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Original Research

Age, Gender and Diabetes as Risk Factors for Early Mortality in Dialysis Patients: A Systematic Review

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Objective: To study the impact of age, gender, and presence of diabetes (any type) on the risk of early deaths (180-day mortality) in patients starting long-term hemodialysis (HD) therapy.

Design: Systematic review of the literature.

Setting: Out-patient (non-hospitalized), community-based HD therapy world-wide.

Participants: Patients with advanced chronic kidney disease (CKD) starting long-term HD treatment for end-stage renal disease (ESRD).

Methods: Medline and EMBASE were searched for studies published between 1/1/1985 and 12/31/2017. Observational studies involving adult subjects commencing HD were included. Data extracted included population characteristics and settings. In addition, patient or treatment related factors studied with reference to their relationship with the risk of early mortality were documented. The Quality in Prognosis Studies tool was used to assess risk of bias in individual studies. Findings were summarized, and a narrative account was drawn.

Results: Included were 26 studies (combined population 1,098,769; representing 287,085 person-years of observation for early mortality). There were 17 cohort and 9 case-control studies. Risk of bias was low in 13 and high in a further 13 studies. Patients who died in the early period were older than those who survived. Mortality rates increased with advancing age. Female gender was associated with slightly increased early mortality rates in larger and higher quality studies. The available data showed conflicting results in relation to the association of diabetes and risk of early mortality.

Conclusions: This systematic review evaluated the impact of key demographic and co-morbid factors on risk of early mortality in patients starting maintenance HD. The information could help in delivering more tailored prognostic information and planning of future interventions.

Keywords: Dialysis; End-stage renal disease; Mortality; Early-mortality; Elderly

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Chronic kidney disease (CKD) represents an ever-increasing public health problem world-wide. Its prevalence is increasing,[1,2] as are the numbers of patients who require regular dialysis treatment.[3] The onset of hemodialysis (HD) therapy in patients with advanced CKD heralds a period of abrupt changes; patients experience severe disruptions in their lifestyles from frequent hospital visits and are exposed to multiple medical procedures.[4,5] HD treatment itself imposes additional physiological demands on patients, as it is associated with impairment of myocardial function[6] and accelerated loss of residual renal function.[7] Combined with worsening indices of nutrition and inflammation with advancing CKD,[8-10] an increasing burden of comorbid illnesses[11] and a decline in functional status in the elderly,[12] the risk of decompensation is high in the early days of HD therapy.[13] Mortality rates are highest in the first few weeks of treatment before stabilizing to lower levels.[14-16]

As research progresses towards delivering interventions to reduce early mortality in new HD starters, eg, by better preparing patients for dialysis through pre-dialysis educational programs,[17] pro-actively anticipating and managing common problems faced by dialysis starters,[18] and starting HD incrementally rather than abruptly;[19] there is a growing need to coalesce the global literature on risk factors for early mortality by subjecting it to a rigorous review process. An authoritative understanding of the impact of key risk factors on early mortality rates can help in counselling patients who are about to make the life-changing transition in to dialysis-dependency.[20-22] It can also help ensure that new interventions are targeted towards those at highest risk to maximize their impact.

A systematic review of the literature was conducted to summarize the impact of key risk factors for early mortality after initiation of maintenance HD. In this paper, we report our findings in relation to three such factors: age, gender, and a background of diabetes, and their association with risk of early mortality in patients starting long-term HD treatment.

Materials and Methods

Search Strategy

Medline and EMBASE databases were searched using keywords and subject headings encompassing three separate themes: (a) hemodialysis [h*modialysis or 'renal replacement' or subject headings 'dialysis' or 'renal replacement therapy']; (b) mortality [mortality or death* or survival* or outcome*]; and (c) early or initial [initia$ or early or (first adj2 day$) or (first adj2 week$) or (first adj2 month$) or (soon adj1 after) or (short adj1 term)]. The results were combined using the operator AND, ie, A AND B AND C. Hence, the search strategy aimed to retrieve records of studies related to *early mortality* in patients starting *hemodialysis*. Searches were restricted to publications between January 1, 1985 and December 31, 2017 in English language. Publications before 1985 were deemed unlikely to represent current practices and the changed patient demographics in the modern era. Reference lists of relevant studies were also screened for additional publications.

Eligibility Criteria

Observational studies involving subjects starting HD for end stage renal disease (ESRD), evaluating any baseline factor for its relationship with post-HD mortality, and reporting mortality as one of the outcome measures were eligible for inclusion. *Early mortality* was defined as all-cause mortality with in the first 6 months of starting HD. Studies primarily focusing on those receiving other forms of renal replacement therapy (RRT) (ie, peritoneal dialysis and transplantation) were excluded.

Data Items

Basic study characteristics including the study objectives, settings, selection and number of participants, proportion of patients stating HD (as opposed to other forms of RRT), duration of follow-up, and measurement of outcomes (ie, definition and ascertainment of early mortality) were extracted. Baseline patient characteristics and risk factors studied (eg, age, gender), number of subjects with and without the risk factors, the number of deaths or mortality rates in each group (if available) were documented. The summary risk estimates were extracted (if available), which included odds ratios, relative risks, or hazard ratios (with confidence intervals and *P* values). If studies adjusted their risk estimates for confounding factors, the adjusted estimates were also recorded. A note was made of the statistical method used to compare means or proportions.

Risk of Bias in Individual Studies

Risk of bias within studies were assessed using the Quality in Prognosis Studies (QUIPS) instrument.[23] This tool prompts users to assess the risk of bias in six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting. In the QUIPS instrument, summated scores for each study are not recommended.[24] Instead, an overall judgement of the risk of bias is suggested based on the relative impact of biases in the six main domains. We attributed a lower risk of bias to studies that carefully recruited their subjects, ie, an unselected cohort of adult patients starting maintenance HD for ESRD with a complete follow-up record of all study participants, attention to ascertainment of the outcome measure (all-cause mortality), and non-selective reporting of the outcome. Based on these principles, studies were classified as low or high risk of bias:

- Low risk: low risk rating in all domains
- High risk: any high or moderate risk domains

Synthesis of Results

The included studies are summarized in Table 1 along with key study and participant characteristics. A narrative account was constructed for each risk factor and presented in the free

Table 1. List of included studies with key study and participant characteristics.

Study	Settings	Objective	N	Ave. age (yrs)	% Male	HD as first RRT modality	Definition of EM (days)
Foley et al, 2014[36]	US; Nationwide. Data from United States Renal Data System	To enumerate weekly mortality rates during the first year of RRT	498,566	51% >65 yrs	56%	94%	90
Chan et al, 2011[35]	US; Dialysis centers operated by Fresenius Medical Care North America with 1500 dialysis facilities	To describe the characteristics, mortality and hospitalization risks for a cohort of patients starting chronic dialysis	303,289	63	54%	94%	90
Robinson et al, 2014[40]	Participating dialysis units in 11 countries across western Europe, US, Japan, Australia and NZ	To evaluate mortality patterns over the course of HD treatment in 11 countries participating in the DOPPS study	86,886	63	59%	100%	120
Tsakiris et al, 1999[45]	Dialysis centers across 28 European countries affiliated with ERA-EDTA	To define the incidence and factors related to deaths within 90 days of starting RRT	78,534	54	59%	82%	90
Yazawa et al, 2016[49]	Japan; National ESRD registry	To study the impact of functional status on early deaths	33,281	69	65%	100%	90
Ivory et al 2017[46]	Australia and New Zealand; population-wide data from ANZDATA registry	To develop a risk prediction tool for 6-month mortality	23,658	61	60%	NS	180
Lukowsky et al, 2012[31]	US; Multicenter; centers affiliated with a large private dialysis provider	To test if patterns and risk factors associated with early mortality differ from those in later dialysis therapy periods	18,707	63	55%	100%	90
Soucie et al, 1996[41]	US; three states: Georgia, North Carolina and South Carolina	To identify factors associated with mortality at the onset of dialysis	15,245	57	49%	80%	90
Zhao et al, 2017[50]	China; Beijing regional ESRD registry	To study risk factors for early mortality	11,955	58	56%	100%	120
Roca-Tey et al, 2016[48]	Spain (Catalonia); regional ESRD registry	To evaluate the impact on vascular access type of mortality	9,956	NS	NS	100%	120
McQuillan et al, 2012[42]	Canada; Multicenter, 35 dialysis sites covering a population base of 7.6 million people	To determine the incidence and risk factors for 90-day mortality	4,807	66	60%	100%	90
Bradbury et al, 2007[43]	US; multicenter. Randomly chosen dialysis facilities in DOPPS 1 and DOPPS 2 studies	To examine the magnitude of associations between various patient characteristics and mortality	4,802	26% >75 yrs	56%	100%	120
Couchoud et al, 2009[33]	France; population based. Patients starting dialysis in 16 French regions (covering 79% of French population)	To develop and validate a clinical score to assess risk of mortality within 6 months of starting RRT in elderly patients with ESRD	2,500	81	60%	NS	180

Chua et al, 2014[39]	Singapore; Single-center	To examine factors associated with early death. To enable formulation of an effective risk prediction scoring system	983	60	52%	72%	90
Wolf et al, 2007[34]	US; multicenter, 569 dialysis facilities in 37 states	To test if decreased levels of untreated 25D and 1,25D are associated with increased early mortality	825	63	53%	100%	90
Barrett et al, 1997[38]	Canada; multicenter. 11 dialysis centers affiliated with Universities across Canada.	To predict factors for early death in patients starting dialysis	822	58	59%	62%	180
Serafinceanu et al, 2014[26]	Romania; Single center in Bucharest	To identify demographic and clinical risk factors associated with early mortality in diabetic patients	788	56	58%	65%	90
Metcalf et al, 2000[27]	Scotland; nationwide study	To determine the major influences on death within the first 90 days of RRT	532	65	60%	77%	90
Kessler et al, 2003[29]	France; Multicenter. All 13 Nephrology units in the metropolitan region of Lorraine	To study the impact of nephrology referral on outcomes after the start of HD	502	63	59%	80%	90
Khan et al, 1995[32]	UK; Aberdeen, single center	To study the influence of various factors on deaths during 90 days of starting RRT	459	65	50%	NS	90
De Lima et al, 1998[44]	Brazil; single center in Sao Paulo	To determine the relationship between baseline characteristics and prognosis of dialysis patients	395	NS	NS	NS	90
Biesenbach et al, 2007[28]	Austria; single center	To evaluate differences in risk of early death between diabetics and non-diabetics	334	NS	NS	NS	90
Foley et al, 1994[30]	Canada; Newfoundland, single tertiary care center	To identify and quantify the accuracy of predictors of death within 6 months of starting maintenance dialysis	325	35% >70 yrs	65%	NS	180
Fabian et al, 2016[51]	South Africa, multi-center	To evaluate the impact of 'Healthy Start' intervention on mortality	269	54	64%	78%	90
Arai et al, 2014[37]	Japan; single-center, Yokosuka Kyosai Hospital	To investigate the 6-month mortality of Japanese patients aged > 75 years who recently started dialysis	202	80	60%	97%	180
Rubio et al, 2017[47]	Spain (Malaga); multi-center	To study the impact of clinical parameters of mortality	147	68	71%	100%	180

US: United States; UK: United Kingdom; NZ: New Zealand; HD: hemodialysis; EM: early mortality; NS: not specified; ESRD: end-stage renal disease; RRT: renal replacement therapies; DOPPS: Dialysis Outcomes and Practice Patterns Study; N: number of participants; Ave: Average.

text. As much as possible, attempt has been made to quantify the risks, but due to the heterogeneity found within the studies in terms of their base population, selection methods, evaluation of risk factors, presentation of data, and follow-up, a meta-analysis was not conducted. In some cases, limited pooling of data from different studies (restricted to only those studies where raw data could be extracted) have also been presented; this has been done to show a comparison of early deaths (numbers or rates) in each risk category. Crude early mortality rates were calculated for these studies from raw data and are presented along with their 95% confidence intervals (CI). In the narrative synthesis, more emphasis has been placed in reporting the findings of higher quality studies. Findings linked with lower quality evidence have been highlighted

Protocol and Registration

A four-member academic advisory panel at Hull York Medical School regularly reviewed the methods and conduct of the systematic review throughout its course. It was registered with the International Prospective Register of Systematic Reviews (PROSPERO)[25] on April 2, 2016 (registration number: CRD-42016037016).

Results

Search Results

After removing duplicates, a total of 3,000 citations were obtained from database searches (Figure 1). Screening of titles and abstracts resulted in the exclusion of 2,833 citations. Full texts of the remaining 167 citations were reviewed; 26 studies met the eligibility criteria and were included.

Description of Included Studies

The included studies[26-51] are listed in Table 1. These collectively represented a population of 1,098,769 new dialysis starters and 287,085 person-years of observation for early mortality. There were 17 cohort[27,29-31,33,35-38,40-43,45,48-50] and 9 case-control[26,28,32,34,39,44,46,47,51] studies. Six studies were based in the United States (combined number of participants: 841,434);[31,34-36,41,43] three in Canada (5,954 participants);[30,38,42] two each in United Kingdom,[27,32] France,[29,33] Spain,[47,48] and Japan[37,49] (47,579 participants); and one each in Austria,[28] Brazil,[44] China,[50] Romania,[26] Singapore,[39] and South Africa[51] (14,724 participants). In addition, there were three multinational studies involving the Australia-New Zealand region,[46] European countries,[45] and a group of 11 industrialized nations[40] (189,078 participants).

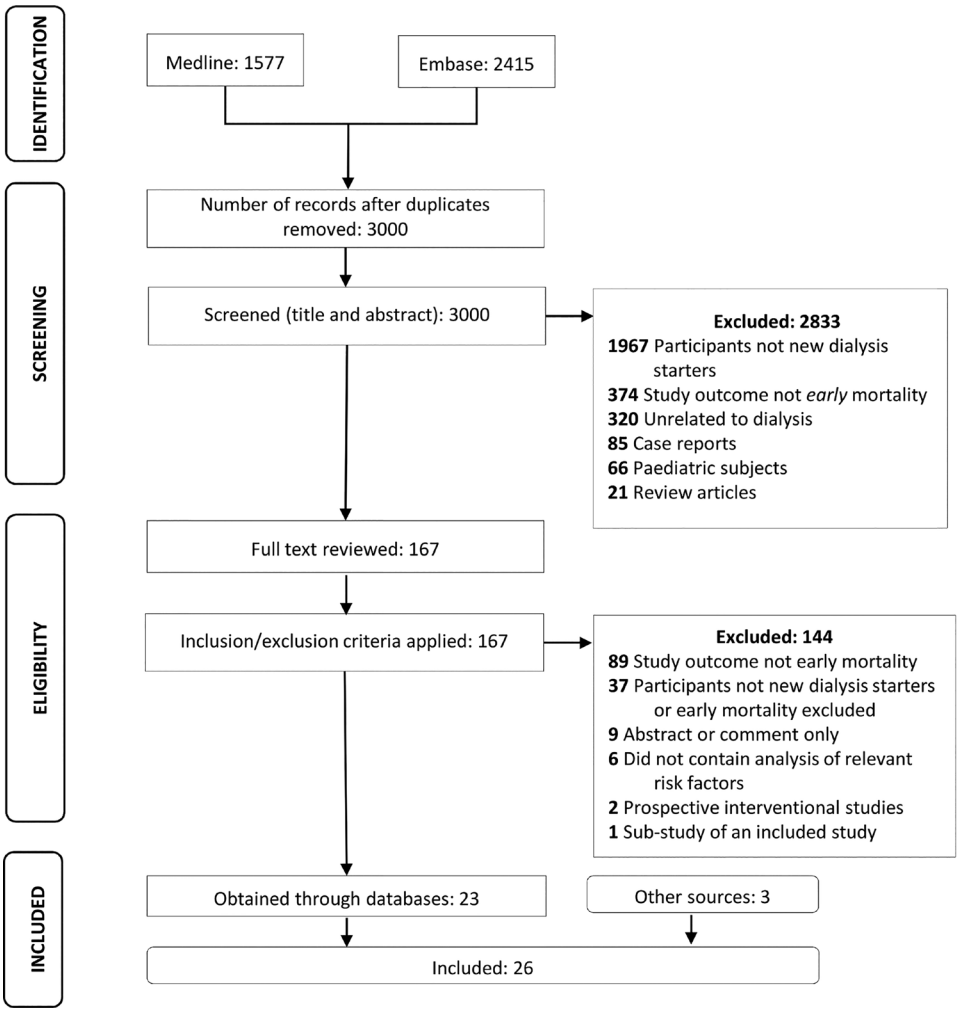

Figure 1. Prisma flow chart showing study selection process.

Numbers of participants in the included studies ranged between 147[47] and 498,566;[36] median duration of follow-up for early mortality: 90-days (range 90–180 days); and average age of participants: 54 years[45,51] to 81 years.[33] The proportion of men ranged between 49%[41] and 65%;[30] this figure was not reported in some studies.[28,44,48] The proportion of patients receiving HD as first RRT modality ranged between 62%[38] and 100%,[31,34,40,42,43,48-50,52-54] although this information was not reported in several studies.[28,30,32,44,46]

Risk of Bias

Of the studies included, 13 were at low risk of bias[27,29,31,32,34,36,38,40,41,43,46,49] and 13 at high risk.[26,28,30,33,37,39,42,44,45,47,48,50,51] The summary of risk of bias assessment is presented in Supplementary Table S1 (available online).

The Impact of Age on Early Mortality

In total, 25 studies [26,28-51] with a combined population of 1,098,237 people examined age as a risk factor. The presentation of data differed in these studies. Eleven

studies[26,28,31,32,34,35,39,44,46,47,51] compared mean ages in those who died early vs. the survivors (case-control design). Patients who died early were older in all instances. In one study (n=1,000), the mean ages (± standard deviation [SD]) of patients who died in the first 90 days (n=250) and of those who survived this period (n=750) were 71 (±13) and 61 (±16) years, respectively; t-test $P < 0.01$.[34] Some studies also adjusted for potential confounding factors,[31,35,39,44] producing similar outcomes; ie, patients who died early were older. Lukowsky et al,[31] reported the mean age of patients who died in the first 3 months vs. those who survived > 2 years were 72 and 60 years, respectively. For every 10 year increase in age, the hazard ratio of mortality increased by 1.50 (95% CI 1.43-1.56).

Ten studies[30,33,40-43,45,48-50] presented their findings as number of early deaths within various age brackets (longitudinal cohort design). All these studies demonstrated higher early mortality rates in older subjects. Soucie et al[41] (n=15,245) showed that in age groups < 45, 45–64, 65–74, and ≥ 75 years, percentage of deaths in the first 90-days of starting HD were 2.3%, 4.6%, 9.5%, and 11.6%, respectively; P value < 0.001. Similarly, Robinson et al[40] stratified their cohort (n=86,899) into age groups of < 45, 45–54, 55–64, 65–74, and > 75 years; crude mortality rates were 6.0, 11.4, 17.4, 28.2, and 45.6 per 100 person-years, respectively, in these groups. This equated to adjust hazard ratios for early mortality of 1.08, 1.24, 1.55, 1.53, and 1.59, respectively, in the groups when compared to those who survived to between 121- and 365-days post-HD, after accounting for confounding factors. Every 5-year increase in age was associated with 1.22 (95% CI 1.21 – 1.23, P value < 0.001) times increased risk of early mortality (adjusted for sex, race, and diabetes).

Four studies[29,36-38] reported summary statistics only (ie, odds or hazard ratios for early deaths) in pre-defined age brackets, again confirming higher risk of early mortality with increasing age. In Kessler et al,[29] the odds (and 95% CI) of 90-day mortality were reported at 2.9 (0.7-12.4), 6.0 (1.7-21.0), 4.4 (1.3-15.3), and 11.2 (3.0-41.4) in age groups 50–60, 60–70, 70–80, and > 80 years when compared to those aged < 50. Studies that recruited only elderly patients did not demonstrate any association between increasing age and early mortality.[33,37]

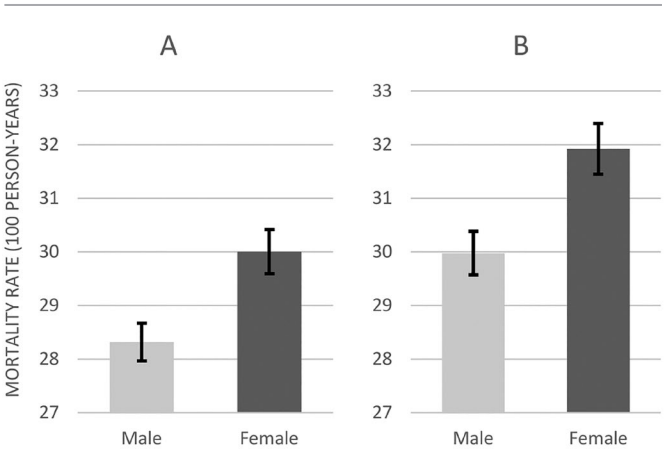

Figure 2. Early mortality rates in male and female participants when data from 14 studies (see text) were pooled together (A) for all 14 studies (B) for studies with low risk of bias.

The Impact of Gender on Early Mortality

There were 21 studies[26,28-31,33-37,39-48,50] with a combined population of 1,063,406 participants, that examined gender and its association with risk of early mortality. This included 14 cohort[29-31,33,35-37,40-43,45,48,50] and 7 case-control[26,28,34,39,44,46,47] studies. The number of participants ranged between 147[47] and 498,566.[36] Risk of bias was rated as low and high in 9 studies[29,31,34-36,40,41,43,46] and 12 studies,[26,28,30,33,37,39,42,44,45,47,48,50] respectively. The proportion of males in these studies averaged 55.8% and ranged between 49.4%[41] to 65.0%.[30]

Risk of early mortality was higher in women in three studies[26,36,40] and higher in men in two studies;[41,42] whereas, the remaining 16 studies showed no overall increased risk in either gender. The three studies[26,36,40] showing increased risk in women were larger (combined population of 586,240), with the risk of bias in these studies rated as low in two[36,40] and high one study.[26] In contrast, the two studies[41,42] showing increased risk in men were smaller (combined population of 20,052), with risk of bias being low and high (one study in each category).

The largest study by Foley et al,[36] a retrospective cohort study involving 498,566 patients (56.1% male), showed that after adjusting for multiple potential confounding factors, the risk of early mortality in women was higher compared to men, hazard ratio 1.06 (95% CI 1.04-1.09). The overall risk of bias in this study was low. Of the six studies with low risk of bias,[29,31,35,36,39,43] one[36] showed increased risk of early mortality in women, and none showed increased in men.

Of the 21 studies examining gender as a risk factor, 14[26,31,33-35,39-43,45,46,48,50] contained data amenable to extraction and further analysis. Data from these studies were pooled together to construct a cohort of 563,110 patients, which included 315,224 males and 247,886 females. The number of early deaths in each group was 24,696 (7.8%) and 20,256 (8.2%). This equated to crude early mortality rates of 28.3 (95% CI 28.0-28.7) and 30.0 (95% CI 29.6-30.4) per 100 person-years in men and women, respectively (Figure 2A). When analyses were restricted to high-quality studies only (ie, low risk of bias), 453,587 remained in the cohort overall: 250,447 men and 203,140 women. The number of patients who died in the early period in these two groups were 20,906 (8.3%) and 17,708 (8.7%), respectively. This equated to crude early mortality rates of 30.0 (95% CI 29.7-30.4) and 31.9 (95% CI 31.4-32.4) per 100 person-years in men and women, respectively (Figure 2B). Hence, the risk of early mortality was marginally higher in women compared to men.

The Impact of Diabetes on Early Mortality

A total of 17 studies[27-29,32-34,36,39-41,43-48,50] were found in this category, combined population 736,279. Number of subjects ranged between 147[47] and 498,566;[36] median 1,000. The proportion of patients with diabetes as the cause of ESRD ranged between 7.1%[32] and 64.6%.[39] Number of studies with high and low risk of bias were eight[28,33,39,44,45,47,48,50] and nine,[27,29,32,34,36,40,41,43,46] respectively.

Eight studies[27,28,32,34,39,44,46,47] compared the proportion of subjects with diabetes in those who died early vs the survivors (case-control design). Overall, subjects with diabetes were not at increased risk of early mortality. In the largest study in this group, Wolf et al[34] compared characteristics of 250 patients who died early to 750 matched controls. The proportion of subjects with diabetes as the cause of ESRD were identical; 43% in both groups. Khan et al[32] compared 42 patients who died within 90 days of starting HD with 42 controls; the proportion of patients with diabetes in both groups were identical (3/42 in each group). In contrast, two small studies with high risk of bias[28,44] did report an association between early mortality and a background of diabetic nephropathy. De Lima et al[44] compared those who died early to a group of subjects who survived more than 10 years of HD treatment. The proportion of subjects with diabetes were 35% and 0%, respectively. The results were not adjusted for any potential confounders.

Nine studies[29,33,36,40,41,43,45,48,50] compared mortality rates in patients with and without history of diabetes (cohort design). Overall, results were mixed, with some showing diabetes to confer an increased risk of early mortality whilst others demonstrating a protective effect. Robinson et al[40] included 86,886 new dialysis starters. Within the first 120 days of starting HD, 8.1% of patients with diabetic nephropathy died; in comparison, this rate was 9.2% in those with other renal etiologies. Hence, diabetes was said to be protective. Another large study, however, appeared to show an opposite effect. In the study by Tsakiris et al[45] (n=78,534), percentage of early mortality was 5.0% in patients with background of diabetes and 2.6% in those without. In the remaining six studies in this category, three[29,33,41] showed increased risk, two[36,43] no overall effect, and one[27] showed a protective effect of diabetes.

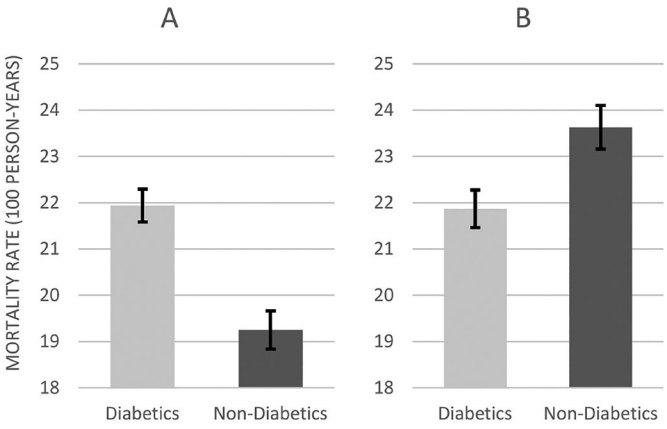

Figure 3. Early mortality rates in patients with and without diabetes when data from 9 studies (see text) were pooled together (A) for all 9 studies (B) for studies with low risk of bias.

In total, nine studies[27,33,39-41,43,45,46,48] with a combined population of 223,096 participants contained data that enabled the construction of two cohorts of patients: one with diabetes (n=59,893) and another without diabetes (n=163,203). The number patients who died in the early period were 4,514 (7.5%) and 10,354 (6.3%) in the two groups, respectively. This equated to crude early mortality rates of 21.9 (95% CI 21.3-22.6) and 19.2 (95% CI 18.9-19.6) per 100 person-years in patients with diabetes and those without diabetes, respectively (Figure 3A). When analyses were restricted to high-quality studies only (ie, low risk of bias), 131,085 remained in the cohort overall: 45,119 patients with diabetes and 85,966 without diabetes. The number of patients who died in the early period in these two groups were 3,406 (7.5%) and 7,118 (8.3%), respectively. This equated to crude early mortality rates of 21.9 (95% CI 21.1-22.6) and 23.6 (95% CI 23.1-24.2) per 100 person-years in diabetics and non-diabetics, respectively (Figure 3B). Hence, although initial analyses not accounting for quality suggested higher mortality in diabetic patients, this effect was not found after restricting analyses to high quality studies.

Discussion

This systematic review of the literature examined the impact of key risk factors on early mortality after commencement of maintenance HD. The results confirm previous findings that increasing age is associated with increased risk of death soon after starting maintenance HD. We have also shown a slightly increased risk of early mortality in women. The current data do not allow for firm conclusions to be drawn on the association of diabetes with increased risk of early mortality.

Experience from pre-dialysis care shows that many patients with CKD who are about to start dialysis have limited understanding of the outcomes of dialysis treatment.[55] Providing tailored information to this patient group may be particularly difficult given the paucity of available resources to inform any discussions about the *early days* of dialysis, a particularly risky period in the care of patients with advanced CKD. This systematic review, therefore, goes some way in addressing this knowledge gap and aims to help patients make informed choices about their future care. It is hoped that the findings of this systematic review will stimulate further efforts to design interventions for reduction in the risk of early mortality.

The data reported in this paper formed part of a wider systematic review of literature examining risk factors and interventions related to reducing the risk of early mortality in the

incident HD population. It was not possible to include findings related to all the risk factors examined due to space limitations. The reporting here prioritizes the most commonly studied or the most important modifiable risk factors for early mortality.

Studies included in this systematic review were quite diverse in terms of their design, settings (originating 12 different countries), baseline differences in participant characteristics, duration of observation for early mortality (90, 120 or 180 days), types of comparator groups used, and the reporting of outcomes. Consequently, a quantitative synthesis of all the available evidence was not possible. We were able to draw a limited comparison of crude mortality rates in isolated risk groups (depending on the reporting of raw data). This was done mainly to support the narrative account; these comparisons were not adjusted for potential confounding factors due to lack of sufficient data. Therefore, the results are to be interpreted with caution.

Overall, 13 studies were judged to be at high risk of bias. Selection bias was the largest contributor to the high overall risk of bias. Only a minority of studies set out specifically to investigate risk factors for early mortality in unselected incident dialysis population.[27,30,31,35,38-43] In most cases, the studies' primary focus was not necessarily to investigate risk factors for early mortality, but rather on addressing other objectives such as quantification of weekly mortality rates in new dialysis starters,[36] comparison of baseline characteristics between patients who died early and those who survived long-term on dialysis,[44] mortality risk prediction in the elderly,[33] risk associations in diabetic subjects,[26,28] and the study of specific and limited risk factors for early mortality (eg, mobility in the elderly,[37] vitamin D status in those not previously treated with vitamin D supplements,[34] and basic patient demographics).[32,45] This had implications on the selection of study participants, measurement of risk exposure, analytical methods used, and reporting of outcomes. The reporting of these studies was generally in keeping with their respective pre-defined objectives; however, for the purposes of this systematic review, there were significant omissions in the design and reporting of these studies that led to them being judged as at high risk of bias. The majority of studies reporting early mortality rates in new HD starters, and those examining the effects of risk factors and interventions on early mortality, in this patient population, were of low quality.

Elderly patients are disproportionately affected by early mortality. Introducing HD incrementally, rather than abruptly starting HD at *full doses*, has been proposed as a way of making the start easier for this patient group.[56] This could attenuate the disruptive effects of regular HD regimen on patients' life-styles and preserve residual renal function,[57,58] which could improve survival and quality of life. Female gender was also associated with a slightly increased risk of early mortality. Interestingly, this observation seems to corroborate findings that the most commonly used measure of dialysis effectiveness (the 'Kt/V_{urea}') under-estimates true dialysis requirements in women.[59,60] It raises the possibility that women may be under-dialyzed if put on the same treatment program as men. Further research is needed before this can be proven definitively.

Conclusions

This systematic review of literature summarizes the impact of age, gender and diabetes on risk of early mortality after commencement of maintenance HD. Results show that older age and possibly female gender are associated with higher risks of early mortality whereas the literature currently does not support the notion of increased risks in those with diabetes. Future interventions[61] should aim to target these high-risk groups as this is likely to lead to highest impact in terms of reducing early mortality rates.

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