Comparative Survival among Older Adults with Advanced Kidney Disease Managed Conservatively Versus with Dialysis

Wouter R. Verberne, A.B.M. Tom Geers,* Wilbert T. Jellema,* Hieronymus H. Vincent,* Johannes J.M. van Delden,† and Willem Jan W. Bos**

Abstract

Background and objectives Outcomes of older patients with ESRD undergoing RRT or conservative management (CM) are uncertain. Adequate survival data, specifically of older patients, are needed for proper counseling. We compared survival of older renal patients choosing either CM or RRT.

Design, setting, participants, & measurements A retrospective survival analysis was performed of a single-center cohort in a nonacademic teaching hospital in The Netherlands from 2004 to 2014. Patients with ESRD ages ≥70 years old at the time that they opted for CM or RRT were included. Patients with acute on chronic renal failure needing immediate start of dialysis were excluded.

Results In total, 107 patients chose CM, and 204 chose RRT. Patients choosing CM were older (mean±SD: 83±4.5 versus 76±4.4 years; $P<0.001$). The Davies comorbidity scores did not differ significantly between both groups. Median survival of those choosing RRT was higher than those choosing CM from time of modality choice (median; 75th to 25th percentiles: 3.1, 1.5–6.9 versus 1.5, 0.7–3.0 years; log-rank test: $P<0.001$) and all other starting points ($P<0.001$ in all patients). However, the survival advantage of patients choosing RRT was no longer observed in patients ages ≥80 years old (median; 75th to 25th percentiles: 2.1, 1.5–3.4 versus 1.4, 0.7–3.0 years; log-rank test: $P=0.08$). The survival advantage was also substantially reduced in patients ages ≥70 years old with Davies comorbidity scores of ≥3, particularly with cardiovascular comorbidity, although the RRT group maintained its survival advantage at the 5% significance level (median; 75th to 25th percentiles: 1.8, 0.7–4.1 versus 1.0, 0.6–1.4 years; log-rank test: $P=0.02$).

Conclusions In this single–center observational study, there was no statistically significant survival advantage among patients ages ≥80 years old choosing RRT over CM. Comorbidity was associated with a lower survival advantage. This provides important information for decision making in older patients with ESRD. CM could be a reasonable alternative to RRT in selected patients.

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*Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands; and †University Medical Center Utrecht, Julius Center for Health Sciences, Utrecht, The Netherlands

Correspondence: Dr. Wouter R. Verberne, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands. Email: w.verberne@antoniusziekenhuis.nl

Introduction

The number of older patients with ESRD is increasing worldwide (1–3). Contributing factors are aging of the population, increasing prevalence of diabetes mellitus and hypertension, and earlier recognition and referral for ESRD (3,4). Nowadays, one half or more of all patients on dialysis are ages ≥65 years old in countries like The Netherlands (5), the United Kingdom (2), and the United States (6).

It has been questioned whether older patients with ESRD, who often have multiple comorbidities (4,7), are likely to benefit from RRT. Patients with an anticipated poor prognosis on RRT may choose to forego dialysis and decide to be treated conservatively instead. Conservative management (CM) entails ongoing care with full medical treatment, including control of fluid and electrolyte balance and correcting anemia, and provision of appropriate palliative and end of life care.

Shared decision making has been recommended to come to a joint decision on RRT by considering potential benefits and harms of all treatment options and the patient's preferences (8). Data on outcomes, including survival and quality of life, are needed to foster the decision making. However, adequate survival data, specifically on older patients, are limited. A number of studies, predominantly from the United Kingdom, has determined survival of older patients managed conservatively compared with RRT (9–17). In these studies, the numbers of recruited patients are generally small, the studies are performed in heterogeneous study populations, and there is significant variability in starting points used in survival analyses (18). We performed the first Dutch study in a large series of older patients slowly approaching ESRD, enabling the use of several starting points in survival analyses. The aims of the study were to compare

survival in patients with ESRD ages ≥70 years old choosing either CM or RRT and determine predictors of survival.

Materials and Methods

Patient Selection

We performed a single–center retrospective cohort study in a nonprofit, nonacademic teaching hospital in The Netherlands. Clinical databases were searched for all patients with advanced CKD receiving nephrology care during the last 10 years (October 31, 2004 to October 31, 2014). Patients who had chosen either CM or RRT and were age ≥70 years old at the time that they opted for CM or RRT were included. Because the decision process usually takes place over several weeks or even longer, inclusion was on the basis of the recording note of the decision in the electronic medical records. Patients with acute or acute on chronic renal failure needing immediate start of dialysis were excluded. The study was approved by the local research ethics committee.

Decision-Making Process

Decision making on RRT was started when the eGFR fell to <20 ml/min per 1.73 m^2. There was in-depth discussion between patient and nephrologist, during which oral and/or written information was given about practicalities, benefits, and risks of RRT and CM. If preferred, patients got additional counseling provided by a specialist nurse and social worker, including a visit to the patient's home. Patients were designated as CM if they chose to forego dialysis should their kidney failure progress. Full medical treatment and multidisciplinary care, including specialist nurses, dieticians, and social workers, were continued for patients on CM. Patients were designated as patients on RRT if they made the decision to start hemodialysis (HD) or peritoneal dialysis or decided to undergo renal transplantation (censored in survival analysis at the date of transplantation). Patients were also designated as patients on RRT if they chose to commence dialysis but died before initiation or dialysis had not been started yet at the end of the study. Analyses were performed according to the original treatment choice.

Data

Data on age, sex, primary renal diagnosis, and comorbidity were collected from electronic medical records on all patients at the time of modality decision. Primary renal diagnosis was classified according to the codes of the European Renal Association–Dialysis and Transplantation Association. Comorbidity was scored according to the comorbidity score by Davies *et al.* (19). The Davies comorbidity score is based on the presence of seven comorbid conditions: ischemic heart disease (defined as prior myocardial infarction, angina pectoris, or ischemic changes on electrocardiograph), left ventricular dysfunction (defined as clinical evidence of pulmonary edema not caused by errors in fluid balance), peripheral vascular disease (including distal aortic, lower extremity, and cerebrovascular diseases), malignancy, diabetes mellitus, systemic collagen vascular disease, and other significant disorder (*e.g.*, chronic obstructive pulmonary disease). The score assigns one point for each present condition and produces three groups: no comorbidity (Davies score =0), intermediate comorbidity (Davies score =1–2), and severe comorbidity (Davies score ≥3). An additional composite variable on cardiovascular comorbidity (CVC) was formulated and defined as positive if one or more of the individual cardiovascular comorbid factors used in the Davies comorbidity score were present (*i.e.*, ischemic heart disease, left ventricular dysfunction, and peripheral vascular disease).

We identified date and eGFR calculated with the four–point Modification of Diet in Renal Disease formula at the time of modality choice and the times of the first eGFRs<20, <15, and <10 ml/min per 1.73 m^2. To determine and compare the rate of decline in eGFR, time from the first eGFR<20 ml/min per 1.73 m^2 to the first eGFR <15 ml/min per 1.73 m^2 was calculated. The rate of decline of eGFR was dichotomized about the mean to designate patients as slow or rapid decliners. Date of death was recorded for those who had died before the study end point (*i.e.*, November 1, 2014). This was verified in the municipal personal records database.

Statistical Analyses

Descriptive statistics were performed on both treatment groups. Differences between the two groups were tested using the unpaired *t*, chi-squared, or Mann–Whitney *U* test as appropriate. Survival analysis was performed using the Kaplan–Meier method, with assessment of differences using the log-rank test. Survival was calculated from different starting points: from the time when the treatment decision between CM and RRT was made and from the times when eGFRs were first <20, <15, and <10 ml/min per 1.73 m^2. Time of modality choice was used as the main starting point. Cox proportional hazards regression models were used to determine independent predictors of survival. First, univariate analysis was performed between each single variable and survival as a dependent variable using age, sex, primary renal diagnosis, Davies comorbidity score, eGFR at modality choice, and treatment modality in turn. Second, Cox multiple regression analysis was carried out using the statistically significant variables found in univariate analysis. A P value <0.05 was considered statistically significant. IBM SPSS Statistics version 22 (IBM SPSS, Chicago, IL) was used for all statistical analyses.

Results

Patients

In total, 311 patients were included:107 patients chose CM, and 204 patients chose RRT (Figure 1). There were 12 patients who initially opted for RRT but changed to CM and two patients who changed their decision *vice versa*. The main reasons for changing to CM were deterioration of clinical condition (n=6) and change in personal preference (n=5). The two patients who changed to RRT did so because of physical complaints after a sudden decline in renal function. From the patients who chose RRT (n=204), 40% (n=82) did not actually receive RRT during the study period, because either they died before initiation of dialysis (n=31) or dialysis had not been started yet at the end of the study (n=51). From those who started with RRT (n=122), 79% (n=96) started on HD, and 21% started on

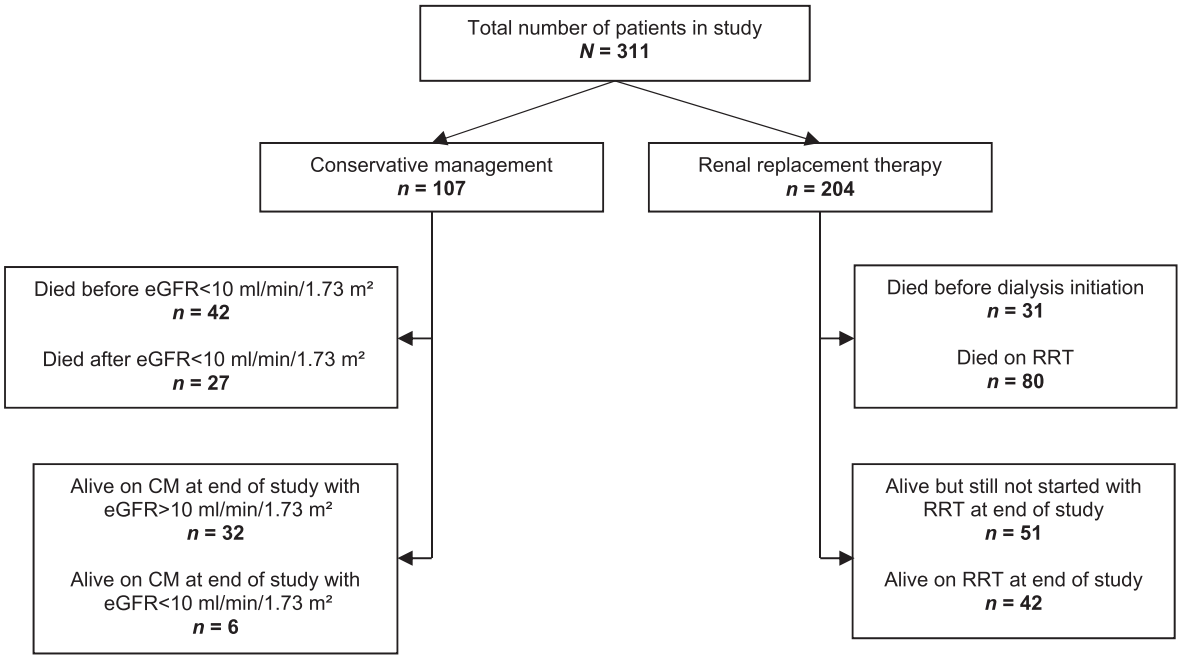

Figure 1. | **Flowchart of patients and outcomes.** Twelve patients who initially opted for RRT changed to conservative management (CM), and two patients who initially opted for CM changed to RRT. Analyses were performed according to the original treatment choice.

peritoneal dialysis (n=26). Four patients underwent renal transplantation, three of them after having started dialysis. Some were referred with an eGFR<20 ml/min per 1.73 m^2, and therefore, the numbers at this starting point were smaller (93 CM and 196 RRT). Also, several patients died before their eGFR fell to <15 or <10 ml/min per 1.73 m^2, resulting in 73 patients choosing CM and 167 patients choosing RRT at the first mentioned starting point and 33 patients choosing CM and 116 patients choosing RRT at the second point. Over the last years, a threefold increase was

Table 1. Baseline characteristics at the time when treatment decision between conservative management and RRT was made

Clinical Characteristics	CM Group No. (%) or Mean (SD), n=107	RRT Group No. (%) or Mean (SD), n=204	P Value
Age, yr	82.5 (4.5)	75.9 (4.4)	<0.001
Age ≥80 yr old	79 (74%)	40 (20%)	<0.001
Sex (men)	59 (55%)	135 (66%)	0.06
Davies comorbidity score			0.46
No comorbidity, score 0	9 (8%)	24 (12%)	
Intermediate comorbidity, scores 1–2	62 (58%)	123 (60%)	
Severe comorbidity, score ≥3	36 (34%)	57 (28%)	
Cardiovascular comorbidity	82 (77%)	148 (73%)	0.44
eGFR at time of decision, ml/min per 1.73 m^2	15.3 (5.0)	13.1 (4.3)	<0.001
Median time of decline in eGFR from <20 to <15 ml/min per 1.73 m^2, d (IQR)	190.0 (511.4; n=73)	226.0 (398.1; n=167)	0.57
eGFR at start of dialysis, ml/min per 1.73 m^2		8.3 (2.8; n=122)	
Primary renal diagnoses			0.25
Renal vascular disease	50 (47%)	70 (34%)	
Diabetes mellitus	16 (15%)	35 (17%)	
Hypertension	6 (6%)	17 (8%)	
Pyelonephritis	4 (4%)	5 (3%)	
Polycystic kidneys	1 (1%)	6 (3%)	
GN	0 (0%)	5 (3%)	
Cause unknown	25 (23%)	50 (25%)	
Other	5 (5%)	16 (8%)	

CM, conservative management; IQR, interquartile range.

observed in the number of patients choosing CM (five in 2005 and 16 in 2013), whereas the number of patients choosing RRT increased modestly (13 in 2005 and 20 in 2013).

Demographic data are presented in Table 1. Patients choosing CM were significantly older than those choosing RRT (mean±SD: 82.5±4.5 versus 75.9±4.4 years; $P<0.001$), and they had higher eGFRs at the time of modality choice (mean±SD: 15.3±5.0 versus 13.1±4.3 ml/min per 1.73 m^2; $P<0.001$). However, both patient groups did not differ significantly in terms of sex, primary renal diagnosis, Davies comorbidity scores, CVC, and rate of decline in eGFR. Ethnicity was predominantly white.

Survival Analyses

In total, 180 patients died during follow-up: 69 patients choosing CM and 111 patients choosing RRT ($P=0.09$) (Figure 1). The overall median survival of patients with ESRD ages ≥70 years old choosing RRT was higher compared with patients choosing CM from all four starting points: the time of modality choice (median, 75th to 25th percentiles: 3.1, 1.5–6.9 versus 1.5, 0.7–3.0 years; $P<0.001$), the time of first eGFR<20 ml/min per 1.73 m^2 (4.5 versus 2.4 years; $P<0.001$), the time of first eGFR<15 ml/min per 1.73 m^2 (3.1 versus 1.5 years; $P<0.001$), and the time of first eGFR<10 ml/min per 1.73 m^2 (2.8 versus 0.5 years; $P<0.001$) (Figure 2).

In patients ages ≥80 years old, there was no longer a statistically significant survival advantage of choosing RRT (median, 75th to 25th percentiles: 2.1, 1.5–3.4 versus 1.4, 0.7–3.0 years; $P=0.08$) (Figure 3). This was found in all survival analyses using different starting points.

The survival advantage of the RRT group was also substantially reduced in patients ages ≥70 years old with Davies comorbidity scores of ≥3, corresponding with severe comorbidity, although RRT maintained its advantage at the 5% significance level (median, 75th to 25th percentiles: 1.8, 0.7–4.1 versus 1.0, 0.6–1.4 years; $P=0.02$) (Figure 4). Similar results were found in survival analyses using different starting points (data not shown).

The presence of CVC substantially, although not significantly, reduced the survival advantage of patients choosing RRT over CM (without CVC: 7.3 versus 1.9 years; $P<0.001$; with CVC: 2.3 versus 1.5 years; $P=0.003$) (Supplemental Figure 1). Use of different starting points showed similar results (data not shown). Only patients choosing RRT had a significant lower median survival if CVC was present (2.3 versus 7.3 years; $P<0.001$) (Supplemental Figure 2). Such survival differences were not observed within the CM group (1.5 versus 1.9 years; $P=0.66$).

Considering the rate of decline in eGFR, the survival advantage of those choosing RRT over CM was observed in patient groups with both rapid and slow eGFR declines at

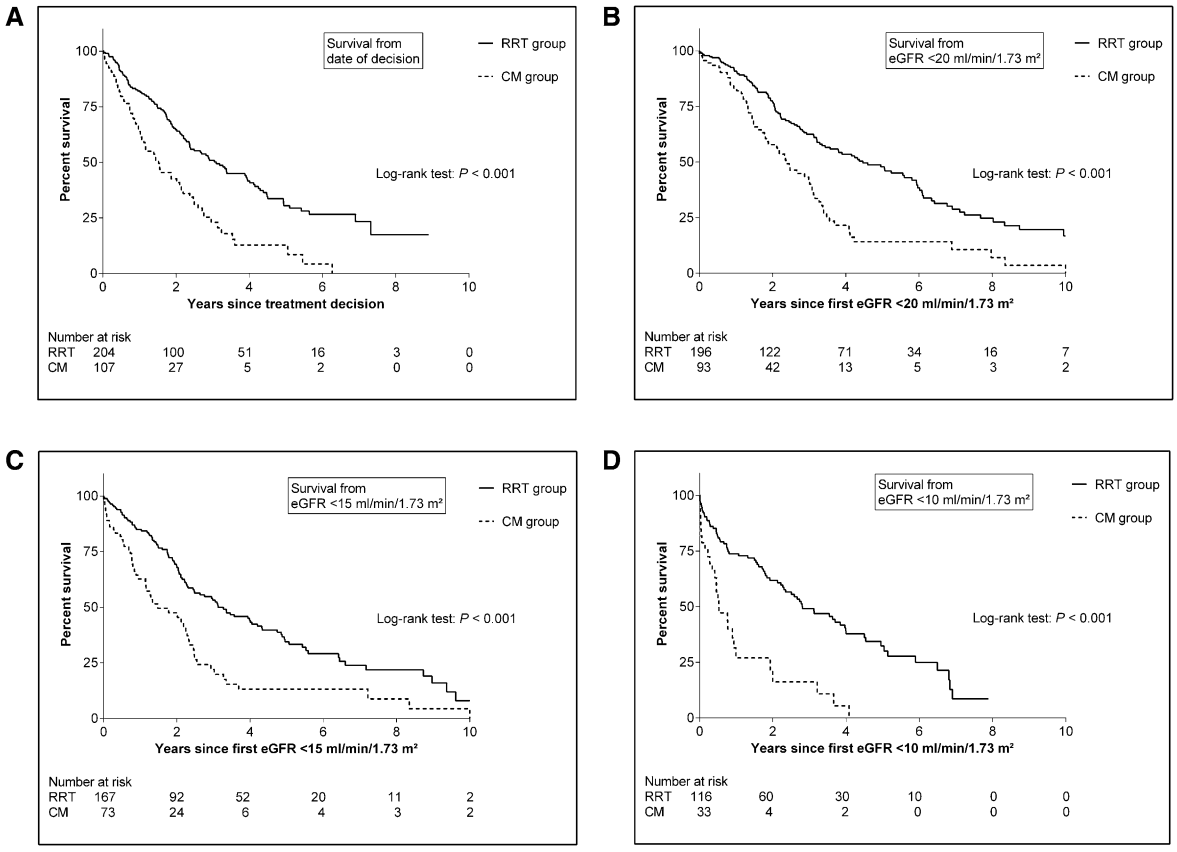

Figure 2. | Kaplan–Meier survival curves comparing patients ages ≥70 years old treated with conservative management (CM) with patients on RRT using different starting points in survival calculation. (A) Time of treatment decision. (B) Time of first eGFR<20 ml/min per 1.73 m^2. (C) Time of first eGFR<15 ml/min per 1.73 m^2. (D) Time of first eGFR<10 ml/min per 1.73 m^2.

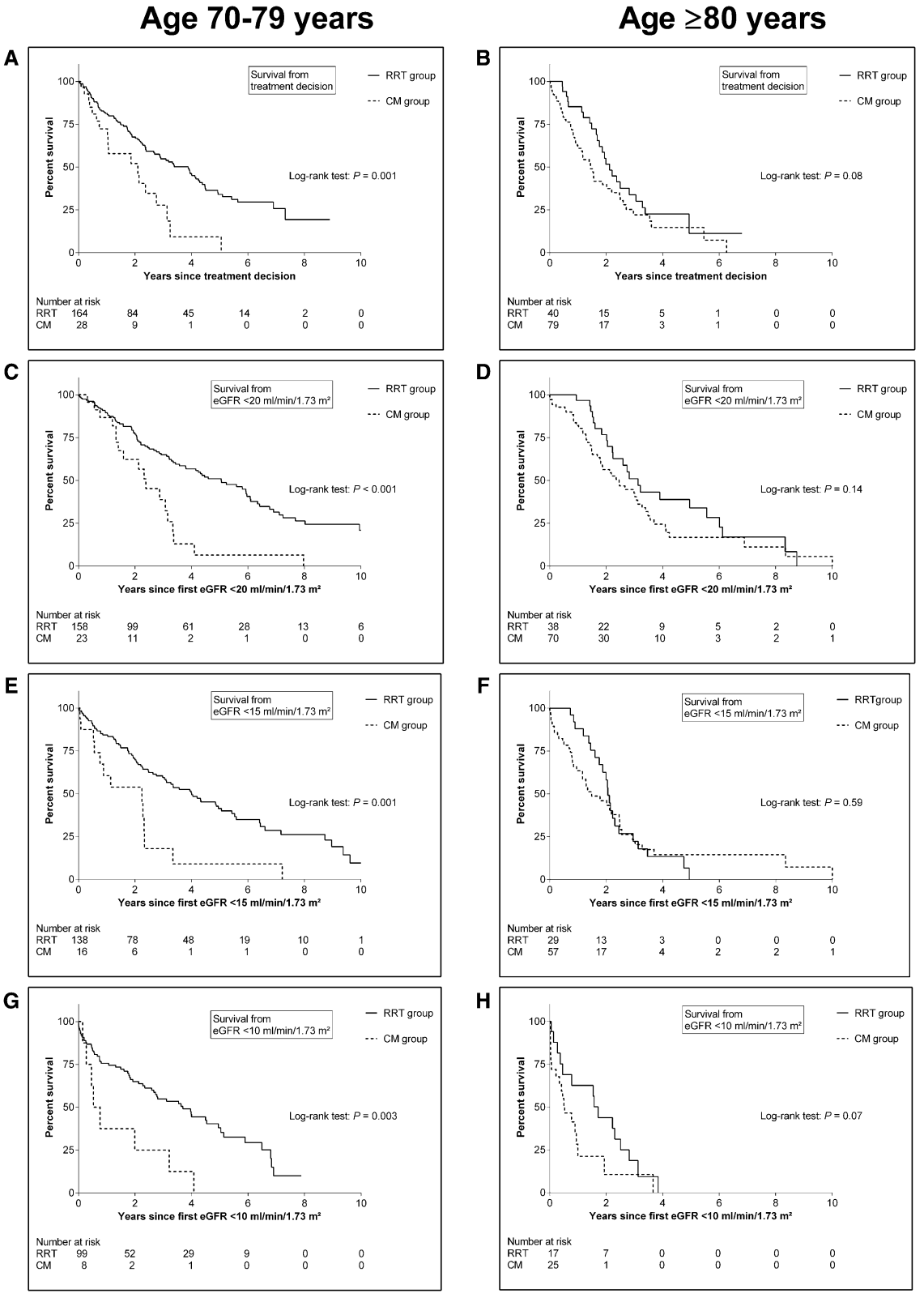

Figure 3. | Kaplan–Meier survival curves comparing both treatment groups with stratification of age using different starting points in survival calculation. (A and B) Time of treatment decision. (C and D) Time of first eGFR<20 ml/min per 1.73 m^2. (E and F) Time of first eGFR<15 ml/min per 1.73 m^2. (G and H) Time of first eGFR<10 ml/min per 1.73 m^2. CM, conservative management.

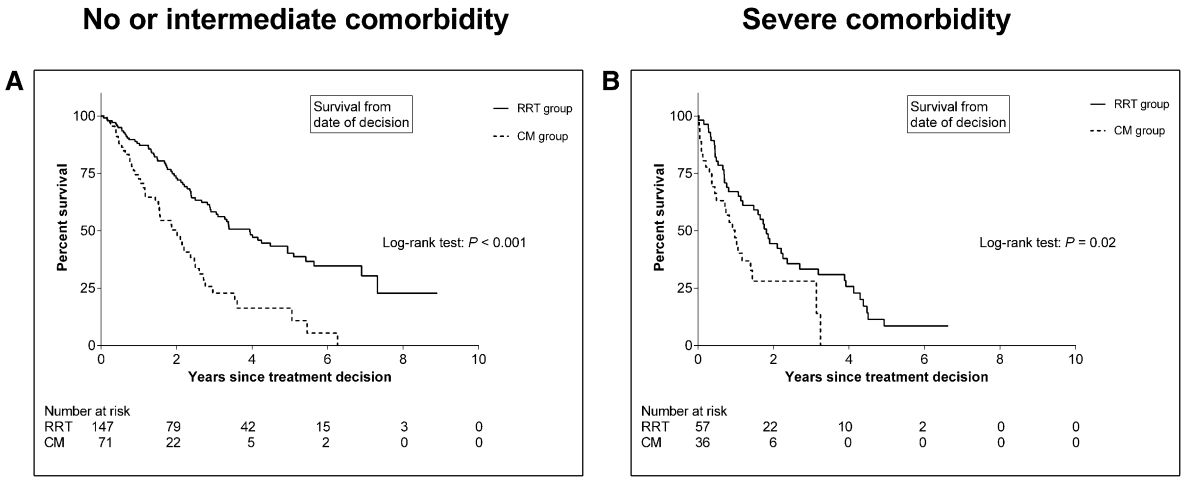

Figure 4. | Kaplan–Meier survival curves for both treatment groups ages ≥70 years old with stratification of comorbidity. (A) No and intermediate comorbidity are taken together and correspond to Davies comorbidity scores of 0–2. (B) Severe comorbidity corresponds to Davies comorbidity scores of ≥3. Only survival calculated from time of modality choice is shown. Similar results were observed using the other starting points. CM, conservative management.

ages ≥70 years old (rapid eGFR decline: 2.6 versus 1.9 years; P=0.01; slow eGFR decline: 6.0 versus 3.4 years; P<0.001).

In univariate Cox regression analysis with survival measured from modality choice, the following variables were identified as significant predictors of survival: age, Davies comorbidity score, and treatment modality. No association with survival was observed for the variables sex, eGFR at modality choice, and primary renal diagnosis. In a multivariate regression model, the variables age, Davies comorbidity score, and treatment modality were entered. All were independent predictors of survival (Table 2). Choice of RRT was associated with lower mortality (0.6-fold; 95% confidence interval, 0.42-fold to 0.92-fold). Older age and presence of intermediate (1.9-fold; 95% confidence interval, 1.0-fold to 3.5-fold) and severe comorbidity (4.1-fold; 95% confidence interval, 2.2-fold to 7.9-fold) were associated with higher mortality, regardless of treatment modality.

Discussion

In this cohort study of older patients with ESRD, including the second largest CM group reported so far, we found that patients ages ≥70 years old choosing RRT had better survival compared with patients choosing CM. However, this survival advantage was lost in patients ages ≥80 years old. We also observed a considerable negative effect of comorbidity on survival, particularly of CVC. These results indicate that CM could be a valid treatment option in selected patients.

Our findings are consistent with results from previous studies and are a validation in a first Dutch cohort, although comparison is hampered by use of different starting points in survival calculation and heterogeneous study populations. The most frequently used starting point is the time of first eGFR<15 ml/min per 1.73 m^2, indicating entry into ESRD (9,11,13,15,17,18,20). Median survival of patients on CM from this point ranges from 13 (9) to 28.2 months (17). We found a median survival of patients on CM of 17.8 months. Another frequently used starting point is the time of modality choice or dialysis assessment (9,12,14,21,22). The reported median survival of patients on CM ranged from 8.9 (14) to 41.3 months (21). We found a median survival of 18.2 months in patients on CM, which is comparable with the results in the works by Brown *et al.* (9) and Wong *et al.* (22), which found median survival rates of 19 and 23.4 months, respectively, in compatible patient groups regarding age and eGFR. The wide range can be explained by the lack of a consistent definition of the starting point and patient differences

Table 2. Multivariate Cox proportional hazards model for survival in 311 patients ages ≥70 years old (107 patients with conservative management and 204 patients with RRT) using the time of modality choice as the starting point in survival calculation

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Age, yr	1.05	1.01 to 1.08	0.01
Davies comorbidity score (no comorbidity as reference)			<0.001
Intermediate comorbidity	1.89	1.01 to 3.52	
Severe comorbidity	4.11	2.15 to 7.85	
Treatment modality (CM versus RRT; CM as reference)	0.62	0.42 to 0.92	0.02

CM, conservative management.

between studies. A definition is difficult, because the decision-making process usually takes place over several weeks or even longer. We defined this as the time when the treatment modality was chosen and recorded in the electronic medical record. However, we actually found a significant difference in eGFR at the time of decision between the RRT and CM groups, indicating bias. The reason for this is unclear.

Considering comparison of survival between patients on CM and patients on RRT, Brown *et al.* (9) performed the largest prospective cohort study reported so far, analyzing survival of 122 patients choosing CM and 273 patients choosing RRT. Brown *et al.* (9) observed no significant survival advantage of choosing RRT in patients ages >75 years old with two or more comorbidities, although the number of these patients was small. We found similar results in a larger number of patients ages ≥70 years old but fewer differences between both treatment groups with regards to age and comorbidity. Hussain *et al.* (13) showed in the largest retrospective analyses reported so far that the survival advantage of choosing RRT was lost in patients ages >80 years old and patients ages >70 years old with poor performance status and substantially reduced in patients ages >70 years old with high comorbidity. Chandna *et al.* (11) and Murtagh *et al.* (15) both found no survival advantage of choosing RRT over CM in patients >75 years old with high comorbidity scored with a self–designed comorbidity score and the Davies comorbidity score, respectively. The major contribution of our study is the validation of these previous results, predominantly from the United Kingdom, in a large Dutch population, confirming that high age and comorbidity offset the survival advantage of patients choosing RRT over CM; this is the case from several different levels of disease severity.

Another factor associated with survival is CVC. Murtagh *et al.* (15) also found ischemic heart disease as a predictor of survival, with loss of the survival advantage of the RRT group when ischemic heart disease was present. We still observed a significant survival benefit in patients with CVC choosing RRT, although the lower mortality among the RRT group was less pronounced in patients without CVC. Interestingly, we did not observe an association of CVC with survival in the CM group. Possibly, dialysis treatment rather than uremia itself unveils the negative effect of CVC on survival. Eckardt *et al.* (23) recently showed a high incidence of cardiovascular events in the first weeks after HD initiation.

A limitation of our study is that adjustment for all confounders was not possible, because of its observational and retrospective nature. The two patient groups choosing CM or RRT were comparable on most demographic data, except that patients choosing CM were older. We were able to adjust for age and comorbidity in survival analyses, but it is likely that other confounders were missing. For example, we did not collect data on frailty, performance status, malnutrition, and cognitive impairment. This could have altered the survival differences. Another concern is the almost uniformly white population in our study, limiting the generalizability. Also, such as in other studies, patients with acute on chronic kidney failure needing immediate start of RRT were excluded. Studies comparing outcomes of this patient category are needed.

Another important consideration is that the found survival differences are not exclusively the result of received treatment but rather are associated with being in the group who chose RRT or CM. For example, a major part of mortality is observed in both groups before eGFR<10 ml/min per 1.73 m^2 is reached or before dialysis has been initiated. The selection of the group could explain the survival differences with a younger and likely fitter RRT group, although we found equivalence in the Davies comorbidity score. Additional research with larger patient groups or probably, a pooled analysis is needed to determine survival and directly compare CM with RRT using start of actual treatment as starting point. However, selection bias will be difficult to rule out in a cohort study because of preferential selection of patients for each pathway on the basis of the advice of their professional team. A randomized, controlled trial could probably solve these problems, but such a study design raises difficult ethical and practical dilemmas. It is clear, however, that future studies are needed to determine more precisely which patients are likely to benefit or not benefit from RRT. In our opinion, this is a mandatory first step before effective decision aids can be developed.

To predict survival of patients with ESRD choosing between CM or RRT, fluctuations in eGFR and individual differences in eGFR decline have to be taken into account. In our analyses, the survival advantage of the RRT group over the CM group was observed in patient groups with both rapid and slow eGFR declines. It would be interesting to study this in more detail, questioning whether patients who are rapid decliners are more likely to benefit from RRT, to gain more insight into individual differences in eGFR decline.

Our study provides important information for decision making in older patients with ESRD choosing either CM or RRT. Shared decision making has been recommended to come to a joint decision on RRT (8). Our findings contribute to the understanding of survival in older patients with ESRD, which could improve counseling. CM could be a reasonable alternative to RRT in selected patients. More work needs to be done to determine survival and other outcome data, like quality of life, that are needed to truly foster decision making.

Disclosures

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