sensory symptoms and neurological signs. _J Peripher Nerv Syst_ 2003; 8: 190


The deadly risk of late referral

Roel M. Huisman

Department of Internal Medicine, Division of Nephrology, University Hospital Groningen, The Netherlands

**Keywords:** chronic kidney disease; dialysis; late referral; mortality; predialysis

**Introduction**

In the last few years, studies have appeared that finally provide conclusive evidence that adequate predialysis care improves survival. The recent evidence comes from large-scale cohort studies, which constitutes not the highest level of scientific evidence but the next best. Clearly the best possible evidence, a randomized study of early vs late referral, will be ethically inadmissible so the next best level is the one we will have to accept as the best possible evidence. This relative certainty is new but the idea itself is not: timely referral to a nephrologist of patients with chronic renal failure has been suggested for many years to improve outcome [1].

Although this was common knowledge, at least among nephrologists, the evidence so far was not flawless, since it was based mainly on retrospective, single centre studies with their intrinsic bias. Some of these studies had not been able to find a negative effect of late referral on survival at all [2,3]. Since we can be certain at present that the clinical outcome of patients with chronic kidney disease is improved by early referral to a nephrologist, non-nephrologists should be made aware of this knowledge, since they are responsible for the referrals.

**Benefits of early referral**

Much of our recently gained knowledge on the positive effects of timely referral to a nephrologist stems from the use of multiple logistic regression analysis in recent studies. An overview of these studies is provided in...
### Table 1. Publications on mortality of late referral using multiple logistic regression analysis, with correction for effects of age and co-morbidity (and in some cases also for socio-economic circumstances)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Years in which dialysis was started</th>
<th>Country</th>
<th>Patient number</th>
<th>Population studied</th>
<th>Pre-dialysis follow-up (months)</th>
<th>Mortality period (months)</th>
<th>Hazard ratio for mortality compared to early referral</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–4</td>
<td>0–3</td>
<td>2.8</td>
<td>1.0–8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;1</td>
<td>0–3</td>
<td>5.0*</td>
<td>2.2–12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–4</td>
<td>After 3</td>
<td>2.2*</td>
<td>1.4–3.5</td>
</tr>
<tr>
<td>Winkelmayer et al. [5]</td>
<td>2003</td>
<td>1991–1996</td>
<td>USA</td>
<td>3014</td>
<td>Regional</td>
<td>&lt;3</td>
<td>0–3</td>
<td>1.8*</td>
<td>1.5–2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;3</td>
<td>After 3</td>
<td>1.0</td>
<td>0.8–1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;4</td>
<td>0–12</td>
<td>1.7*</td>
<td>1.3–2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;4</td>
<td>0–24</td>
<td>1.2*</td>
<td>1.0–4.7</td>
</tr>
<tr>
<td>Kinchen et al. [9]</td>
<td>2002</td>
<td>1995–1998</td>
<td>USA</td>
<td>828</td>
<td>Regional sample</td>
<td>&lt;4</td>
<td>0–24</td>
<td>1.6*</td>
<td>1.1–2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4–12</td>
<td>0–24</td>
<td>1.2</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>Roderick et al. [8]</td>
<td>2002</td>
<td>1996–1997</td>
<td>UK</td>
<td>124</td>
<td>Regional</td>
<td>&lt;1</td>
<td>0–6</td>
<td>1.5</td>
<td>0.7–2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0–12</td>
<td>4.2*</td>
<td>1.7–10.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0–24</td>
<td>2.3*</td>
<td>1.2–4.0</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.
was compared. The late referral group had a relative mortality in the first 3 months and later dialysis. 1039 pairs of patients from the early and late seen by a nephrologist at least 90 days before onset of patients with similar probability for a timely referral have influenced mortality. In this case use was made of kind of study is whether sufficient correction is applied non-nephrologist physician. An important issue in this the first dialysis, but a third of this group was seen by a been known to have renal disease at least a year before dialysis from 1991 to 1996. All selected patients had mortality of nearly all patients with chronic renal insufficiency starting dialysis in the state of New Jersey, USA, using Medicare and Medicaid data. Their study consisted of 3014 patients who started dialysis in 1997 and 1998. Data on the predialysis period were gathered retrospectively. Using multiple logistic regression these authors found that the relative risk of mortality increased to ~5-fold, the shorter the time between referral to a nephrologist and the start of dialysis. Dividing the patients in five groups, of which one was a group with possible acute onset renal failure, they found the best survival with predialysis care of longer than 12 months [odds ratio (OR) = 1]. With a follow-up of 4–12 months the OR was 2.7, with follow-up of 1–4 months the OR was 2.8 and <1 month of predialysis care yielded an OR of 4.9, whereas the (possible) acute onset group had an OR of 5.2. The mortality surplus occurred only in the first 3 months of dialysis. Thereafter no difference in mortality between the groups could be shown. Non-elective start of dialysis occurred in 46% of all patients, ranging from 30% in the early referral group to 85% in the possible acute onset group. If non-elective start of dialysis was entered as a parameter in the model, the effect of predialysis care duration disappeared. This suggests that non-elective start of dialysis is a major factor in the additional mortality of late referral to a nephrologist.

Winkelmayer et al. [5] retrospectively studied mortality of nearly all patients with chronic renal insufficiency starting dialysis in the very recent studies late referral and non-elective start of dialysis is a relatively frequent finding. In the French study [4], 23% of the patients were referred <1 month before the start of dialysis and 8% were referred only 1–4 months before dialysis. Again, these results are surprisingly similar to the studies from the USA: 34% referred shorter than 3 months before dialysis [13], 33% referred shorter than 4 months before dialysis [6] and 25% referred shorter than 1 month before dialysis [8]. Apparently, at present still about a third of the
patients starting chronic dialysis therapy are in a high risk group caused by late referral, both in Europe and the USA.

**Patient-related factors associated with late referral**

The question comes to mind whether the increased mortality could be due to unfavourable characteristics of the late referred patients. Late referred patients are in general older and sicker [4,8,10]. In some studies from the USA [8,14], patients referred late were more often uninsured. Correction for known negative factors for survival such as comorbidity and age has been applied in all recent studies and the increased mortality, as shown above, is what remains after this correction. A confounding factor could be access to medical care in general. An Australian study [15] showed that late referrals occurred more often from areas of social disadvantage. When in one study [5] the effects of socio-economic status and other determinants of health care utilization were eliminated by comparing pairs of patients, who were matched with respect to these factors, as well as with respect to age, gender, race and comorbidities, the detrimental effect of late referral remained. All the available evidence therefore indicates that, although late referral is generally associated with unfavourable patient-related factors such as increased age, comorbidity and lower socio-economic status, a substantial negative effect of late referral remains after correction for these factors.

A possible cause of better survival with earlier referral might be an earlier start of dialysis so that these patients enjoy the benefits of better residual renal function during their first months on dialysis. This does not appear to be a major factor at present, although it may have been more important in the past. The differences between the early and late referred groups in this respect are nowadays surprisingly small, if present at all. In three of the larger recent studies, which were described in detail above, data on residual renal function at the start of dialysis are given. In the study of Kessler et al. [4] residual creatinine clearance was not significantly different between groups and ranged from 10.3 ml/min/1.73 m² in the early referral group to 7.4 and 7.5 ml/min/1.73 m² in the very late referred group. Stack [6] found that residual glomerular filtration rate (GFR) was nearly identical in the late and early referred groups: 7.4 and 7.5 ml/min/1.73 m². In the study of Kinchen et al. [8] the proportion of patients with a serum creatinine >884 μmol/l was not different between the groups (~25% of patients), but there was a slight but significant difference in the fraction of patients with a GFR <7.3 ml/min/1.73 m² in the early vs the late referred group: 52 vs 59%. Summing up these results it appears safe to conclude that so-called lead time bias, although it may occur to some extent, plays a minor role in causing the beneficial effects of timely referral.

**What causes the positive effects of early referral?**

The majority of late referrals occur in patients who were known to have renal insufficiency.

First of all one might ask what would prevent early referral at all in patients known to have some stage of renal insufficiency and, secondly, what is it that non-nephrologists do not do and can be accomplished by nephrologists to provide such substantial and consistent benefits? To both of these answers no clear answers are available because data are lacking. The association of late referral with age and comorbidity perhaps indicates some hesitation of the referring physician as to whether the patient would in fact benefit from dialysis at all, leading to a delay in referral. The association with socio-economic status and insurance probably reflects a mixed doctor and patient delay, whereas a small fraction of patients starting dialysis have so much apprehension that they put referral off as long as possible, even though their physician may have insisted.

A very interesting question is what exactly is the activity of the nephrologist that causes the positive effects on survival, and even in such graded fashion. An obvious aspect is avoiding both the dangers of acute complications of uraemia and those of a central venous catheter. Patients referred late present not only with higher urea and creatinine levels but also with a greater degree of acidosis, anaemia, hypoalbuminaemia and hyperphosphataemia compared with early referrals [16]. Hospitalization with serious complications such as pulmonary oedema, pericarditis or severe hypertension is more often necessary in this group. Some of these patients develop their symptoms acutely and unexpectedly. Even though their renal disease may be chronic, they were in apparently good health before the complications occurred. Such cases could be called the unavoidable late referrals. In the recent French study [4], 11% of patients starting chronic haemodialysis belonged in this category. Much larger is the group of late referred patients with known renal failure, in which the dangers of an acute dialysis start could have been avoided. This acute start may be the most important issue since the increased mortality of late referral occurs mainly in the first 3 months of dialysis. Alternatively, this may be explained by the fact that in these months exposure to nephrological care has corrected previous therapeutic shortcomings, or by so-called ‘depletion of susceptibles’: the most vulnerable die quickly, the more robust remain and the remaining group is therefore more likely to have better survival. Be it as it may, when emergency dialysis was first included in the multivariate model used by Kessler et al. [4] this replaced the referral pattern as an independent prediction of death. Both parameters were strongly correlated, as expected. So, avoiding emergency dialysis is a major benefit of early referral.

What are other probable causes of the positive effect of the nephrologist’s work? In the French study [4], prolonged predialysis care was associated with higher
levels of haemoglobin, calcium, albumin and cholesterol. The higher cholesterol levels may raise some concern. They were, however, associated with a better survival in the French study. This is similar to findings in dialysis patients, in whom a higher cholesterol level generally represents a better nutritional status and causes better survival, similar to higher albumin levels [17]. Other studies confirm better use of erythropoietin by nephrologists. In a recent study from the USA [6] only 10.5% of late referred patients were using erythropoietin before starting dialysis, whereas this amounted to 32% in the early referrals, leading to a higher haemoglobin level in the latter group. The same study also showed higher albumin levels in the early referrals. Similar results, although with even lower erythropoietin use, were found in a slightly older study [18].

A retrospective Canadian study [19] investigated in some detail the deficiencies of pre-nephrological care. Nearly all new patients with renal insufficiency, referred to a nephrologist in two Canadian provinces in 1998 and 1999, were included in the study (n = 411). Of these patients, 54% had a creatinine clearance less than 30 ml/min (stages 4 and 5 chronic kidney disease). In 32% of these patients, blood pressure was >160 mmHg systolic or 100 mmHg diastolic; only 44% of all patients used an ACE inhibitor or AII receptor blocker; 21% had haemoglobin levels of <10 g/dl; only 14% of those with a high phosphate level used a phosphate binding agent; only 4% had supplemental vitamin D; 25% had metabolic acidosis whereas only two of 411 patients had bicarbonate supplementation; only 9% had had any kind of dietary advice. The conclusion of the study was that, in all areas, the quality of prereferral care was suboptimal. It is not difficult to see why these patients would be in a much better condition after a few months of nephrological care, although this was not investigated. This kind of study is rare but valuable. We only know these data from Canada but there is no reason to suppose that the situation is much better in other developed countries in which this problem has not been studied.

From the data presented above it appears likely that, apart from avoiding emergency dialysis, the (potential) advantages of early referral to a nephrologist are multiple. A list of possible factors is given in Table 2. This list does not imply the pretention that all aspects in this list are always covered adequately by all nephrologists. Rather, its point is that the nephrologist is equipped to do so and the challenge to nephrologists is to perform this task according to the standards of the profession. It would be interesting to know the relative contribution of each of the factors from Table 2 to the increased survival of early referred patients but, apart from the knowledge that avoiding a non-elective start of dialysis is probably most effective, we can only speculate on this subject. Nevertheless, this is an important issue since some of these problems occur early in the course of renal insufficiency, when many patients are not being seen by nephrologists but by other practitioners. It would probably be advantageous if the number of treatment guidelines for these physicians, should they encounter a patient with mild renal insufficiency, be kept to a minimum.

Patients with chronic kidney disease stage 2 (GFR 60–90 ml/min, normalized for body surface area) can probably be treated by their family physician or general internist if there are no diagnostic problems. A prerequisite is that physicians should be familiar with estimations of GFR, such as the Cockcroft–Gault formula [20] or the (modified) MDRD equation [21]. Besides, they should be aware of the fact that even
patients with a GFR of 60–90 ml/min (stage 2 chronic kidney disease) are already at a higher risk for cardiovascular diseases [22–24], making aggressive treatment of risk factors necessary. Below a GFR of 60 ml/min, referral to or consultation of a nephrologist is indicated, as advised in the American K/DOQI standards [24], since this provides an optimal chance for prevention of further renal function deterioration and early treatment of uraemic complications. The nephrologist will then face the challenge of preventing terminal renal failure in as many of these patients as possible and preparing the remaining patients adequately for renal replacement therapy. In many institutions this last task would not be possible without the valuable cooperation of predialysis nurses, social workers and dietitians. Formal evidence of the additional benefit for the patient of a multidisciplinary predialysis team remains to be reported, however.

Conclusion

Evidence is strong to date that early referral to a nephrologist, which means more than 1 year before the start of dialysis, improves patient survival. At present, both in Europe and the USA, about one third of patients are referred <4 months before the start of dialysis, causing a 3-fold increase in the risk of death during the first months of dialysis. Most of these late referrals could have been prevented because the patients were known by their physicians to have chronic kidney disease. Education of non-nephrologist physicians about diagnosis and treatment of chronic kidney disease, about the preferred moment of referral to a nephrologist and about the consequences of late referral should therefore be intensified, especially in the light of present knowledge.

Acknowledgements. The author would like to thank Professor Dr P. E. de Jong and Dr C. F. M. Franssen for their helpful comments.

Conflict of interest statement. None declared.

References