 were on patients of advanced age (≥80 years).

In a meta-analysis of mortality based on univariate analysis results on short-term survival (<1 year), mortality was 2.49 times higher for unplanned dialysis than planned dialysis (n=3, HR 2.49, 95% CI 2.11~2.94, I^2=0%). In an analysis of studies on elderly patients only, mortality was 2.29 times (n=1, 95% CI 1.09~4.81) higher for unplanned dialysis than planned dialysis. For patients of advanced age, mortality was 2.55 times higher (n=1, 95% CI 1.16~5.61) for unplanned dialysis than planned dialysis. However, after combining the results of multivariate analyses, the difference in mortality between the two groups was no longer found (HR 1.51, 95% CI 0.74~3.08, I^2=58%). In an analysis of studies on patients of advanced age, mortality was 3.98 times higher for unplanned dialysis than planned dialysis; this difference in mortality was higher than the one based on the combined univariate analysis results (n=1, 95% CI 1.18~13.42).

Based on the combined results of univariate analyses, overall mortality (≥1 year) was 2.06 times higher for unplanned dialysis than planned dialysis; however, high heterogeneity was found among the studies (n=7, HR 2.06, 95% CI 1.53~2.76, I^2=75%). Heterogeneity was reduced through a subgroup analysis by country of research (Asia HR 3.59, 95% CI 2.16~5.97, I^2=48%; Non-Asia HR 1.50, 95% CI 1.35~1.68, I^2=0%). In subgroup and sensitivity analyses, mortality was 2.84 times higher for patients with unplanned dialysis in studies with one-year follow-up (I^2=39%), 1.52 times higher in studies using registries (I^2=16%), and 2.84 times higher in studies on patients of

advanced age (I^2=39%) with insignificant heterogeneity across the studies. After combining the results of multivariate analyses of ≥1-year mortality, mortality was 1.98 times higher for patients on unplanned dialysis than those on planned dialysis, but the heterogeneity among the studies remained high (n=5, HR 1.98, 95% CI 1.25~3.12, I^2=78%). Heterogeneity was resolved via subgroup analysis by country of research (Asian countries HR 3.10, 95% CI 1.76~5.45, I^2=48%; Non-Asian countries HR 1.30, 95% CI 0.97~1.75, I^2=45%) and confounding variables (HR 3.10, 95% CI 1.76~5.45, I^2=48% for (<5 confounding variables; HR 1.30, 95% CI 0.97~1.75, I^2=45% for ≥5 confounding variables). In one study on patients of advanced age, mortality was significantly higher for patients on unplanned hemodialysis (HR 3.19, 95% CI 1.51~6.74).

▢ Conclusions

This study examined the clinical effect of dialysis and the factors influencing the prognosis of unplanned dialysis in elderly patients with CKD through a systematic review.

In elderly patients with chronic kidney disease, dialysis group showed better survival benefits than conservative care. We confirmed that overall quality of life or symptom improvement in CKD may be better in dialysis group. In the comparison of peritoneal dialysis and hemodialysis in elderly patients with CKD, mortality was higher for patients on peritoneal dialysis. Therefore, well-designed studies are needed to produce more evidence for dialysis.

It was confirmed that the mortality was significantly increased when receiving unplanned dialysis treatment compared to planned dialysis treatment in elderly patients with chronic kidney disease. The factors significantly affecting the survival of patients on unplanned dialysis in the three studies were age, blood potassium levels, dialysis type, and undergoing AVF surgery following the dialysis

Overall, evidence is insufficient and many methodological limitations of the study have been identified. High-quality observational studies of elderly chronic kidney disease patients in Korea or long-term follow-up on a large scale require the clinically meaningful outcomes such as cognitive, functional, and nutritional status.

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Key words

Systematic review, Elderly, Chronic renal failure, Dialysis, Prognosis