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How late referral impacts CKD

HOW DOES LATE NEPHROLOGICAL CO-MANAGEMENT IMPACT CHRONIC KIDNEY DISEASE? AN OBSERVATIONAL STUDY

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Running headline: How late referral impacts CKD

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ABSTRACT

Aims: To assess the impact of late referral for nephrological co-management (LR) compared to early referral (ER) on morbidity and mortality in chronic kidney disease (CKD), and to identify individual factors associated with higher mortality in LR, correcting for lead-time and immortal time bias.

Patients and Methods: Retrospective observational study comparing 46 LR with 103 ER patients. The quality of CKD management was assessed by measures to prevent CKD progression, and to modify CKD complications and cardiovascular risk factors according to current guidelines. One year mortality of LR and ER was compared and factors associated with mortality were identified. Analysis was performed with equivalent GFR of ER and LR at baseline to correct for lead-time and immortal time bias.

Results: LR was associated with inferior control of most risk factors for CKD progression, CKD complications, and cardiovascular risk factors. Especially, glycaemic control, the use of angiotensin converting enzyme inhibitors and angiotensin-2-receptor blockers in diabetic nephropathy or proteinuria, the control of nutritional and volume status were inferior in LR. One year mortality was significantly higher in LR (RR 5.9 (95% CI 1.5 – 19.6); $p < 0.01$). Inadequate control of blood pressure, anaemia, and volume status, malnutrition, and emergency initial dialysis but not LR itself were independently associated with mortality.

Conclusions: LR was associated with a substantially lower survival after correction for lead-time and immortal time bias, and with inferior control of most risk factors for CKD progression, complications, and cardiovascular risk factors. CKD patients may particularly profit from adequate control of blood pressure, anaemia, nutritional and volume status, and avoidance of emergency initial dialysis as these factors may predominately contribute to survival.

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Key Words: Chronic kidney disease - dialysis – end stage renal disease - late referral – mortality

WHAT'S KNOWN

Chronic kidney disease (CKD) is a major cause of morbidity and mortality. To be most beneficial, effective interventions to reduce morbidity and mortality associated with CKD need to be initiated as early as possible and in the setting of early nephrological co-management. Currently, late referral (LR) is still common in 30 – 40 % of all advanced CKD patients worldwide.

WHAT'S NEW

LR is associated with a substantially lower survival after correction for lead-time and immortal time bias. Of all factors associated with LR, inadequate control of blood pressure, anaemia, nutritional and volume status, and emergency initial dialysis predominately impact one year mortality.

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INTRODUCTION

The high incidence and prevalence of chronic kidney disease (CKD) are an enormous and increasing worldwide public health problem (1, 2). CKD and associated complications, especially cardiovascular disease (CVD) have been identified as major causes of morbidity and mortality (1, 3, 4). Cardiovascular morbidity and mortality are particularly high in advanced CKD (3, 4). Furthermore, CKD may progress to end-stage renal disease (ESRD) which aggravates CVD (3). There are effective interventions to reduce the morbidity and mortality associated with CKD by delaying CKD progression, ameliorating comorbidity, and correcting cardiovascular risk factors (1, 5 – 10). These interventions should to be initiated as early as possible in the course of CKD to be most effective. In contrast, late and irregular referral to nephrologists for co-management (LR) was demonstrated to be deleterious in CKD and to increase morbidity and mortality compared to early referral (ER) (11 – 17). Currently, LR is still common in 30 – 40 % of all advanced CKD patients worldwide (11, 13 – 17).

In contrast to the wealth of studies demonstrating the contribution of ER on outcome in CKD, there is limited data which components of LR actually exert its deleterious effects and impact mortality. Focussing on these individual deleterious factors in the complexity of LR may be more efficient to improve care and outcomes in CKD. Of note, virtually all previous studies reporting a disadvantage of LR have not addressed the effects of lead-time and immortal time bias (11, 13 – 18). Lead-time is the interval between the start and the endpoint of a study. Conclusions from a study may be incorrect if patients are entered at different disease stages. Any perceived higher endpoint rate may simply be due to later inclusion time points of patients, that is, by recording a shorter lead-time. In the context of this study, lead-bias bias refers to the perceived differences in mortality and morbidity over time when comparing cohorts at different CKD stages instead of

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investigating outcome in all cohorts from a similar GFR (19). Immortal time again is the time a patient is guaranteed to be alive between the patient's study entry and exposure to a treatment. Immortal time bias is called the perceived survival benefit originating from the time between study entry and treatment when patients are included who received ER (20). The objectives of this study were, while correcting for lead-time and immortal time bias, (i) to further assess the impact of LR in comparison to ER on morbidity and mortality in patients with advanced CKD, and (ii) to identify individual factors associated with LR and its higher mortality.

PATIENTS AND METHODS

Patients

This is the longitudinal observational extension from 2003 to 2004 of a previous retrospective cohort study (21). We identified all 174 consecutive adult incident chronic dialysis patients from 7 nephrological centers. These centers serve a catchment area of approximately 950.000 inhabitants in the metropolitan Ruhr area of Germany. We excluded patients with acute renal failure (n = 7) and bilateral nephrectomy (n = 2) whose ESRD did not provide time for interventions, patients with renal transplant failure who returned to dialysis (n = 10), as they had been in nephrological care, and patients with inconclusive records (n = 6). This resulted in the inclusion of 149 patients of whom prior to referral for nephrological co-management, 89 patients were treated by general practitioners, 52 by general internal medicine specialists and 8 by physicians of other specialities. In all patients, health care was provided by the German statutory health

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3 insurances which permit open access to both primary care physicians and nephrologists,
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5 and cover the costs for diagnostics and therapy, apart from a small own contribution.

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8 Patients' characteristics, clinical and laboratory data, and medication were obtained from
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10 referring primary care physicians' and nephrologists' records.
11

12 13 14 15 **Definitions of variables and of targets to assess the quality of CKD management**

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17 LR was defined by an interval of less than 4 months, ER by an interval of at least 4 months
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19 from initiation of continuous nephrological co-management to initiation of chronic dialysis
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21 treatment with visits to the nephrologists at least every 12 weeks. As specific national
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23 guidelines for management of CKD and its complications are lacking, predominately
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25 recommendations of the Kidney Disease Outcomes Quality Initiative (KDOQI) are currently
26
27 acknowledged as recommendations in primary care and nephrology in Germany.
28
29 Consequently, CKD was defined and classified according to the stages proposed by
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31 KDOQI (5). Serum creatinine was measured with an enzymatic colorimetric assay (Crea
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33 Plus, Roche Diagnostics, Mannheim, Germany) and glomerular filtration rate (eGFR) was
34
35 estimated by the modified simplified equation of the Modification of Diet in Renal Disease
36
37 study (22). Global patients comorbidity was stratified according to the Khan index into low,
38
39 medium and high level (23). Blood pressure control in CKD stage IV was classified as
40
41 adequate below 135/85 mm Hg, especially in patients with diabetic nephropathy or
42
43 proteinuria above 1 g per day below 125/75 mm Hg. In CKD stage V, adequate blood
44
45 pressure control was defined below 140/90 mm Hg (5). To delay progression of CKD in
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47 patients with diabetic nephropathy or proteinuria above 1 g per day, the use of angiotensin
48
49 converting enzyme inhibitors (ACEI) and angiotensin-2-receptor blockers (ARBs) was
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51 considered appropriate (6). Adequate glycaemic control was achieved by a haemoglobin
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53 A_{1C} below 7%, and adequate anaemia control by haemoglobin levels above 110 g/L (6, 7).
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59
60 Bone disease was adequately controlled when at least 2 of the following 3 markers were

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3 within the target range: serum calcium from 2.10 to 2.37 mmol/L, serum phosphorus from
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5 0.87 to 1.48 mmol/L in CKD stage IV, and from 1.13 to 1.78 mmol/L in CKD stage V, and
6
7 plasma parathyroid hormone from 7.7 to 12.1 pmol/L in CKD stage IV, and from 16.5 to
8
9 33.0 pmol/L in CKD stage V (8). Good nutritional status was defined by serum albumin
10
11 above 35 g/L together with body mass index above 20 kg/m² (10). Serum potassium
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13 values below 5.6 mmol/L were considered adequate. Volume overload was defined by
14
15 clinical and radiological signs of peripheral and pulmonary oedema, otherwise it was
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17 considered adequate. Calcium-phosphorus product was adequately controlled by levels
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19 below 4.44 mmol²/L², and serum bicarbonate by levels at least 22 mmol/L (8, 9). CVD was
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21 defined by the presence of coronary heart disease (angina, myocardial infarction, coronary
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23 intervention), cerebrovascular accident (transient ischemic attack, stroke), peripheral
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25 arterial disease (claudication, ischemic gangrene, amputation) and/or congestive heart
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27 failure diagnosed by history, physical examination and the appropriate diagnostic tests.
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29 Low-density lipoprotein (LDL) cholesterol above 2.59 mmol/L was considered inadequate
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31 and an indication for hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (10).
32
33 Additionally, antiplatelet agents were considered adequate in atherosclerotic CVD. The
34
35 quality of delivered dialysis was assessed by the normalized urea clearance using the
36
37 single pool method (Kt/V), the rate of patients with Kt/V < 1.2, and in haemodialysis by the
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39 treatment time and blood flow rate. When available the mean of the respective values 3
40
41 and 6 months after initiation of dialysis were calculated, otherwise the values closest to 3
42
43 months after initiation of dialysis were taken. Causes of death were grouped as cardiac
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45 (arrhythmia, congestive heart failure, coronary heart disease), vascular (cerebrovascular
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47 accident, peripheral arterial disease), infectious (severe infection, sepsis) and malignancy.
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Data analysis

ER and LR cohorts were compared in regard to demographic and clinical characteristics, the management of potentially modifiable progression factors and complications of CKD, cardiovascular risk factors and one year survival. The time of comparison which was also the baseline for the one year survival analysis, was chosen by balancing LR and ER patients according to eGFR (Table 1). As both groups demonstrated similar eGFR levels, we successfully corrected for both lead-time and immortal time bias. At baseline, LR patients had been exclusively managed by primary care physicians except for a brief period of nephrological co-management of 1 ± 1 month. ER patients had been in nephrological co-management for 23 ± 17 months (LR vs. ER $P < 0.001$). To quantify the quality of care, we classified the rate of patients which achieved targets as the control of CKD progression factors, of CKD complications, and of cardiovascular risk factors according to a recent proposal: 90-100 % above standard, 75-89 % standard, 50-74 % sub-standard, 0-49 % poor, with adequate quality of care being standard or above standard (21). Data are expressed as mean \pm SD or percent. After testing for normal distribution, continuous data were compared by Student's t-test or Mann Whitney rank-sum test, categorical data by Chi square or Fisher's exact test. Comparison of one year survival was made by log rank test and expressed as Kaplan-Meier plots. Potential risk factors associated with one year mortality were coded as present or absent, and assessed by bivariate analysis. Variables with a $P < 0.10$ were included in the multivariate, logistic regression analysis. Two-sided $P < 0.05$ was considered to be statistically significant. The study was approved by the local institutional review board and informed consent was waived due to the retrospective nature of the study. The study protocol is in accordance with the Helsinki Declaration.

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RESULTS

One third of the patients in this study were referred late for nephrological co-management. LR and ER cohorts did not differ in regard to age, gender, rate of active smoking, primary renal disorders, or speciality of the primary care physician referring to nephrological co-management, as summarized in Table 1. In LR and ER, CKD was advanced and renal function at baseline balanced as demonstrated by serum creatinine, eGFR and CKD stages which did not differ between both groups (Table 1). CVD was present in the majority of patients in both groups. A higher percentage of LR patients demonstrated severe comorbidity according to the Khan index, compared to ER patients.

Potentially modifiable progression factors of CKD

Blood pressure was substantially higher in LR patients and control worse compared to ER patients. Blood pressure control was sub-standard in ER and poor in LR patients. LR patients with diabetic nephropathy displayed a fair mean HbA_{1c} value and glycaemic control was poor, in contrast to standard glycaemic control in ER patients (Tables 2 and 3). Only a minority of those LR patients received ACEI or ARBs, and therapeutic intervention for proteinuria scored poorly, which is also reflected by higher proteinuria in LR patients. This is in contrast to the overwhelming majority of ER patients with diabetic nephropathy or proteinuria above 1 g per day who received ACEI or ARBs with a treatment rating above standard.

Complications of CKD

In LR patients, mean haemoglobin level was substantially below the recommended 110 mg/L, and control of anaemia was categorized as poor (Tables 2 and 3). In comparison,

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3 haemoglobin levels in ER patients were markedly higher, target levels were achieved in
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5 the majority of patients, and anaemia control was rated sub-standard. Significantly more
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7 LR than ER patients demonstrated inadequate control of bone disease by serum calcium,
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9 serum phosphorus and parathyroid hormone. This scored poor in LR and sub-standard in
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11 ER. In LR, nutritional and volume status were sub-standard, whereas serum potassium
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13 was well controlled. In ER, nutritional status, volume status and serum potassium were
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15 well controlled. Control of metabolic acidosis was poor in LR and sub-standard in ER. C-
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17 reactive protein was significantly higher in LR patients, suggesting more microinflammation
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19 in this cohort.
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27 **Potentially modifiable risk factors of and interventions in atherosclerotic CVD**

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29 Besides the results for the cardiovascular risk factors blood pressure, glycaemic, anaemia
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31 and volume control, and microinflammation which are reported above, control of calcium –
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33 phosphorus product and LDL cholesterol, as well as administration of HMG-CoA
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35 reductase inhibitors were poor and administration of antiplatelet agents rated sub-standard
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37 in LR (Table 3). In ER, control of calcium – phosphorus product, administration of HMG-
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39 CoA reductase inhibitors and of antiplatelet agents rated sub-standard, and control of LDL
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41 cholesterol control was poor.
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49 **Dialysis therapy, length of stay in hospital, and mortality**

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51 In ER patients, dialysis was initiated at the time of comparison and in LR patients 1 ± 1
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53 month later. LR patients required more frequently emergency initial dialysis (43.5 vs. 7.8
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55 %, $P < 0.001$), and dialysis was less frequently started with a permanent access compared
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57 to ER patients (28.2 vs. 95.1 %, $P < 0.001$). Both aspects rated below average and poor
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59 respectively in LR, but above standard in ER. Peritoneal dialysis was less often the
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modality for chronic dialysis treatment in LR than in ER patients (2.2 vs. 7.8 %, $P = 0.28$). The quality of dialysis did not differ between LR and ER. There were neither statistical differences in Kt/V (1.33 ± 0.28 vs. 1.36 ± 0.31 ; $P = 0.51$), nor in rate of Kt/V < 1.2 (28.2 vs. 30.4 %; $P = 0.78$), haemodialysis treatment time (LR vs. ER; 4.2 ± 0.4 vs. 4.4 ± 0.5 h; $P = 0.09$) and blood flow rate (258 ± 36 vs. 266 ± 32 ml/min; $P = 0.28$). During the first year starting from the time of comparison, the total length of stay in hospital (LOS) in LR patients was 17.9 ± 9.3 days compared to 9.1 ± 5.6 days in ER patients ($P < 0.001$). One year mortality, starting from the time of comparison with equivalent eGFR, was significantly higher in LR than in ER patients (Fig. 1). The curves diverged almost immediately with deaths occurring in the LR groups predominately during the initial 6 months of observation. Thereafter the difference between the survival in LR and ER remained constant. There was a trend towards more deaths in LR compared to ER patients from cardiac (4 vs. 1 patients) and infectious diseases (3 vs. 0 patients), while death from malignancy (0 vs. 1 patients), and vascular disease (1 vs. 1 patients) did not differ ($P = 0.17$). Multivariate analysis identified inadequate control of blood pressure, anaemia, volume status, and malnutrition and emergency initial dialysis as independent factors associated with mortality during the first year (Table 4). LR itself was not an independent factor of one year mortality.

DISCUSSION

Our data indicate that after correcting for lead-time and immortal time bias, late nephrological co-management (LR) has a substantial, deleterious impact on morbidity and

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3 mortality in patients with advanced CKD. In comparison to early nephrological co-
4 management, LR is associated with inferior control of most risk factors for CKD
5 progression, complications of CKD, and risk factors of CVD. Furthermore, LR patients
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fared worse in respect to the rate of emergency initial dialysis, LOS and one year mortality, all corrected for lead-time and immortal time bias. Inadequate control of blood pressure, of anaemia and volume status, malnutrition, and emergency initial dialysis treatment but not LR itself were identified as factors independently associated with one-year mortality, and may be the major contributors to higher one-year mortality in LR.

In CKD patients, LR has been a universal problem, and its association with poor outcome has uniformly been demonstrated (11 – 17). Our cohort, which is representative for Germany, Europe and North America, demonstrated a considerable rate of LR which is of the same magnitude as previously reported (11, 12, 14, 16 - 18, 24, 25). This is a major cause of concern as the 30 to 40 % rate of LR has remained unchanged despite major efforts to reduce this rate during the last 20 years (11, 13 – 17).

With the exception of higher comorbidity in LR patients, the distribution of age, gender, rate of diabetic nephropathy or CVD did not differ between LR and ER in previous reports (4, 11, 14). This is in accordance to our data and demographic and clinical characteristics may have only moderately influenced LR and mortality. The few data available on the management of modifiable CKD progression factors demonstrated that blood pressure was better controlled, and ACEI or ARBs were more frequently administered in ER compared to LR (14, 26). However, in prior studies these CKD progression factors were generally managed rather inadequately in both ER and LR which contrasts our findings in ER. Previously, the management of complications associated with CKD was inferior in LR, which is similar to our results. In both ER and LR, control of bone disease, volume status and potassium matched that in our study, and control of nutritional status was slightly worse (4, 11, 14, 15, 17). In contrast to our data, anaemia and

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3 metabolic acidosis were generally sub-standard to poor and only marginally better
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5 controlled in ER (4, 11, 14, 15, 17). Risk factors of and interventions in atherosclerotic
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7 CVD other than blood pressure, anaemia and volume status, as calcium - phosphorus
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9 product, and use of HMG-CoA reductase inhibitors and antiplatelet agents were managed
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11 worse in LR compared to ER which did not differ from our results (14). Our excellent
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13 results in regard to the use of a permanent access at the initiation of dialysis in ER differed
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15 considerably from most prior studies, in which ER patients demonstrated inadequate
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17 results in this respect (14, 27). Previously, emergency initial dialysis was more frequent in
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19 LR, which is similar to our results (13). In LR, the rate of peritoneal dialysis as the chronic
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21 dialysis modality was lower, LOS within the first year after initiation of dialysis was
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23 substantially longer and one year mortality was substantially higher in previous studies,
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25 which is in accordance with our findings (4, 11, 13). Of further note, the detrimental
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27 association of LR with mortality in recent studies had its effect in the first 6 months after
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29 initiation of dialysis, which is also consistent with our findings (4, 11 - 15, 18). Our data
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31 show little evidence that the quality of dialysis has affected mortality as it did not differ in
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33 LR and ER.
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41 This suggests that LR and the associated management of advanced CKD have a
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43 rapid and persistent, deleterious impact on outcome. However, not LR per se but
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45 inadequate control of blood pressure, anaemia, nutritional and volume status, and
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47 emergency initial dialysis were identified as the actual deleterious factors as they were
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49 independently associated with one year survival, unlike LR. To our knowledge, this is the
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51 first report which identifies single, modifiable therapeutic targets of CKD care which were
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53 formerly summed up as the effect of LR. What could be the clinical relevance of our
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55 findings? It is assumed that worldwide the management of most CKD patients will remain
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57 a primary care domain (1, 28). This assumption is based on studies which showed an
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59 increasing prevalence of CKD that will easily exceed the workforce of nephrological
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3 services (2, 29). Further promotion of co-management of advanced CKD patients by
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5 primary care physicians and nephrologists could improve their outcome (11 – 13, 15, 16,
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7 18). Second, our results suggest that early co-management of advanced CKD should
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9 focus on adequate control of blood pressure, anaemia, nutritional status, and volume
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11 status and timely creation of a permanent access for dialysis to be most efficient and to
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13 provide the care associated with lowest one year mortality. These aspects should be
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15 expected within the scope of nephrological co-management in ER. These findings are of
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17 even more relevance as they are corrected for lead-time and immortal time bias to prevent
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19 false lower mortality rates, which was previously considered only in few studies (19, 20).
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25 This study is limited by its observational and retrospective design with potential
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27 confounding, information and selection bias (30). Approaches to reduce confounding were
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29 the comprehensive search and inclusion of potential confounders as factors in the
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31 statistical analyses. Furthermore, we made every effort to reduce confounding by
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33 indication, selection or information bias would have had substantial effects on the outcome
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35 presented as (i) ER and LR cohorts did not markedly differ with respect to demographic
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37 and clinical characteristics, (ii) follow-up data were complete for all patients, (iii) potential
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39 confounding factors were exactly defined and (iv) measurement of outcomes were
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41 identical in all patients (29). Although statistically not significant, selection bias could have
42
43 existed as late referred patients were generally in poorer health as demonstrated by older
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45 age, higher stages of CKD, rate of CVD, diabetic nephropathy, anaemia and
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47 microinflammation, possibly explaining on its own the deleterious outcome of these
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49 patients. A further limitation is the use of a dichotomous variable for late referral. In
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51 addition the 4 month cut-off may be somewhat arbitrary but was employed most frequently
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53 in the literature (11-15). This permits comparison of the presented data with previous one.
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55 However, late referral has also been defined by cut-offs of 1, 3, 6 and 12 months (12, 14,
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57 15). In addition, variables to assess quality of care in CKD were only measured at study
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3 initiation which does not necessarily evaluate the quality of control for the entire duration of
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5 exposure. Although laborious, the concept of ER was demonstrated to be feasible in
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7 recent studies (11, 31). Despite the superior outcome associated with ER in our study,
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9 quality of nephrological co-management in ER was still suboptimal and a number of
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11 targets were not consistent with current recommendations. Especially anaemia, calcium –
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13 phosphorus product, hypertension, LDL cholesterol and metabolic acidosis require more
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15 intensive treatment and correction, which is consistent with previous findings in ER (4, 14,
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17 24, 25). Our results may have differed if all targets had been adequately met. By focusing
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19 on advanced CKD patients who were subsequently treated by dialysis, we may have
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21 selected patients with particular negative outcome which may limit generalizability.
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23 Nonetheless, advanced CKD progressing to ESRD has the most impact on morbidity and
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25 mortality, it carries the highest cardiovascular risk and requires most medical and
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27 economic resources (3, 4). Hence, it seemed plausible to study particularly these patients
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29 who may profit most from improved care. The management of patients with advanced
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31 CKD who did not reach dialysis treatment was not captured and these patients certainly
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33 require separate, detailed evaluation. Finally, we performed a small multi-center study.
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35 Despite providing a typical cross-section of patients with advanced CKD in Germany and
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37 Europe, our results require validation in larger multinational studies.
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46 In summary, LR was associated with a substantial excess mortality after correction
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48 for lead-time and immortal time bias. In comparison to early nephrological co-
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50 management, care performed by primary care physicians was associated with inferior
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52 control of most of risk factors for CKD progression, of CKD complications, and of CVD risk
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54 factors. Outcome in advanced CKD may particularly be affected by inadequate control of
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56 blood pressure, anaemia, nutritional and volume status, and emergency initial dialysis as
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58 these factors were independently associated with and thus predominately contributed to
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one year mortality. Therefore, care of CKD patients should focus on the adequate management of these factors to improve the outcome of advanced CKD most efficiently.

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AUTHOR CONTRIBUTIONS

All authors have read, critically reviewed and approved the manuscript. Study concept and design: SHR, CL, TQ, AK; data collection: CL, MH; statistical analysis and data interpretation: SHR, CL, MH, TQ, VJ, AK; drafting manuscript: SHR, MH, TQ, VJ, AK.

DISCLOSURES

None

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LEGEND TO FIGURE

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Fig. 1. One year survival of 149 patients with advanced CKD. Patients were split into late (n = 46) and early referral groups (n = 103). Late referral was defined by an interval of < 4 months, early referral by an interval of \geq 4 months from initial nephrological referral to initiation of dialysis.

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Table 1. Baseline characteristics

Characteristics	Late referral (n = 46)	Early referral (n = 103)	<i>P</i>
Age (years)	64 ± 14	60 ± 15	0.10
Female gender (%)	46.2	45.6	0.73
Primary renal disorder			
• Diabetic nephropathy (%)	39.1	30.0	
• Hypertension / vascular (%)	13.0	11.7	
• Glomerulonephritis (%)	6.5	12.6	
• Autoimmune disease / vasculitis (%)	2.2	6.8	
• Interstitial nephritis (%)	10.9	11.7	
• Obstructive uropathy (%)	8.7	4.9	
• Polycystic disease (%)	0	5.8	
• Other nephropathies (%)	4.4	9.7	
• Unknown (%)	15.2	6.8	0.25
Speciality of primary care physician			
• General practice (%)	63.1	58.3	
• General internal medicine (%)	32.6	35.9	
• other (%)	4.3	5.8	0.84
Active smoking (%)	37.0	28.2	0.38
Serum creatinine (µmol/L)	605 ± 172	631 ± 149	0.20
Estimated GFR (mL/min/1.73 m ²)	10.4 ± 2.9	10.1 ± 2.4	0.32
CKD stage IV (%)	0	3.9	
CKD stage V (%)	100	96.1	0.42
Prevalence of cardiovascular disease (%)	56.5	48.5	0.47
Comorbidity (Khan index)			
• low (%)	21.7	30.1	
• medium (%)	26.1	36.9	
• high (%)	52.2	33.0	0.09

CKD - chronic kidney disease. GFR - glomerular filtration rate.

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Table 2. Potentially modifiable progression factors and complications of CKD in patients referred late or early for nephrological co-management

Characteristics	Late referral	Early referral	<i>P</i>
Systolic blood pressure (mm Hg)	152 ± 19	138 ± 14	< 0.001
Diastolic blood pressure (mm Hg)	86 ± 14	78 ± 10	0.007
HbA _{1C} in diabetic nephropathy (%)	7.2 ± 1.1	6.4 ± 0.8	0.005
Proteinuria (g/day)	3.1 ± 2.2	1.6 ± 1.0	< 0.001
Haemoglobin (g/L)	95 ± 10	113 ± 16	< 0.001
Serum calcium (mmol/L)	2.2 ± 0.3	2.3 ± 0.3	0.55
Serum phosphorus (mmol/L)	2.4 ± 0.6	2.0 ± 0.4	< 0.001
Plasma PTH (pmol/L)	30.8 ± 15.0	22.9 ± 13.2	0.01
Serum albumin (g/L)	34 ± 5	40 ± 4	< 0.001
Body mass index (kg/m ²)	24.8 ± 3.4	25.7 ± 5.6	0.29
Serum potassium (mmol/L)	5.3 ± 0.7	4.9 ± 0.7	0.002
Serum bicarbonate (mmol/L)	18.2 ± 2.7	22.2 ± 2.1	< 0.001
C-reactive protein (mg/L)	26 ± 18	8 ± 5	< 0.001
Calcium - phosphorus product (mmol ² /L ²)	5.6 ± 1.1	4.5 ± 1.0	< 0.001
LDL cholesterol (mmol/L)	3.1 ± 0.6	2.8 ± 0.5	0.02

CKD – chronic kidney disease. PTH - parathyroid hormone. LDL - low density lipoprotein.

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Table 3. Adequacy of management and control of CKD progression factors and complications in patients referred late or early for nephrological co-management

	Late referral	Early referral	P
Blood pressure (%)	39.1	68.9	< 0.001
Hb A _{1c} < 7% in diabetic nephropathy (%)	44.4	81.5	0.02
ACEI/ARB use in diabetic nephropathy or non diabetic CKD with proteinuria > 1g/d (%)	36.0	95.7	< 0.001
Anaemia (%)	8.7	52.4	< 0.001
Bone disease (%)	38.6	65.6	0.005
Nutritional status (%)	65.0	80.9	0.08
Volume control (%)	67.4	82.5	0.07
Serum potassium (%)	76.1	84.5	0.32
Metabolic acidosis (%)	17.1	54.4	< 0.001
C-reactive protein < 10 mg/L (%)	20.6	67.4	< 0.001
Calcium – phosphorus product < 4.44 mmol ² /L ² (%)	25.0	56.2	0.003
LDL cholesterol ≤ 2.59 mmol/L (%)	31.0	36.5	0.71
HMG-CoA reductase inhibitors in atherosclerotic CVD with LDL cholesterol > 2.59 mmol/L (%)	37.0	54.2	0.22
Antiplatelet agents in atherosclerotic CVD (%)	53.6	68.9	0.21

ACEI – angiotensin converting enzyme inhibitor. ARB – angiotensin-2-receptor blocker.

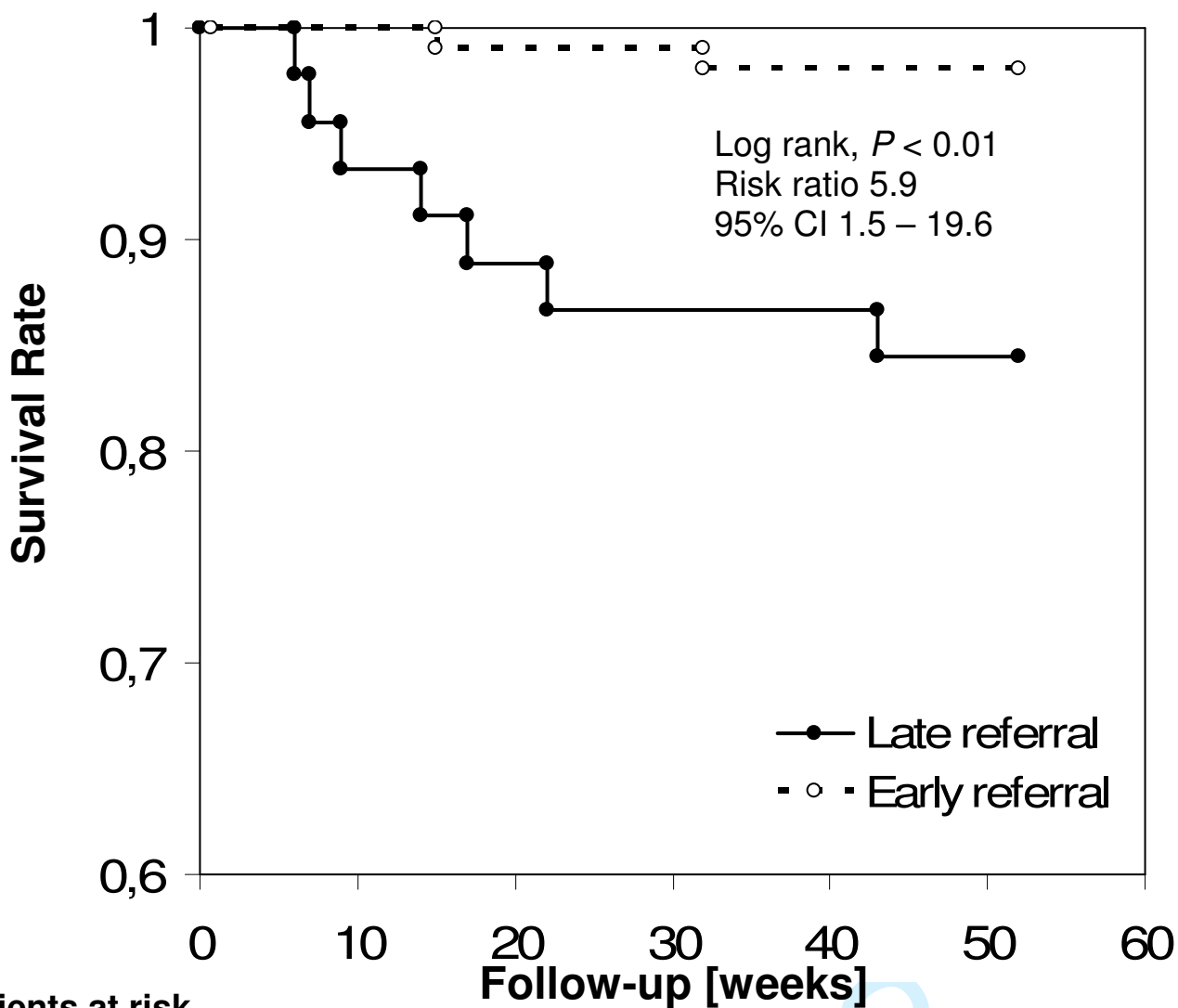
CKD - chronic kidney disease. CVD - cardiovascular disease. HMG-CoA – hydroxymethylglutaryl-CoA. LDL - low density lipoprotein.

Table 4. Potential risk factors associated with one year mortality in patients with advanced chronic kidney disease

	Bivariate analysis			Multivariate analysis		
	Risk ratio	95 % Confidence limits	<i>P</i>	Risk ratio	95 % Confidence limits	<i>P</i>
Late referral	5.9	2.2 – 15.9	0.005	2.7	0.7 – 7.2	0.33
Age (> 65 years)	2.8	0.7 – 9.6	0.20	-	-	-
Diabetic nephropathy	2.5	0.7 – 7.0	0.24	-	-	-
Hb A _{1c} in diabetic nephropathy ≥ 7%	2.3	0.6 – 9.2	0.39	-	-	-
High comorbidity (Khan index)	6.3	2.5 – 15.7	0.007	4.3	0.8 – 16.9	0.11
Blood pressure inadequately controlled	14.4	5.8 – 35.9	0.001	11.6	1.4 – 28.8	0.01
No ACEI/ARB use in diabetic nephropathy or proteinuria > 1g/d	6.6	1.9 – 22.0	0.008	4.1	0.6 – 13.6	0.34
Anaemia inadequately controlled	11.1	2.4 – 27.7	0.006	8.7	1.1 – 21.5	0.04
Bone disease inadequately controlled	1.6	0.6 – 4.5	0.62	-	-	-
Malnutrition	3.5	0.9 – 12.2	0.08	4.6	1.8 – 10.2	< 0.001
Volume inadequately controlled	6.2	2.3 – 16.9	0.002	5.9	1.6 – 15.4	0.002
Serum bicarbonate < 22 mmol/L	1.9	0.5 – 6.3	0.47	-	-	-
C-reactive protein ≥ 10 mg/L	4.5	0.8 - 13.0	0.13	-	-	-
Ca x P-product ≥ 4.44 mmol ² /L ²	2.5	0.8 – 6.5	0.29	-	-	-
Emergency initial dialysis	7.3	1.3 – 28.1	0.02	5.0	1.2 - 16.4	0.04

ACEI – angiotensin converting enzyme inhibitor. ARBs – angiotensin-2-receptor blockers. Ca x P - calcium - phosphorus

Figure 1.



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Patients at risk

Late referral	46	43	40	39	38
Early referral	103	103	102	101	100