Patient Survival Comparisons Between Peritoneal Dialysis and Hemodialysis

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Contents

Abstract

The choice between hemodialysis (HD) and peritoneal dialysis (PD) has been discussed for decades and outcomes have been compared inevitably between dialysis modalities. Many studies have been performed comparing costs of treatment, quality of life, and hospitalization and results have been variable. Most important and most controversial have been the studies that have attempted to compare patient survival on PD to that on HD. There is, however, still no final consensus on whether HD or PD treatment modality gives the best results. Consequently, both options have to be weighed in individual patients according to their specific

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needs, preferences, and clinical characteristics, with the aim of providing a patient-tailored kidney replacement therapy.

Keywords

Peritoneal dialysis · Hemodialysis · Dialysis modality · Patient survival · Mortality · Outcomes · Epidemiology

Introduction

Ever since the emergence of peritoneal dialysis (PD) as a widely used, feasible, and successful home-based therapy in the 1980s, there has inevitably been interest in comparing outcomes on this modality with those on hemodialysis (HD). In the past three decades numerous studies comparing costs of treatment, quality of life, and hospitalization have been performed and results have been variable [1–8]. Most important and most controversial, however, have been the studies that have attempted to compare patient survival on PD to that on HD. The background to this controversy is that in most developed countries, PD is less costly for payers and providers than HD [5–8]. Pressure from payers to use PD has therefore been significant and the question that arises is whether survival is equivalent or better and whether the therapy can consequently be deemed to be more cost-effective.

Despite the positive attributes of PD, the proportion of patients treated with the modality has fallen in many countries over the last decades. Jain and colleagues gave an overview of the use of PD treatment in 130 countries worldwide between 1997 and 2008 [9]. They showed that there was an enormous variation in the proportion of patients that received PD as opposed to HD; in Hong Kong this proportion was as high as 79.4%, while there were no patients on PD at all in several developing countries and only very few in some developed countries such as Luxembourg (0.7%) and Japan (3.3%). Over 12 years, the number of PD patients increased in developing countries by 24.9 patients per million population and in developed countries by 21.8 per million population. The proportion of all dialysis patients treated with PD did not change in developing countries but significantly declined in developed countries by 5.3% [9]. This trend towards a more expensive modality mix emphasizes the importance of resolving the relative benefits of the two modalities.

As this chapter will show, historically, most comparative survival studies have utilized renal registry data. Head-to-head randomized controlled trials directly comparing PD to HD survival have never been successfully completed [10, 11]. The literature is therefore imperfect and so is a source of ongoing controversy. Another striking feature of the literature comparing survival between PD and HD is that results seem to differ greatly between different countries or when different methods of analysis are used. This confusing situation is partly related to different study designs, and the variety of statistical methods that have been applied to compare overall patient survival [12–15].

In this chapter historical and more contemporary survival outcomes of PD and HD are critically reviewed. In addition, we will review changes in statistical methodology that have been utilized over time to compare survival across treatment modalities and discuss the merits and drawbacks of each study and its design.

Points to Consider When Interpreting Survival Analyses in Dialysis Therapy

Two key points need to be remembered when considering the design and methodology of studies comparing mortality on PD and HD. First, modality switches from PD to HD are much more frequent than those in the opposite direction [16–19], as illustrated in Fig. 1.

Second, almost all studies indicate that PD compares best with HD in the early months and years after onset of end-stage kidney disease (ESKD) [16–18]. The cause of this is unclear, though it may be related to better retention of residual renal function on PD or to unrecognized baseline case-mix differences between patients on the two modalities. It is often referred to as an

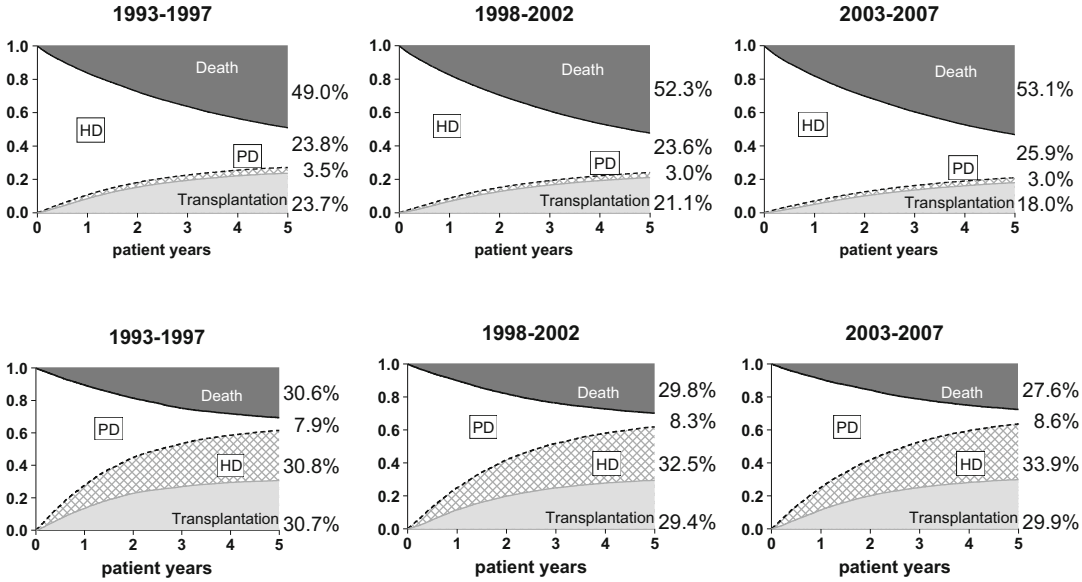

Fig. 1 Unadjusted cumulative incidence survival curves for a switch to the other dialysis modality, transplantation, or death for patients who started HD (upper row) and PD (bottom row) in 1993–1997, 1998–2002, and 2003–2007. (From van de Luijtgaarden et al. [19])

example of disproportionate hazards and it greatly complicates comparative survival analysis [11, 12].

Furthermore, there are several factors that could potentially explain the differences in findings between studies comparing mortality in HD and PD patients. These factors include methodological issues and other, clinical, factors such as practice patterns and patient characteristics. Below, a variety of factors that have to be taken into account in designing and evaluating studies done in this area are discussed.

The Use of Prevalent Versus Incident Patients

The prevalence of a treatment modality describes the number of existing cases at a certain point in time, whereas the incidence represents the number of cases new on the treatment within a certain time period. Studies that compare survival between PD and HD could use prevalent patients only, incident patients only, or a mix of both. However, it is preferable to include only incident patients who are new on the dialysis modality, because an early adverse effect will be missed in a purely prevalent study. Because of the disproportionate hazards phenomenon mentioned above, HD, the modality with the higher early mortality, will look misleadingly good in a purely prevalent study. Studies that use prevalent patients only should therefore be interpreted with caution and for that reason become less and less common [20].

As-Treated (AT) Versus Intent-to-Treat Analysis (ITT)

Careful consideration of each of these study design methods is important as the choice can have a significant impact on study outcomes in analyses that compare survival in PD and HD.

ITT attributes a patient's death to the treatment that the patient was originally placed on or "intended" to be receiving. AT attributes a patient's death to the therapy that the patient was actually receiving at the time of their death. ITT has been used in many of the survival analyses and does not allow the researcher to account for switches in therapy. It attributes a patient's death to the initial therapy they received without

accounting for the "actual" therapy, or multiple therapies, the patient may have received during their course of treatment.

The different types of analyses aim to answer subtly different research questions. An ITT analysis asks the most clinically relevant question, which is whether initial modality assignment influences patient survival. This is what a physician needs to know when advising patient about modality choice prior to initiation of dialysis. An AT analysis tries to determine which modality is likely to be associated with better survival while a patient is receiving it. In a sense, the AT analysis compares the actual modalities while the ITT compares two strategies: "HD first" versus "PD first." Often, the comparative studies use a modified ITT approach with censoring of patients either at the time of any modality switch, including transplantation, or at some designated time period after a switch.

Most statisticians would suggest that both ITT and AT analyses should be performed when comparing outcomes, as each answers a distinct question and because differences in those answers can indicate that more detailed analyses are required. AT models require more complicated statistical models to deal appropriately with modality switches and are likely to yield the more accurate results when large administrative datasets are being used.

When to Enter Patients in Comparative Studies

Most studies assign patients to the modality they are being treated with 90 days after initiation of dialysis and the period prior to that is omitted from the comparison, for example, in [18–20]. Intuitively, it might appear more appropriate to use the true initial modality to assign patients and to include all treatment time in the analysis. However, in most centers, patients presenting acutely or late are all treated with HD and because these patients tend to be sicker and to have a worse prognosis, a survival comparison based on initial modality would be biased against HD. Also, deaths in the first 90 days are likely to be more affected by preexisting comorbidity than by dialysis modality per se. The notion is that by 90 days these patients will have stabilized or recovered renal function or died and that some will even have switched to PD and that, overall, the comparison will be fairer.

In contrast, others argue that the 90-day approach removes from the analysis part of the time period where PD is most successful and this introduces a bias in favor of HD from Weinhandl et al. [21]. Furthermore, this is a period when HD patients are most likely to be using venous catheters for blood access and these are associated with significant complications so that omitting this period might again leads to a bias against PD. The 90-day rule is probably a fair compromise. However, it is important that the large influence of this issue on the results of the analysis be clearly understood. One US study by Winkelmayer surprisingly reports a bias in the opposite direction, with more deaths on PD in the first 90 days, but the cohort studied was small and comprised only elderly patients and the findings did not quite reach statistical significance and seem out of line with those in other studies [23].

Adjustment for Baseline Confounders

None of the comparative survival studies is randomized and so adjustment for baseline population differences is important. In most developed countries, patients treated with PD tend to be younger and healthier than those on HD and so, in countries such as the USA, Canada, Australia, and the largest part of Europe, an unadjusted analysis will show misleadingly better results for PD [24].

Clearly, adjustment of comparisons for age, sex, and baseline comorbidity is crucial. However, comorbidity information is often lacking or incomplete in renal registries, while prospective studies typically have more detail available and attempt to quantify comorbidity by using scoring systems [22, 24, 25]. They may also adjust for functional characteristics, residual renal function, and laboratory measurements [24].

A key point about adjustment for comorbidity is that only baseline data be used. It is completely inappropriate to adjust for data points or events occurring after initiation of dialysis as the modality may be influencing these. For example, outcomes should not be adjusted for residual renal function after initiation of dialysis as this may be better preserved on PD than HD and the adjustment may therefore take a key advantage of PD out of the analysis. Similarly, adjustment for serum albumin after initiation is inappropriate because it tends to be systematically lower on PD due to dialysate protein losses and the adjustment would introduce a bias against HD.

Adjustments will inevitably be incomplete, even in the most detailed of prospective cohort studies there are always factors that are not measured. Factors such as motivation and family support may be critical but are difficult to measure. Consequently, even after adjustment for potential confounders in the statistical analysis, there is usually at least some amount of residual confounding due to unmeasured variables. This may prevent a fair comparison of outcomes between patient groups, something which is usually feasible from well-conducted randomized controlled trials [15].

Adjustments are complicated and over time awareness has increased about complex interactions between modality and factors such as age, sex, and diabetic status and their effects on survival. As a result, more and more studies nowadays report their findings separately for men and women, younger and older patients, diabetic and nondiabetic patients etc. [16–19]. There is a realization that there is not one simple answer to the question of which modality is best and that the answer varies between the different subpopulations with ESKD.

Statistical Methods for Comparison of Patient Survival

An important issue regarding treatment comparisons is the difficulty of making causal inference based on observational studies. The most important weakness of observational studies is that selection bias by the clinician – also called confounding by indication – may occur [26]. There are several strategies to reduce the influence of such selection bias. Of these, multivariable adjustment for potential confounders during statistical analysis is most commonly applied.

In the last years, more and more research groups started to apply advanced statistical methods in addition to the conventional methods of survival analysis, i.e., Kaplan–Meier and standard Cox proportional-hazards models, to assess the associations between dialysis modality and mortality risk [15]. Such methods include time-dependent Cox regression models (for example, in [19, 27]), marginal structural models (for example, in [27–30]), and the use of treatment propensity scores in statistical models by means of adjustment, stratification, or matching (for example, in [19, 21, 27–32]).

As already mentioned, the relative mortality risks between patients on HD and PD do not appear to be constant with time on dialysis. Most studies suggest PD is at its best in the initial 2 years after initiation of dialysis and that HD is at its best with longer-term patients. Indiscriminate application of the Cox proportional hazards model to such a "disproportionate" situation is clearly inappropriate. Some studies have therefore done repeated analyses using different start points, i.e., redoing the analysis at 6 months, 12 months, 24 months, etc. [22]. In this case, the adjustments involved must still be based on predialysis baseline characteristics, as explained above.

Some other longitudinal studies used adjustment for time-dependent covariates [19, 27]. It is, however, important to keep in mind that this technique is inappropriate in comparative survival studies if adjustment would be made for a time-dependent covariate that is affected by the treatment that is being studied, potentially adjusting out the effect that is being measured.

Another advanced method that has been applied in some HD versus PD survival comparisons is marginal structural model [27–30]. This method can help to minimize the effects of case-mix differences and the potential for confounding in registry-based and observational studies but

requires substantial statistical expertise. The most popular method (with the same aim) is the use of propensity scores. A propensity score can be calculated based on observed covariates and represents the probability of a patient of being assigned to a particular treatment modality. This score can subsequently be used for standard statistical adjustment, weighting or for matching. An advantage of propensity score matching is that the patients who are being compared are more similar than when using a standard approach for survival analysis. However, a drawback of propensity score matching is that part of the patients cannot be matched and are excluded from the analysis. Another important disadvantage is that both propensity score methods and marginal structural models are only based on those variables that are measured, and cannot take into account any effects of unmeasured variables. Only a randomized trial can do this. So, usually there is at least some amount of residual confounding due to unmeasured variables and this may prevent a fair comparison of treatment outcomes. Applying propensity scores is most useful in dealing with situations where there are complex interactions between covariates that influence treatment assignment and also where there may be significant center effects influencing outcomes. This is clearly relevant in PD versus HD comparisons. To date, propensity scores have been applied relatively often [19, 21, 27–32] and very recently even a systematic review with meta-analysis was published by Elsayed et al. summarizing those studies that used this method for the comparison of PD and HD survival [33]. Their meta-analysis of 17 studies including a total of 113,578 propensity score-matched incident dialysis patients suggests that PD and in-center HD treatment carry equivalent survival benefits [33].

The fact that so many different statistical methods are being applied can partly explain the inconsistency in study results.

Clinical Factors

Other issues that deserve consideration when comparing survival outcomes in PD and HD include dissimilarities either in quality of the dialysis modality provided or in patient population characteristics across continents or by a combination of both. Firstly, dialysis modality–specific practice patterns may affect dialysis modality–specific outcomes. Factors, such as treatments times and the types of vascular access, peritoneal catheters, and PD or HD fluids used, may contribute to the efficiency and quality of the dialysis provided. It is often not taken into account to which extent PD and HD are provided in a state-of-the-art manner. For example, in many survival comparisons the type of vascular access used for HD is not included in the analyses, whereas Perl et al. showed that type of vascular access plays an important role in the relationship between dialysis modality and mortality [34]. They found in a Canadian cohort that starting HD with a central venous catheter largely explained the higher early-mortality risk of HD [34]. It should be kept in mind, however, that the use of a central venous catheter is tightly correlated with an urgent start of HD, which is associated with acute illnesses and complications and could thus be driving the higher mortality.

Another example of a clinical factor that is usually not taken into account is the circumstance in which a patient started dialysis. It has been postulated that patients who start dialysis urgently are at high risk of death and as they are treated predominantly with HD, this could induce selection bias in the comparison of mortality between HD and PD patients. Couchoud et al. showed in 2007 that mortality risk was significantly increased with 50% among elderly patients (75 years or older) with an “unplanned” start of HD when compared to patients with a “planned” start suggesting that a comparison between both dialysis modalities would be more balanced after removing the unplanned HD starts [35]. Two Canadian studies confirmed these findings. In 2011, Quinn et al. showed that PD and HD were associated with similar survival in incident patients starting dialysis electively as outpatients [36]. More recently, Wong et al. reported that HD and PD are associated with similar mortality among incident dialysis patients who are eligible for both modalities [37]. They claim that – to

better reflect the outcomes for patients who have the opportunity to choose between HD and PD in clinical practice – future comparisons of dialysis modality should be restricted to patients who are deemed eligible for both modalities [37].

Finally, the experience with a treatment modality within a certain center or even country could play a role. There is significant literature suggesting improved outcomes with increased experience in many areas of medicine including ESKD [38].

The Studies

The first study comparing continuous ambulatory PD with HD in incident patients was performed in the UK more than 30 years ago [39]. The investigators used Kaplan-Meier analyses to show that patient survival was not different between the two dialysis modalities during 3 years of follow-up. Since then, several survival comparisons between the dialysis modalities have been published, but their findings were inconsistent [12, 15].

Over the last three decades, the study design has evolved from single-center and multicenter studies in the 1980s and early 1990s, to either prospective cohort studies or those using data from national registries of dialysis patients thereafter. Below, the results of studies with the most important study designs are summarized.

Randomized Trials

Ideally, the decision on which dialysis modality gives the best outcomes should be based on results of randomized controlled trials in which the allocation of the dialysis modality is not influenced by attitudes or preferences of the nephrologist and the patient.

In the 1990s, Baxter attempted to enroll patients in a worldwide randomized trial comparing HD and PD. The study was abortive because once interested patients completed the pre-randomization education session, the large majority had developed a preference and were no longer willing to undergo randomization. This has been a recurring problem and underlines the point that there is a limit to the types of therapies that patients will accept on a random basis. Between 1997 and 2000, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) initiative aimed to enroll in a randomized trial all new dialysis patients who had no contraindication to either HD or PD at 38 dialysis centers in the Netherlands [10]. The primary and secondary outcomes were quality-of-life-adjusted life year (QALY) score and survival, respectively. The study was stopped early due to low enrollment, with only 38 patients (5% of the 773 eligible subjects) agreeing to participate. In the first 2 years, there was only a slight difference in mean QALY score, which favored HD over PD. After 5 years of follow-up there was no persisting difference in quality of life but the hazard ratio for death with HD versus PD was significant at 3.8, suggesting that long-term survival favors PD. However, it could be argued that low study enrollment makes these results difficult to interpret and the small number of patients who agreed to participate in the study may have been "different" from the large number who chose not to be included [10].

Despite these failures, a new attempt for setting up a trial started in China in 2011 (trial registration NCT01413074 at clinicaltrials.gov). However, 5 years later, it also was terminated. Consequently, outcomes in HD and PD patients can only be compared based on the results of observational and registry-based studies.

Registry-Based Studies

Since the mid-1990's several studies reporting patient outcomes based on data from regional, national, and international renal registries have been published. Most of these studies were based on data from the US Renal Data System (USRDS), Canadian Organ Replacement Register (CORR), Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), and the European Renal Association-European Dialysis Transplant Association (ERA-EDTA) Registry.

One of the first large registry-based studies was published in 1995 by Bloembergen et al. [20]. They used Poisson regression to analyze a large sample of prevalent-only patients from the USRDS for the years 1987–1989 with adjustment for demographic characteristics and showed 19% higher all-cause mortality in prevalent PD patients in the USA as compared to HD. The excess risk of death was significant for patients aged over 55 years and was most pronounced in females and those with diabetes. However, the methodology used here was unusual. In addition to the prevalent-based analysis method, the study only started analyzing patients who had completed 90 days of treatment on 1 January of each of the 3 years concerned and so systematically omitted the majority of the first 12 months of treatment in many patients. This introduced a substantial bias against PD.

A few years later, Vonesh et al. did a similar analysis with the USRDS dataset, but included both incident and prevalent patients from 1990 to 1993, and for these more contemporary cohorts reported no significant difference between PD and HD mortality although there was still a trend favoring HD in older diabetics and PD in younger diabetics [40].

Comparable US results were reported by Collins et al. in 1999 in a study that comprised incident patients from 1994 to 1996 followed for the first 2 years of dialysis [41]. The authors used Poisson regression to compare death rates and adjusted for age, gender, race, and primary renal disease. A Cox model was utilized to evaluate cause-specific mortality with the issue of proportionality addressed through a separation of patients with and without diabetes. This study showed a significant survival advantage for PD over the first 2 years compared with HD in younger patients with and without diabetes and in older nondiabetic patients also (Fig. 2). The effect was most apparent, being almost 40%, in the younger nondiabetics. Only in older patients with diabetes did the authors report a survival advantage for HD [41].

The first study on this topic from the Canadian colleagues from CORR was published only somewhat later than that by Bloembergen et al. Fenton and colleagues published results of incident PD and HD patients who initiated therapy between 1990 and 1994, and were followed up for 5 years [42]. After adjustment for baseline differences including age, primary renal disease, center size, and comorbidity at the initiation of dialysis, and using both an ITT and AT approach, the authors showed that, in Canada, there was a significant 27% survival advantage for PD patients compared to HD and that this advantage was greater in the first 2 years of dialysis and for younger patients [42].

Subsequent US studies have, however, been less favorable to PD. In 2003, Ganesh et al. and Stack et al. from the same research group published two US registry-based studies that compared mortality differences among PD and HD patients with ischemic heart disease and

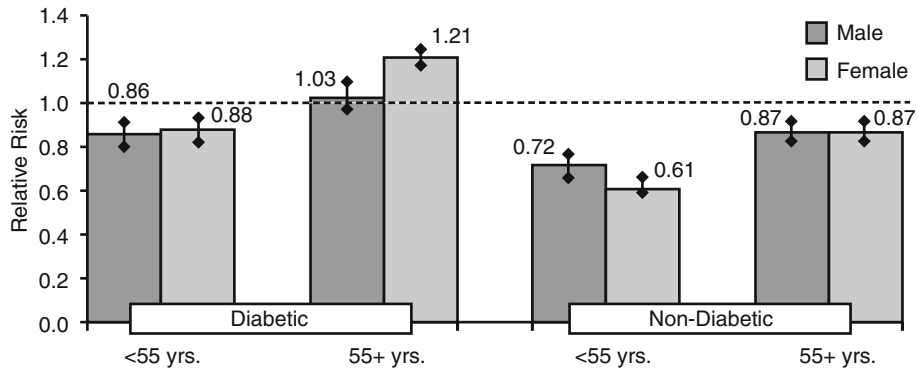

Fig. 2 Relative risks of mortality in incident US PD versus HD patients by age and diabetic status. (From Collins et al. [41])

congestive cardiac failure, respectively [16, 17]. They used Center for Medicare and Medicaid Services Medical Evidence Forms to define comorbidity data and they linked this to mortality data from the USRDS. These studies were very similar and both were based on the same population of patients and compared outcomes over the first 2 years of dialysis. Given secular trends in the USA during the time period covered from 1995 to 1997, PD patients tended to be younger and healthier when compared to HD patients initiating dialysis. Both studies attempted extensive adjustment for baseline differences in demographic, clinical, and laboratory covariates and used non-proportional Cox regression models with ITT and AT models for comparison. Results were expressed separately for patients with and without diabetes. Ganesh et al. reported a 23% higher mortality in patients with diabetes and cardiac disease who received PD compared with HD [16]. Those patients with diabetes but without cardiac disease also had a higher mortality on PD by 17% when compared with HD. In those patients without diabetes and with cardiac disease, there was a 20% higher mortality on PD. However, for those without cardiac disease or diabetes there was no significant survival difference. Similarly, Stack et al. reported that after 2 years, mortality was significantly higher for PD patients with congestive heart failure when compared to HD [17]. For patients without congestive heart failure but with diabetes there was also an 11% higher mortality among those who received PD compared with HD. These studies are noteworthy because they were the first to identify explicitly cardiac disease as an important characteristic to consider when determining the effect of dialysis modality on outcomes [16, 17].

Vonesh et al. subsequently published a US registry-based study in 2004 that expanded on the previous USRDS studies and adjusted for numerous clinical and demographic patient characteristics [18]. The effect of age was not reported in the previous studies and the Vonesh study therefore provided new data on the interaction of age on survival. The study was also designed to adjust for a cohort effect in order to account for changes in practice patterns in both PD and HD over the study time period of 1995–2000. The large study size with almost 400,000 incident US Medicare dialysis patients also allowed for extensive subgroup analysis. The results showed that among the patients group with no baseline comorbidity, the adjusted mortality rates for patients without diabetes was significantly higher for HD compared to PD for all age groups [18]. In those with diabetes but no other baseline comorbidity, mortality was higher on HD among 18- to 44-year-olds but the risk of death was significantly lower on HD for those over 65 years. For the group without diabetes and without baseline comorbidity, there was no difference in adjusted mortality rates. For those with diabetes and comorbidity at baseline there was higher mortality for PD among over 65 years but no difference for younger patients [18]. Both the Vonesh and Collins studies used an interval Poisson model whereas Ganesh and Stack utilized Cox models. Both models should be considered acceptable and appropriate for survival analyses that compares PD and HD and, if used correctly, will not impact differently on survival outcomes.

To summarize, these registry-based studies published between 1995 and 2005 demonstrated a number of consistent findings. The US studies clearly showed how incident analyses, such as that by Collins et al., make PD look much better than prevalent ones, such as that by Bloembergen et al. [20, 41]. They also established that, for both countries, the relative mortality favored PD initially but then, over 2–3 years, tended to move towards parity or even to favoring HD [20, 40–42]. They also all showed the interaction between age and modality and between diabetic status and modality, when survival is being considered. It became clear that HD looked best in older patients and in diabetics, and that PD looked best in younger patients and in nondiabetics. It could be concluded that PD survival was overall at least as good as that of HD and that the modality had a particular advantage in the early years of ESKD and especially in younger patients. Furthermore, a Danish registry study published in 2002 showed very similar results to those of Fenton et al. and Collins et al. [43]. All this gave support to the idea that PD was an excellent initial dialysis modality

and the term "integrated dialysis care" was introduced to describe a frequently advocated policy of treating all suitable new ESKD patients with PD, recognizing that many will eventually switch to HD [44, 45].

More recently (i.e., after 2005), research groups started to apply more sophisticated statistical methods to assess whether a different methodology would yield different conclusions regarding the survival outcomes of PD and HD.

Mehrotra et al. applied several statistical methods, including propensity score weighting and proportional and nonproportional hazards marginal structural model with inverse probability weighting to compare the survival of HD and PD patients from the USRDS [29]. They concluded that in the most recent cohort (2002–2004), there was no significant difference in the risk of death between patients who started on HD or PD. These findings were confirmed by investigators from Canada who used a similar approach in comparing the data of their incident dialysis patient cohort [30]. Yeates and colleagues used data on more than 35,000 incident dialysis patients from the Canadian Organ Replacement Register. They performed both a standard ITT analysis and a time-dependent AT analysis for which proportional and nonproportional hazards models were built to compare mortality risks between both groups. For the nonproportional hazards analyses they used a piecewise exponential survival model using successive 6-month intervals in the first 5 years of dialysis treatment. Contrary to their hypothesis that over time survival had worsened for PD when compared to HD treatment, they found that overall adjusted survival remained similar for PD and HD, even in the most contemporary cohort. After stratification for diabetic status, age, and sex, they found that nondiabetic patients in the youngest age group (younger than 45 years) showed survival benefits on PD treatment, while there was no difference in mortality in the older age groups. However, survival on PD was worse than on HD among patients with diabetes, in particular in those with higher age, which confirms the findings from other previous studies from around the globe [27, 29, 35, 46, 47]. For example, in 2009, McDonald et al. used data from ANZDATA and reported that PD patients overall had a better survival in the first year after starting dialysis, whereas HD performed better thereafter. Moreover, younger patients without comorbidities had mortality advantage with PD treatment, but other groups did not [27].

In addition to Yeates et al., also researchers from Europe and Oceania focused their research on whether any changes over time had taken place. Van de Luijtgaarden et al. analyzed data from the ERA-EDTA Registry and compared the survival of PD versus HD patients for patients who started dialysis between 1993 and 1997, 1998 and 2002, and 2003 and 2007 [19]. They found that after adjustment for age, sex, primary renal disease, and country, patient survival was better for patients starting dialysis in the most recent cohort (2003–2007) when compared with those starting dialysis in the first cohort (1993–1997), both for patients treated with PD and HD. Adjusted Cox survival curves and stratified hazard ratios for patients starting on PD versus HD show an initial survival benefit for PD in the first years after starting dialysis (Fig. 3). No difference in overall adjusted patient survival on PD relative to HD was found in the first and second cohorts; however, in the third cohort, a 9% survival benefit was present for patients starting on PD versus HD. Subgroup analysis showed survival benefits of PD for patients younger than 65 years and for nondiabetic patients. For patients aged 65 years and older and for patients with diabetes mellitus as primary kidney disease, patient survival on HD was better than on PD between 1998 and 2002, whereas no survival differences were observed for patients starting between 2003 and 2007 [19]. In addition, they found that although initiating dialysis on PD was associated with favorable patient survival when compared with starting on HD treatment, PD was often not selected as initial dialysis modality.

In the last years, more and more attention has been paid to home-based therapies, including both home HD and PD. Data from ANZDATA demonstrated that outcomes on dialysis therapy are improving with time, and this improvement is most pronounced for home dialysis modalities,

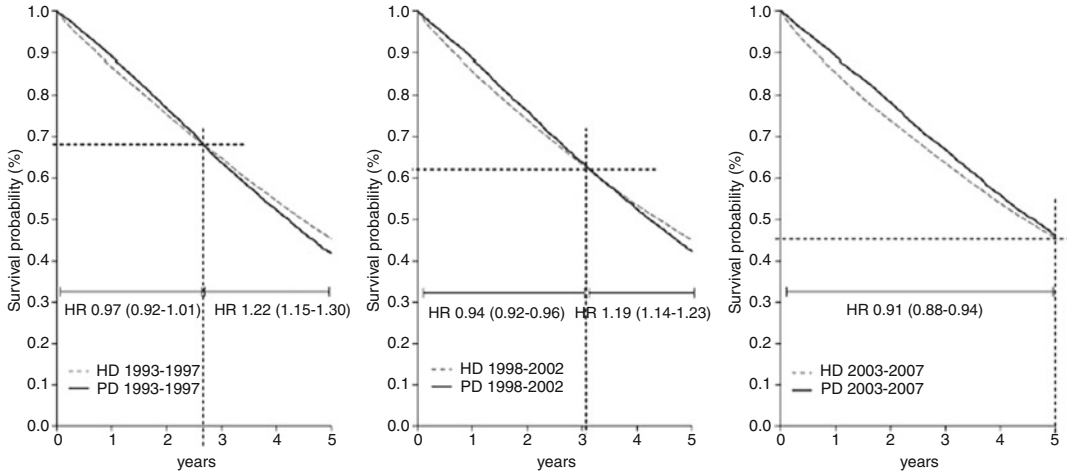

Fig. 3 Five-year patient survival for patients starting dialysis on PD and HD in 1993–97, 1998–2002, and 2003–2007, adjusted for age, sex, primary renal disease, and country. (From van de Luijtgaarden et al. [19])

especially home HD, when compared to conventional in-center HD (Fig. 4) [31, 48].

Finally, to illustrate the variation in findings from different parts of the world, the results of a selection of large renal registry studies comparing patient survival between HD and PD treatment are summarized in Table 1.

Prospective Cohort Studies

Only few large and noteworthy prospective cohort studies have been done comparing survival between PD and HD. First, a Canadian study by Murphy et al. was published in 2000. The investigators enrolled 822 incident patients from 11 dialysis centers across Canada with almost half on PD and half on HD in the period of March 1993 to November 1994 [22]. The study had a long follow-up period to January 1998. A Cox model was applied for the ITT analysis and Poisson regression for the AT model, which used time-dependent covariates with adjustment for case mix, including demographic characteristics such as age, race, and gender and clinical characteristics including diabetes status, heart failure, peripheral vascular disease, myocardial infarction, malignancy, and late referral. The uncorrected data showed the usual survival advantage for PD study but once full adjustments were performed there was no significant overall survival difference between the modalities.

Second, the Netherlands Cooperative Study on the Adequacy of Dialysis 2 (NECOSAD 2) was published in 2003 and enrolled 1222 incident patients (61% HD and 39% PD) during the period from January 1997 to September 2002 [24]. The authors applied proportional and nonproportional Cox models for both ITT and AT models. Adjustment for case mix was carried including baseline demographic (age and gender) and clinical characteristics such as primary renal disease, cardiovascular disease, Davies comorbidity index, and nutritional status as well as baseline glomerular filtration rate, serum albumin, and hemoglobin measurements. As with the Canadian study, there was no overall difference between PD and HD patient survival during the first 2 years of follow-up. Beyond the second year, the Dutch study showed a significantly lower mortality in the HD cohort, however [24].

The CHOICE Study, published in 2005 by Jaar et al., enrolled 1041 incident US patients (74% HD and 26% PD) from 81 dialysis centers in 19 states [25]. Patients were enrolled during the period 1995–1998 with follow-up for 5–7 years. Compared to the previously described prospective cohort studies, the CHOICE Study was designed to capture an even wider variety of demographic and clinical patient variables and adjustment for

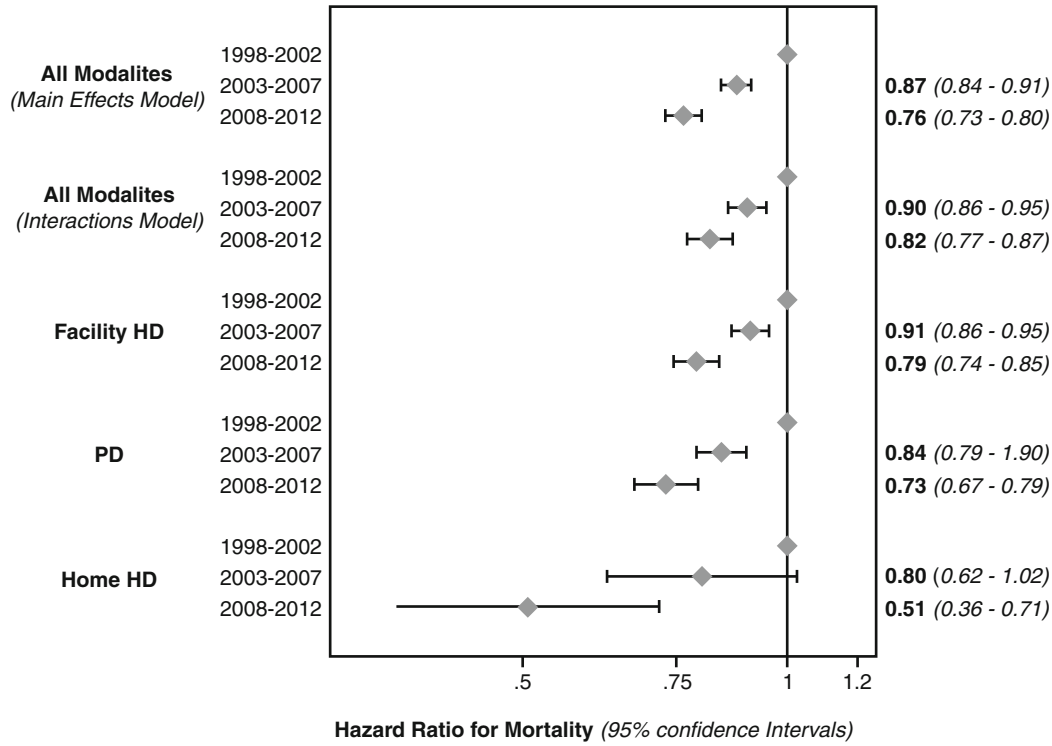

Fig. 4 Hazard ratios for death by era from the time-varying Cox proportional hazards model, fully adjusted for the main effects confounders (the marker represents point estimates; the whiskers, 95% confidence intervals). Hazard ratios are shown from the main effects and interactions models (the latter model includes the era*modality interaction) and for each subgroup of modality. (From Marshall et al. [48])

case mix included a wide variety of characteristics. Demographic factors included age, sex, education level, race, employment status, marital status, and geographic distance from the dialysis clinic. Clinical covariates included body mass index, primary renal disease, cardiovascular disease, glomerular filtration rate, index of coexistent disease, and late referral. Laboratory variables included serum levels of C-reactive protein, albumin, hemoglobin, creatinine, cholesterol, and calcium phosphate product. Both Cox proportional and nonproportional models were applied and showed that, overall, before adjustment for covariates, there was no difference between PD and HD survival. However, after adjustment for clinical and laboratory covariates, there was a significant survival advantage for HD that became very marked after the first year [25].

There is, however, some controversy about the results of the CHOICE study. The findings of the subgroup analysis were widely dissimilar from the previously published registry-based studies of US patients [20, 40]. These differences in outcomes have been postulated as being due to small subgroup sample size and potential bias from the fact that patients in this study were almost entirely recruited from dialysis provider (90%) [13, 25, 40]. Less than half of these centers provided both PD and HD, and given the low PD utilization rate in the USA, a rather contrived method of oversampling of PD patients was required and may have contributed to the discrepancy in the subgroup analysis results when compared to previously published studies. Another criticism is that many of the laboratory parameters were not measured at baseline and were treated as continuous variables rather than analyzed as categories [25, 49].

More recently, investigators from Canada performed large prospective cohort studies [36]. Quinn et al. had a specific research question regarding the comparison of PD and PD patient

Table 1 A selection of studies comparing of mortality between PD and HD patients based on renal registry data

Author, publication year	Country/Region	Inclusion period	N	Effect
North America				
Mehrotra, 2011 [29]	USRDS	1996–2004	624,426	Overall similar survival in the most recent cohorts. Over time greater improvement in survival among PD patients relative to HD at all follow-up periods
Yeates, 2012 [30]	CORR	1991–2004	46,839	Overall similar survival; PD better in first 18 mo, HD better after 36 mo. Women with diabetes aged ≥ 65yr higher risk on PD
Oceania				
McDonald, 2009 [27]	ANZDATA	1991–2005	27,015	Overall PD better in the first 12 mo after starting dialysis, thereafter HD better. Younger patients without comorbidities had mortality advantage with PD treatment, but other groups did not
Asia				
Huang, 2008 [48]	Taiwan renal registry	1995–2002	48,629	Overall similar survival. PD better among nondiabetic patients and those ≤ 55yr; HD better among diabetic patients and those >55 yr.
Kim, 2014 [32]	Korean Health Insurance Review & Assessment Service database	2005–2008	32,280	Overall higher mortality on PD. HD better among patients ≥55 yr in all subgroups except those with no comorbidities and malignancy (similar survival regardless of age)
Europe				
Van de Luijtgaarden, 2016 [19]	ERA-EDTA Registry	1998–2006	196,076	Overall PD better in first years after starting dialysis. Similar survival for diabetic patients and those ≥65 yr.

Abbreviations: *N*, number; *yr.*, years; mo, months; *HD*, hemodialysis; *PD*, peritoneal dialysis

survival [36]. Because patients who need to start dialysis urgently are at a high risk for mortality and are treated almost exclusively with HD, this may introduce bias to such mortality comparisons. To better isolate the association between dialysis treatment modality and patient mortality, they therefore aimed to compare the survival of PD and HD patients who started dialysis urgently with those who received at least 4 months of predialysis care and who started dialysis electively as outpatients. They included a total of 32,285 individuals who received dialysis in Ontario, Canada, during a nearly 8-year period, of whom 6573 patients met criteria for elective, outpatient initiation. No difference in survival between PD and HD was detected after adjusting for relevant baseline characteristics. The relative risk of death did not change with duration of dialysis therapy in the primary analysis. The results of this suggest that both dialysis modalities associate with similar survival among incident dialysis patients who initiate dialysis electively after at least 4 months of pre-dialysis care and that selection bias, rather than an effect of the treatment itself, likely explains differences in survival that were found in previous studies.

What Conclusions Can be Made Regarding Patient Survival in PD Compared with HD?

In this chapter I have attempted to provide a review of study methodologies and various study designs that are meant to highlight features that should be considered when comparing studies on

dialysis survival. For dialysis modality comparison, the evidence base has needed to come from observational studies, despite their drawbacks, because as yet it has not been possible to perform randomized controlled trials. It is possible that, given the apparent nonfeasibility of carrying out a good-quality randomized trial and given the inherent difficulties in comparing two very different modalities, we may never have a conclusive answer about overall comparative survival [10, 12–15].

Some argue that the PD and HD are better seen as complementary and not competitive [44, 45]. There still is a need to improve the practice of both and to address the particular complications of each. The survival debate has, however, been helpful in that it has assisted in our understanding of the two dialysis modalities and their potential strengths and weaknesses. It has also given unique insights into statistical analyses for comparing mortality in ESKD populations. Knowledge, however imperfect, is worth having as long as it is not overinterpreted.

This chapter shows that virtually all the recent observational studies from different parts of the world consistently demonstrate that patient survival on PD and HD is remarkably similar. Hence there is – up to now – no consistent evidence that PD or HD provides an overall survival advantage, even when sophisticated statistical methods are used. When specific patient subgroups were investigated, most studies showed that PD is associated with better survival for younger (mostly younger than 55 years) and nondiabetic patients, but with worse survival for older and diabetic patient subgroups. These results suggest that certain patient groups may have a survival advantage with PD or HD, but it is neither large enough nor sufficiently convincing to override the individual patient-specific factors that drive modality selection in many centers.

It would, however, be wise for PD researchers to pay attention to the possibility that adverse interactions between diabetes, cardiac disease, PD utilization, and survival may reflect real biological causation. The potential negative effects of glucose-based PD solutions and their tendency to induce hyperglycemia and hyperlipidemia, and perhaps hyperinsulinemia and obesity, highlight the need for further research and development of effective non-glucose-based dialysis solutions [50, 51].

In conclusion, both HD and PD can be considered as suitable initial kidney replacement therapy, depending on individual patient circumstances and center characteristics. Patients should receive comprehensive pre-dialysis education about potential advantages and disadvantages of both treatment modalities before the start of dialysis, allowing them to make a well-informed choice together with their physician.

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