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Original Article

Survival outcomes of supportive care *versus* dialysis therapies for elderly patients with end-stage kidney disease: A systematic review and meta-analysis

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SUMMARY AT A GLANCE

Multiple factors may influence the decision-making of initiating dialysis in elderly patients with end-stage renal disease (ESRD). This systematic review of cohort studies or randomized controlled trials found that 1-year survival of elderly patients who were dialyzed had similar 1-year survival with those treated conservatively for their ESRD. However, available data on conservative care are limited and there is probably a substantial publication bias.

ABSTRACT:

Aim: **Elderly people comprise a large and growing proportion of the global dialysis population. Regional differences in rates of dialysis in the elderly suggest multiple factors influence treatment decision-making including beliefs about the relative benefits and harms of dialysis and supportive (non-dialysis) care. We therefore systematically reviewed the literature reporting survival of elderly patients treated with either treatment pathway.**

Methods: **Systematic review and meta-analysis of cohort studies or randomized controlled trials identified in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials published before July 2014. Survival by treatment modality was calculated. Subgroup analyses by study design, study size, patient age and cohort era were conducted.**

Results: **Eighty-nine studies published between 1976 and 2014 reported on 294 921 elderly end-stage kidney disease (ESKD) patients. There was a paucity of data for supportive care (724 patients or 0.2% of the total patients) and supportive care studies were susceptible to lead-time bias. One-year survival for elderly patients treated with undifferentiated dialysis was 73.0% (95% confidence interval (CI) 66.3–79.7%), 78.4% (95% CI 75.2–81.6) for haemodialysis and 77.9% (95% CI 73.8–81.9) for peritoneal dialysis. Supportive care patients had a 1-year survival of 70.6% (95% CI 63.3–78.0%). Residual heterogeneity remained within individual treatment modalities despite subgroup analyses.**

Conclusions: **While the available literature demonstrates a broadly similar 1-year survival in elderly ESKD patients, it does not allow a confident estimate of the relative survival benefits of dialysis or supportive care. This uncertainty needs urgent attendance by further prospective data, which avoid bias and allow comparisons of quality of life and survival.**

In 2010, more than 2.2 million people received dialysis globally.[1] Older patients represent a larger proportion of the treated end-stage kidney disease (ESKD) population and people aged ≥75 now constitute over one-fifth of incident dialysis patients in Australia and the USA,[2,3] and between 9% and 40% of patients in Europe.[4] In the USA, the ‘elderly’ are the fastest growing dialysis age-group, having increased by 57% over the last decade.[2]

Elderly ESKD patients are different to their younger counterparts with respect to clinical profile and treatment preferences. They have greater comorbidity,[5] increasing frailty[6] and reduced functional status,[7] although the full impact of these disparities on outcomes is uncertain. Issues such as treatment burden, quality of life, perceptions of becoming a strain upon their families and life expectancy are important to elderly patients when contemplating dialysis,[8] but may not be as applicable for younger persons. Dialysis and its associated procedures may also be associated with harms that differentially affect the elderly.[9] These differences influence the dialysis decision-making process and increase the need to delineate elderly patient outcomes. Unfortunately, data about fundamental aspects such as survival with supportive (non-dialysis) care or dialysis in the elderly remain unclear, making counselling and treatment for ESKD challenging. One previous review presented the evidence on supportive care and reported a median survival between 6.3 and 23.4 months, but did not examine survival in the elderly with dialysis.[10] We therefore aimed to systematically review reports of survival in elderly ESKD patients treated with supportive care or dialysis.

METHODS

Data sources

We performed a systematic review according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[11] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12] guidelines for conduct of systematic reviews and meta-analyses of observational cohort studies and randomized controlled trials (RCTs), respectively. Relevant studies were identified by searching: MEDLINE (1950 to July 2014), EMBASE (1966 to July 2014) and the Cochrane Central Register of Controlled Trials (to issue 7 of 12, July 2014), using relevant text words and medical subject headings including terms describing elderly patients with chronic kidney disease (CKD) and dialysis-based treatment pathways, and all studies of supportive, non-dialysis care (Supplementary text S1) with no language restriction. Reference lists from identified studies and reviews were scanned to identify other studies. Authors were contacted to provide data on elderly subgroups of supportive care studies if this data was not available in original reports.

Study selection

The literature search, data extraction and quality assessment were conducted independently by two authors using a standardized approach (CF and SK). Inclusion criteria were:

1 All included study author definitions for age of 'elderly' patients were accepted AND/

2 Studies had to report on management of ESKD, defined as an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or the need for renal replacement therapy (RRT) in the setting of CKD AND/

3 All studies reporting supportive, non-dialysis management of ESKD OR/ prospective or retrospective cohort studies or RCTs examining dialysis (undifferentiated dialysis (i.e. haemodialysis and peritoneal dialysis combined), haemodialysis, peritoneal dialysis) reporting quantitative survival for elderly patients were included.

Studies that reported on transplant outcomes or undifferentiated RRT (i.e. included both dialysis and transplantation in their survival estimates) were excluded. As the aim of this review was to provide survival estimates with and without RRT, literature that systematically excluded reports of non-dialysis outcomes, such as registry reports, were excluded.

Data extraction

Published reports were obtained for each study and information was extracted including study characteristics (publication year, cohort era (median year of cohort enrolment), place of study, study type, study centre, treatment type, follow-up duration, definition of elderly); patient characteristics (age, gender, ethnicity, diabetes history, cardiovascular disease history, comorbidity assessment) and survival estimates. Study quality was judged using a checklist developed from the Strengthening the Reporting of Observational studies in Epidemiology (STROBE)[13] criteria for cohort studies and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for RCTs.[14]

Data analysis

All survival or mortality estimates in individual studies were collected regardless of specific time intervals or as a mean/median survival for the cohort. We made an *a priori* pragmatic decision to combine the most commonly reported survival or mortality measure(s) and, when possible, estimates were converted. Studies reporting survival for more than one treatment pathway (i.e. separate estimates for haemodialysis and peritoneal dialysis) were entered separately. Summary estimates of survival for different treatment pathways (undifferentiated dialysis, haemodialysis, peritoneal dialysis, supportive care) were obtained using a random effects model. Percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. We also conducted sensitivity and subgroup analyses to explore the impact of patient age, study type (RCT *vs* cohort), design (prospective *vs* retrospective) and study size (by tertiles) and cohort era (<2000, ≥2000) on our findings. Differences between patient characteristics by treatment type were tested using chi- square and *t*-tests. Statistical analyses were performed with Stata, version 11 (Stata, College Station, TX, USA).

RESULTS

Search results and characteristics of included studies

The literature search yielded 5944 papers, 473 were reviewed in full text (Fig. 1) and a further 384 studies were excluded, leaving 89 studies reporting on dialysis and/or supportive care in which pooled estimates of survival for different treatment pathways were determined. Studies were published between 1976 and 2014 and included a total of 294 921 patients among whom 255 807 were treated with dialysis (undifferentiated) ($n = 32$), 22 994 patients were treated with haemodialysis ($n = 27$), 15 396 were treated with peritoneal dialysis ($n = 36$) and 724 treated with supportive care ($n = 11$). No RCTs were identified. Most studies reported survival as the proportion of patients surviving at 1, 2 and 5 years with the majority reporting 1-year data. We therefore selected 1-year survival as our primary survival outcome measure.

The study sample size ranged from 9[S48] to 89 877 patients[S2] (Table 1). Mean age ranged from 60.5 to 92 years and

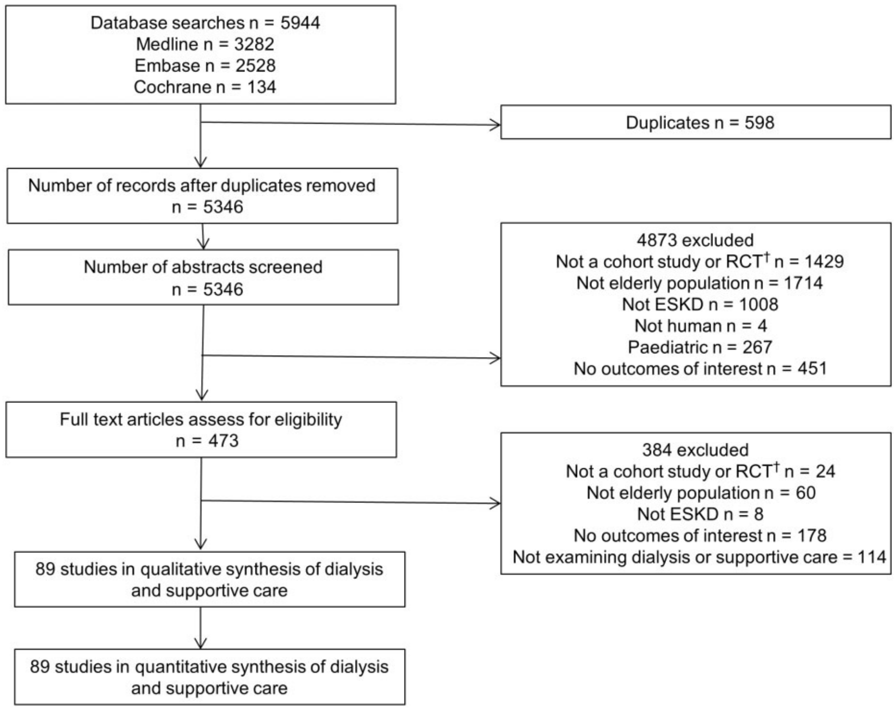

Fig. 1 Study inclusion and exclusion flow diagram. †Reviews, letters, qualitative studies, case reports/series and case–control studies.

follow-up from 7.3 to 132 months. Overall median study quality score was 5 out of 8 (Table 2). The majority of studies were retrospective ($n = 71$) including 7 out of 12 supportive care studies (58%). Dialysis studies consistently measured survival from dialysis initiation. Supportive care studies used different time points including first date of eGFR < 15 mL/min/1.73 m^2 [S1,S6,S24,S36] or eGFR < 10–15 mL/min/1.73m[S19], putative dialysis date[S23,S51], study enrolment[S9,S10] or from decision not to dialyze[S44,S49] making estimates susceptible to lead-time bias (Table 3). Supportive care studies were published more recently than other modalities ($P < 0.05$).

Publications reporting elderly ESKD patient survival increased with each decade with a particular growth in publication of large studies since 2000 (Fig. 2). The threshold used to define 'elderly' also rose in later publications, from as low as 55 years (in studies published prior to 1980) to as high as 80–90 years (in studies published from 2010 onwards) (Fig. 2). The vast majority of studies were conducted in the USA, Europe and Canada with a few studies in developed Asia and Oceania (Figure S1). Importantly, supportive care studies originated in Europe and Developed Asia alone (Table 3).

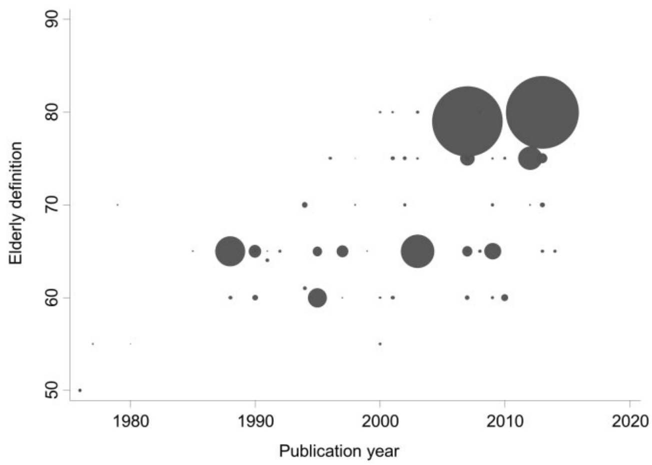

Fig. 2 Authors' minimum age threshold used to define elderly (years) over time (size of dots represent size of studies). Individual study characteristics are listed in Table 1.

Patient characteristics

The overall mean patient age was 76.5 years. Patients treated with supportive care were older and had increased prevalence of diabetes compared to dialysis modalities and this difference was statistically significant (Table 4). Prevalence of cardiovascular disease varied across modalities. A measure of overall comorbidity was provided by 23/89 (25.8%) studies. Overall comorbidity was reported as a standardized score (Charlson comorbidity index[15] ($n = 10$), Davies comorbidity score[16] ($n = 2$)) while some authors devised their own scores ($n = 8$).

Survival of elderly ESKD patients

The combined 1-year survival rate for elderly patients treated with undifferentiated dialysis was 73.0% (95% confidence

Table 1 Study characteristics

Publication Year	Author	Number of patients	Mean age	Female (%)	Diabetic (%)	Follow up (months)	Median cohort year	Mode of therapy	Country or region	Study type	Centre type
2014	Shum[S1]	199	73.8	49.9	55.8	23.52	2007	PD, SC	Hong Kong	Retrospective	Single centre
2013	Arce[S2]	89 877	NR	NR	NR	NR	2001	Undiff DX	USA	Retrospective	Registry
2013	Cheng[S3]	138	72.5	52.3	39	NR	1997	PD	Taiwan	Prospective	Single centre
2013	Gubensek[S4]	214	83	52	26	NR	2007	Undiff DX	Slovenia	Retrospective	Single centre
2013	Hatakeyama[S5]	141	84.2	48.2	NR	NR	2001	Undiff DX	Japan	Retrospective	Registry
2013	Hussain[S6]	441	NR	NR	NR	NR	2008	Undiff DX , SC	England	Prospective	Network
2013	Oliva[S7]	704	79.3	45	17	NR	2006	HD	Spain	Retrospective	Registry
2013	Praga[S8]	1 841	79.6	61.6	32.4	NR	2009	HD	Spain	Prospective	Network
2013	Seow[S9]	63	78	44.4	60.3	24	2008	SC	Singapore	Prospective	Single centre
2012	Da Silva-Gane[S10]	30	77.5	30	NR	27	2006	SC	Europe	Prospective	Single centre
2012	Foote[S11]	1 781	79	38.1	31	27.6	2004	Undiff DX	Australia and New Zealand	Retrospective	Registry
2012	Isaacs[S12]	147	83	28	31.2	NR	2005	Undif Dx, SC	England	Retrospective	Single centre
2012	Madziarska[S13]	51	77.5	62.7	NR	NR	2006	Undiff DX	Poland	Prospective	Network
2012	Nordio[S14]	9 487	NR	NR	NR	NR	2004	Undiff DX	USA	Retrospective	Registry
2011	Jeloka[S15]	18	72.3	32.3	77.7	NR	2008	Undiff DX	India	Retrospective	Single centre
2011	Stroupe[S16]	8 022	75.7	2.5	55	NR	2001	Undiff DX	USA	Retrospective	Registry
2011	Winkelmayer[S17]	23 777	74.9	50.3	61.7	NR	1996	Undiff DX	USA	Retrospective	Registry
2010	Bayat[S18]	940	NR	42.8	40.5	NR	2000	Undiff DX	France	Prospective	Network
2010	Chandna[S19]	183	80.21	32.3	26.2	NR	1999	Undiff Dx, SC	England	Retrospective	Single centre
2010	Genestier[S20]	112	81.3	51	42	NR	2002	PD	France	Prospective	Single centre
2010	Suzuki[S21]	46	79.4	65	21.7	60	1999	PD	Japan	Retrospective	Single centre
2010	Verdalles[S22]	139	78.6	32.4	33.8	39.6	2004	Undiff DX	Spaine	Retrospective	Single centre
2009	Carson[S23]	202	75	31.2	29.5	NR	2000	Undiff DX, SC	England	Prospective	Single centre
2009	Ellam[S24]	69	80	42	38	NR	2005	SC	England	Retrospective	Single centre
2009	Hung[S25]	692	72.6	52.3	43.9	NR	1995	HD, PD	Taiwan	Retrospective	Single centre
2009	Martin Navarro[S26]	211	72.5	NR	25.6	23.1	2003	Undiff DX	Spain	Retrospective	Network
2009	Ounissi[S27]	13	70	23.1	46.2	NR	1994	PD	Tunisia	Retrospective	Single centre
2009	Panzetta[S28]	112	NR	48.2	NR	NR	1997	Undiff DX	Italy	Retrospective	Network
2009	Steele[S29]	168	NR	35	30.9	NR	2005	HD	England	Retrospective	Single centre
2009	Tazza[S30]	4 825	NR	NR	NR	NR	1998	Undiff DX	Italy	Retrospective	Registry
2008	Basic-Jukic[S31]	12	NR	50	33	NR	NR	HD	Croatia	Prospective	Single centre
2008	Kawecka[S32]	133	71.8	39.8	34.6	12.5	1994	HD	Poland	Retrospective	Single centre
2008	Li[S33]	162	74.7	43	45	32.7	2003	HD	Canada	Prospective	Network
2008	Povlsen[S34]	100	74.6	44	26	NR	2002	PD	Denmark	Retrospective	Single centre
2008	Santoro[S35]	26	92	53.8	NR	36	1996	Undiff DX	Italy	Retrospective	Registry
2007	Murtagh[S36]	129	79.6	34.6	25	19.6	2004	Undiff DX, SC	England	Retrospective	Network
2007	Alenabi[S37]	926	NR	NR	NR	NR	1985	PD	France	Retrospective	Registry
2007	Couchoud[S38]	3 512	80	40.7	36	24	2004	Undiff DX	Franceope	Retrospective	Registry
2007	Han[S39]	359	NR	NR	NR	NR	1993	PD	Korea	Retrospective	Single centre
2007	Hiramatsu[S40]	421	76.4	41	29	22.2	2002	PD	Japan	Retrospective	Network
2007	Jassal[S41]	1 739	79.2	41.4	24.8	NR	1992	Undiff DX	Canada	Retrospective	Registry
2007	Kurella[S42]	83 996	84.2	48.5	33	NR	2000	Undiff DX	USA	Retrospective	Registry
2007	Li[S43]	121	71	44.6	66	NR	2002	PD	Hong Kong	Retrospective	Single centre
2007	Wong[S44]	73	79	49.3	NR	NR	2005	SC	England	Prospective	Single centre

2007	Yang[S45]	57	79.7	38.6	31.6	NR	1997	PD	Canada	Retrospective	Network
2007	Lim[S46]	5 176	NR	43	34	NR	1999	PD	Canada	Retrospective	Registry
2004	Sunder[S47]	9	90.61	44.4	22.2	23.3	1998	PD	Canada	Retrospective	single centre
2003	Jager[S48]	18920	NR	NR	NR	NR	1992	Undiff DX	Europe	Retrospective	Registry
2003	Joly[S49]	144	83.2	44.9	6.5	NR	1995	Undiff DX, SC	France	Retrospective	Single centre
2003	Letourneau[S50]	67	NR	NR	37	NR	1998	Undiff DX	France	Retrospective	Single centre
2003	Smith[S51]	26	71	38	43	NR	1998	SC	England	Retrospective	Single centre
2002	Harris[S52]	171	76.9	34.4	NR	12	1996	HD, PD	England	Prospective	Network
2002	Kadambi[S53]	192	NR	42	51	NR	1997	PD	USA	Retrospective	Single centre
2002	Vrtovsnik[S54]	292	81.5	46.6	NR	NR	1989	PD	France	Retrospective	Single centre
2001	Chauveau[S55]	290	79.8	42.4	10.3	NR	1996	HD	France	Prospective	Network
2001	Dimkovic[S56]	38	83.5	35.5	45.1	8.7	1998	PD	Canada	Retrospective	Network
2001	Kutner[S57]	316	68.4	NR	26.3	132	1994	Undiff DX	USA	Retrospective	Network
2001	Peri[S58]	95	83.7	50.5	22	NR	1993	HD	USA	Retrospective	Single centre
2000	Choi[S59]	101	NR	NR	NR	NR	NR	PD	Korea	Retrospective	Single centre
2000	Johnson[S60]	107	65.9	54	12.2	33.6	1995	Undiff DX	Australia	Retrospective	Single centre
2000	Lamping[S61]	125	76.3	44	27	12	1996	Undiff DX	England	Prospective	Network
1999	Arkouche[S62]	30	NR	NR	NR	NR	1986	HD	France	Retrospective	Single centre
1998	Christidou[S63]	23	77.8	21.7	39	NR	NR	PD	Greece	Retrospective	Single centre
1998	De Vecchi[S64]	63	76.5	30.2	0	27	1989	PD	Italy	Retrospective	Single centre
1997	Malberti[S65]	2 447	NR	NR	15	NR	1988	HD, PD	Italy	Retrospective	Registry
1997	Sitter[S66]	56	NR	NR	NR	NR	1990	HD, PD	Germany	Retrospective	Single centre
1996	Issad[S67]	213	79.4	48	19	21.4	1986	PD	France	Retrospective	Single centre
1995	Salomone[S68]	1 501	NR	NR	25.5	NR	1987	HD, PD	Italy	Retrospective	Registry
1995	Schaubel[S69]	6 116	69.9	42	22	NR	1990	Undiff DX	Canada	Retrospective	Registry
1994	Lupo[S70]	458	NR	NR	NR	NR	1985	PD	Italy	Retrospective	Network
1994	Mailloux[S71]	271	NR	NR	23	NR	1980	Undiff DX	USA	Retrospective	Single centre
1992	Churchill[S72]	138	NR	NR	NR	7.3	1989	HD	Canada	Prospective	Network
1991	Gentil[S73]	170	NR	NR	34	NR	1986	HD, PD	Spain	Retrospective	Network
1991	Joglar[S74]	50	73.3	52	36	12.8	1988	HD, PD	Puerto Rico	Retrospective	Single centre
1990	Benevent[S75]	78	72	NR	12	21.5	1980	PD	France	Retrospective	Single centre
1990	Nebel[S76]	26	NR	NR	42.3	21.3	1986	PD	Germany	Retrospective	Single centre
1990	Nissenson[S77]	492	NR	36	20	NR	1983	PD	USA	Retrospective	Network
1990	Piccoli[S78]	763	NR	NR	9	NR	1984	HD, PD	Italy	Retrospective	Registry
1990	Posen[S79]	2 671	NR	NR	NR	NR	1984	HD PD	Canada	Retrospective	Registry
1990	Segolini[S80]	514	71.3	54	10.9	NR	1985	PD	Italy	Retrospective	Registry
1990	Walls[S81]	113	68.5	NR	4.4	NR	1984	HD	England	Retrospective	Single centre
1990	Williams[S82]	58	69.2	36.2	3.4	NR	1984	HD, PD	England	Retrospective	Network
1988	Brunner[S83]	15 620	NR	NR	NR	NR	1977	HD, PD	Europe	Retrospective	Registry
1988	Fauchald[S84]	246	66.7	31	3.3	NR	1983	Undiff DX	Norway	Retrospective	Registry
1985	Rotellar[S85]	26	74	65.4	11.5	NR	NR	HD	Spain	Retrospective	Single centre
1980	Rathaus[S86]	22	62.9	45.5	4.5	NR	1975	HD	Israel	Retrospective	Single centre
1979	Chester[S87]	45	75.2	NR	NR	NR	NR	HD	USA	Retrospective	Single centre
1977	Kolendorf[S88]	26	60.5	42.3	NR	NR	1973	HD	Denmark	Retrospective	Single centre
1976	O'Brien[S89]	154	NR	21.4	NR	NR	1970	HD	USA	Retrospective	Network

Please note that superscript numbers refer to study references in supplementary material.HD, haemodialysis; NR, not reported; PD, peritoneal dialysis; Undiff DX, undifferentiated dialysis; USA, United States of America.

Table 2 Quality assessment of included studies

Author	Study design	Selection criteria defined	Missing data addressed	Loss to follow-up reported and <10%	Exposure defined by records	Outcome defined by medical records	Confounders addressed	Conflicts of interest declared	Score
Alenabi	0	1	0	0	1	1	1	0	4
Arce	0	1	1	0	1	1	1	1	6
Arkouche	0	1	0	0	1	1	1	0	4
Basic-Jukic	1	1	0	0	1	1	0	0	4
Bayat	1	1	1	1	1	1	1	1	8
Benevent	0	1	0	0	1	1	0	0	3
Brunner	1	1	0	0	1	1	1	0	5
Carson	0	1	1	0	1	1	1	1	6
Chandna	0	1	1	0	1	1	1	1	6
Chauveau	1	1	0	0	1	1	1	0	5
Cheng	0	1	0	0	1	1	1	1	5
Chester	0	1	0	0	1	1	1	0	4
Choi	0	1	0	0	1	1	0	0	3
Christidou	0	1	0	0	1	1	0	0	3
Churchill	1	1	0	0	1	1	1	0	5
Couchoud	0	1	0	0	1	1	1	1	5
Da Silva-Gane	1	1	0	0	1	1	1	1	6
De Vecchi	0	1	0	0	1	1	1	0	4
Dimkovic	0	1	0	0	1	1	1	0	4
Ellam	0	1	0	0	1	1	1	1	5
Fauchald	1	1	1	1	1	1	1	1	8
Foote	0	1	0	0	1	1	0	0	3
Genestier	1	1	1	1	1	1	1	1	8
Gentil	1	1	0	0	1	1	1	1	6
Gubensek	0	1	0	0	1	1	0	0	3
Han	1	1	0	0	1	1	1	0	5
Harris	0	1	0	0	1	1	1	1	5
Hatakeyama	0	1	0	0	1	1	0	1	4
Hiramatsu	0	1	0	0	1	1	0	0	3
Hung	0	1	0	0	1	1	1	0	4
Hussain	0	1	0	1	1	1	1	1	6
Isaacs	0	1	0	0	1	1	0	1	4
Issad	0	1	0	0	1	1	0	0	3
Jager	0	1	0	0	1	1	0	0	3
Jassal	0	1	0	0	1	1	1	1	5
Jeloka	0	1	0	0	1	1	1	1	5
Joglar	0	1	1	1	1	1	1	0	6
Johnson	0	1	0	1	1	1	1	0	5
Joly	1	1	0	0	1	1	1	0	5
Kadambi	0	1	0	0	1	1	0	0	3
Kawecka	0	1	0	0	1	1	1	0	4
Kolendorf	0	1	0	0	1	1	1	0	4
Kurella	0	1	0	0	1	1	1	0	4
Kutner	0	1	1	1	1	1	1	1	7
Lamping	0	1	1	0	1	1	1	1	6
Letourneau	1	1	1	1	1	1	1	1	8
Li	0	1	0	0	1	1	1	0	4
Li	0	1	0	0	1	1	0	0	3
Lim	1	1	1	1	1	1	1	1	8
Lupo	0	1	0	0	1	1	1	1	5
Madziarska	0	1	0	0	1	1	0	0	3
Mailloux	1	1	0	0	1	1	1	1	6
Malberti	0	1	0	0	1	1	1	0	4
Martin Navarro	0	1	0	1	1	1	1	0	5
Murtagh	0	1	1	1	1	1	1	0	6
Nebel	0	1	0	0	1	1	0	0	3
Nissenson	0	1	1	1	1	1	1	1	7

Table 2 *Continued*

Author	Study design	Selection criteria defined	Missing data addressed	Loss to follow-up reported and <10%	Exposure defined by records	Outcome defined by medical records	Confounders addressed	Conflicts of interest declared	Score
Nordio	0	1	0	0	1	1	1	1	5
O'Brien	0	1	0	0	1	1	0	0	3
Oliva	0	1	0	0	1	1	1	1	5
Ounissi	0	1	1	1	1	1	1	0	6
Panzetta	0	1	0	0	1	1	0	0	3
Peri	0	1	0	0	1	1	1	0	4
Piccoli	0	1	0	0	1	1	0	0	3
Posen	0	1	0	0	1	1	1	0	4
Povlsen	0	1	0	0	1	1	1	0	4
Praga	1	1	0	0	1	1	1	0	5
Rathaus	0	1	0	0	1	1	1	0	4
Rotellar	0	1	0	0	1	1	1	0	4
Salomone	0	1	0	0	1	1	1	0	4
Santoro	0	1	0	0	1	1	0	0	3
Schaubel	0	1	0	0	1	1	1	0	4
Segolini	0	1	0	0	1	1	1	1	5
Seow	1	1	0	0	1	1	1	1	6
Shum	0	1	1	0	1	1	1	0	5
Sitter	0	1	0	0	1	1	1	0	4
Smith	0	1	0	0	1	1	1	0	4
Steele	0	1	0	0	1	1	1	0	4
Stroupe	0	1	1	1	1	1	1	0	6
Sunder	0	1	0	0	1	1	0	0	3
Suzuki	0	1	0	0	1	1	1	0	4
Tazza	0	1	0	0	1	1	1	1	5
Verdalles	0	1	0	0	1	1	1	0	4
Vrtovsnik	0	1	1	0	1	1	1	0	5
Walls	0	1	0	0	1	1	0	0	3
Williams	0	1	0	0	1	1	1	1	5
Winkelmayer	0	1	0	1	1	1	1	0	5
Wong	0	1	0	0	1	1	1	0	4
Yang	1	1	0	0	1	1	1	0	5

Note: A higher score denotes higher quality. Quality scores in this systematic review range from 3 to 8.Study design: 1 = prospective, 0 = retrospective; selection criteria: 1 = yes, 0 = no; missing data addressed: 1 = yes, 0 = no; loss to follow-up reported and <10%: 1 = yes, 0 = no; exposure defined by records: 1 = yes, 0 = no; outcome defined by medical records: 1 = yes, 0 = no; confounders addressed: 1 = yes, 0 = no; conflicts of interest declared: 1 = yes, 0 = no.

interval (CI) 66.3–79.7, 238 596 patients, 24 studies), 78.4% (95% CI 75.2–81.6, 18 675 patients, 22 studies) in those treated with haemodialysis and 77.9% (95% CI 73.8–81.9, 12 914 patients, 28 studies) in those treated with peritoneal dialysis (Fig. 3a–c). The 1-year survival for supportive care elderly patients was 70.6% (95% CI 63.3–78.0, 661 patients, 10 studies) (Fig. 3d). There was considerable heterogeneity in survival estimates within each treatment type evidenced by all intra-group I^2 values being greater than 65. No difference was seen in sensitivity analyses, which excluded studies with mean study age <65 and studies which defined elderly as <65 (data not shown). Subgroup analyses by mean study age (age 65–79 and age >80) (Figure S2), study size (Figure S3), study design (prospective *vs* retrospective) (Figure S4) and cohort era (<2000, ≥2000) (Figure S5) demonstrated no impact on the main findings except for peritoneal dialysis in which prospective studies had lower survival compared to retrospective studies (61.5% (95% CI 46.8–76.3) and 80.3% (95% CI 76.2–84.9), respectively) (Figure S4).

The combined 2-year survival for undifferentiated dialysis elderly patients was 62.2% (95% CI 55.4–69.1, 17 studies), 64.3% (95% CI 60.0–68.6, 19 studies) for haemodialysis and 62.7% (95% CI 57.6–67.9, 25 studies) for peritoneal dialysis. Ten supportive care studies reported 2-year survival and the combined estimate was 44.4% (95% CI 35.9–52.9).

Survival out to 5 years was reported by a total of 34 studies and was 34.5% (95% CI 19.9–49.0, 10 studies) with undifferentiated dialysis, 35.1% (95% CI 27.2–43.0, 8 studies) with haemodialysis and 38.0% (95% CI 23.5–52.5, 14 studies) with peritoneal dialysis. Two supportive care studies reported 5-year survivals of 8.5 and 10%.

Table 3 Summary of supportive care studies

Author	Number of patients	Median age	Study design	Country	Diabetes (%)	Measure of overall comorbidity	Starting point for survival analysis	Survival
Carson[S23]	29	83	Prospective	England	13.8	Mean CCI3.7	Threshold eGFR for dialysis initiation based on dialysis cohort	Median 13.9months (range 2–44)
Chandna[S19]	106	81.4	Retrospective	England	28.3	Co morbidity score‡ >4 in 50.9%	eGFR < 10–15 mL/min/1.73 m^2 with all subsequent eGFR < 15 mL/min/1.73 m^2	One-year survival 80.2%
Da Silva-Gane[S10]	30	77.5††	Prospective	England	NR	Co morbidity score‡ >3 in 74%	Study enrolment, late stage 4/5 CKD attending low clearance clinic	One-year survival 75%, median survival 913 days
Ellam[S24]†	69	80	Retrospective	England	38	NR	eGFR < 15 mL/min/1.73 m^2	Median 21 months (range 1–100)
Hussain[S6]	172	NR, enrolled >70years	Prospective	England	NR	NR	eGFR < 20, eGFR < 15 and eGFR < 12 mL/min/1.73 m^2	One-year survival 71% from eGFR < 15
Isaacs[S12]‡‡	54	83	Retrospective	England	NR	NR	time of decision not to dialyse	Median 6 months (2.5–11)
Joly[S49]	37	84.1††	Retrospective	France	21.6	32.4% >= 3 comorbid conditions	Survival from decision not to perform dialysis	Median 8.9 months (95% CI 4–10)
Murtagh[S36]	77	83	Retrospective	England	23.4§	18.2% Davies grade 2 score	eGFR < 15 mL/min/1.73 m^2	Median 18months (range 0.1–73.1)
Seow[S9]	63	78	Prospective	Singapore	60.3§	CCI (not age adjusted) score of 5	Study enrolment, eGFR 8–12 mL/min/1.73 m^2	Two-year survival 61.9%
Shum[S1]	42	75.3††	Retrospective	Hong Kong	66.7	CCI mean 4.6	eGFR < 15 mL/min/1.73 m^2	One-year survival 80.7%
Smith[S51]†¶	26	71††	Retrospective	England	27	Mean comorbidity score‡ 4.7 (SD 3.0)	Putative dialysis initiation date	6.3 months
Wong[S44]†	73	79	Prospective	England	28^	Stoke's comorbidity grade = 1	Survival from decision not to perform dialysis	23.4 months

Please note that superscript numbers refer to study references in supplementary material.†Studies conducted in patients of all ages. ‡Comorbidity score = cardiac disease, peripheral vascular disease, cerebrovascular disease and respiratory disease. Severity scored as 0 = none, 1 = minimal, 2 = mild, 3 = moderate and 4 = advanced. Cancer graded (1–4) according to its activity and nature (medium-term survival). Cirrhosis = 4. Scores summed to = combined comorbidity score. §Diabetes as cause of renal disease. ¶Demographics from those recommended SC (SC treated group + recommended SC but chose RRT (n = 37). ††Mean age; ‡‡ not included in meta analysis as no proportion surviving provided.CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N, number of; NR, not reported; S, standard deviation.

Table 4 Characteristics of elderly end-stage kidney disease patients in included studies, mean (standard deviation)

	Overall	Undifferentiated dialysis	Haemodialysis	Peritoneal dialysis	Supportive care
Number of patients	294921	255807	22994	15396	724
Mean age	76.5 (5.9)	77.4 (6.3)	73.5 (6.3)	76.3 (5.3)	79.2 (4.0)
Cohort era	1995 (9.0)	1999 (6.6)	1989 (10.2)	1992 (7.5)	2003 (4.4)
Percentage of female	42.6(11.0)	40.4 (12.6)	44.8 (10.8)	42.8 (10.1)	43.6 (10.1)
Percentage of diabetic	29.5 (16.3)	30.9 (16.5)	23.3 (14.2)	30.2 (16.2)	36.9 (18.9)
Percentage of cardiovascular disease	47.1 (19.2)	40.7 (15.3)	52.0 (25.4)	49.9 (19.4)	45.1 (11.7)

Comparative survival with supportive care and dialysis

Six studies compared survival between dialysis modalities and supportive care for elderly patients (Fig. 4). They demonstrated a 1-year survival for dialysis modalities of 84.2% (95% CI 73.5–94.8%) and 72.7% with supportive care (95% CI 64.2–81.2%). Four studies explored factors which predicted survival according to management with dialysis or supportive care. All reported an overall survival advantage with dialysis, but three demonstrated loss of this survival benefit in the presence of high comorbidity[S1,S19,S36] whereas one showed a marked decrease in survival gain[S6]. Two studies found no difference between the two with decreased function defined as World Health Organization performance score of 3 or more[S6] or impaired function with activities of daily living[S1] whilst others found no advantage with age greater than 80[S6] or in the presence of ischemic heart disease[S36]. There was a 7.4-month survival advantage with dialysis therapy in the absence of high comorbidity (36.8 *vs* 29.4 months: $P = 0.03$) in one study[S19].

DISCUSSION

This study constitutes the most comprehensive summary of survival of elderly ESKD patients treated with supportive care or dialysis. We identified a large number of studies reporting survival on 294 921 elderly subjects. One-year survival for dialysis and supportive care were broadly similar although there was a paucity of survival data for supportive care patients who represented only 724 or 0.2% of the total. Importantly, considerable heterogeneity remained around estimates which could not be explained by study design, size, age definition of elderly patient or cohort era. Survival reports with supportive care were also susceptible to lead-time bias, limiting clinicians' ability to advise patients about prognosis. Comparison of outcomes according to treatment modality therefore requires higher quality prospective studies with equal reporting of comparable outcomes. These studies would ideally include patient-reported quality of life, symptom burden and hospitalization data obtained prior to decisions about treatment pathway for ESKD, with ongoing reporting irrespective of treatment choice until death.

Shared decision-making is advocated in the management of ESKD,[17] with an implied requirement for patient education on individual prognosis and quality of life to inform decisions. European nephrologists recommended supportive care in 10% of patients and an additional 5% of patients chose this pathway despite RRT recommendations.[18] Older age is associated with lower likelihood of RRT initiation in Australia[19] and Canada,[20] but little is known about what proportion of these patients are managed with supportive (non-dialysis) care. Predictive models in dialysis patients have identified age, comorbid conditions and laboratory results[21,22] as important factors for estimating mortality. These have at best moderate prognostic power (e.g. c-stat 0.7)[22] and apply only to those patients selected for and commencing dialysis. Data regarding outcomes of those treated with supportive care is still lacking, which means that counselling of elderly patients approaching CKD stage 5 remains difficult. Despite this uncertainty, some guidelines define elderly patient groups that should be considered for non-dialysis treatment on the basis that they may not benefit from dialysis in terms of increased survival or improved quality of life.[17] Our findings would suggest that the evidence to support such recommendations, at least for survival, is limited by the lack of supportive care registries that allow robust comparison with RRT registries.

Our findings of a median survival between 6 and 35 months for patients managed without dialysis are similar to those of a previous review.[10] Our meta-analysis demonstrated a 1-year survival of 70.6% (95% CI 63.3–78.0%) in elderly patients on supportive care. Few studies directly compared survival with dialysis and supportive care, but they suggested generally comparable survival at 1-year. Larger differences in survival were seen between modalities at 2 and 5 years; however, with only two supportive care studies reporting 5-year survival, this needs further exploration with patient-level data. We found no difference in survival of patients aged 65–79 and those aged 80+ treated with dialysis and supportive care. Other studies, which have mostly focused on haemodialysis patients, have found decreased life expectancy with increasing age within individual cohorts.[21,23] Possible explanations for our finding may be the small number of haemodialysis only studies with mean study age ≥80, the possibility of publication bias and that older age is associated with 6-month mortality rather than 1-year survival.

Four studies explored factors associated with benefit from dialysis therapy and found that high comorbidity[S1,S19,S36],

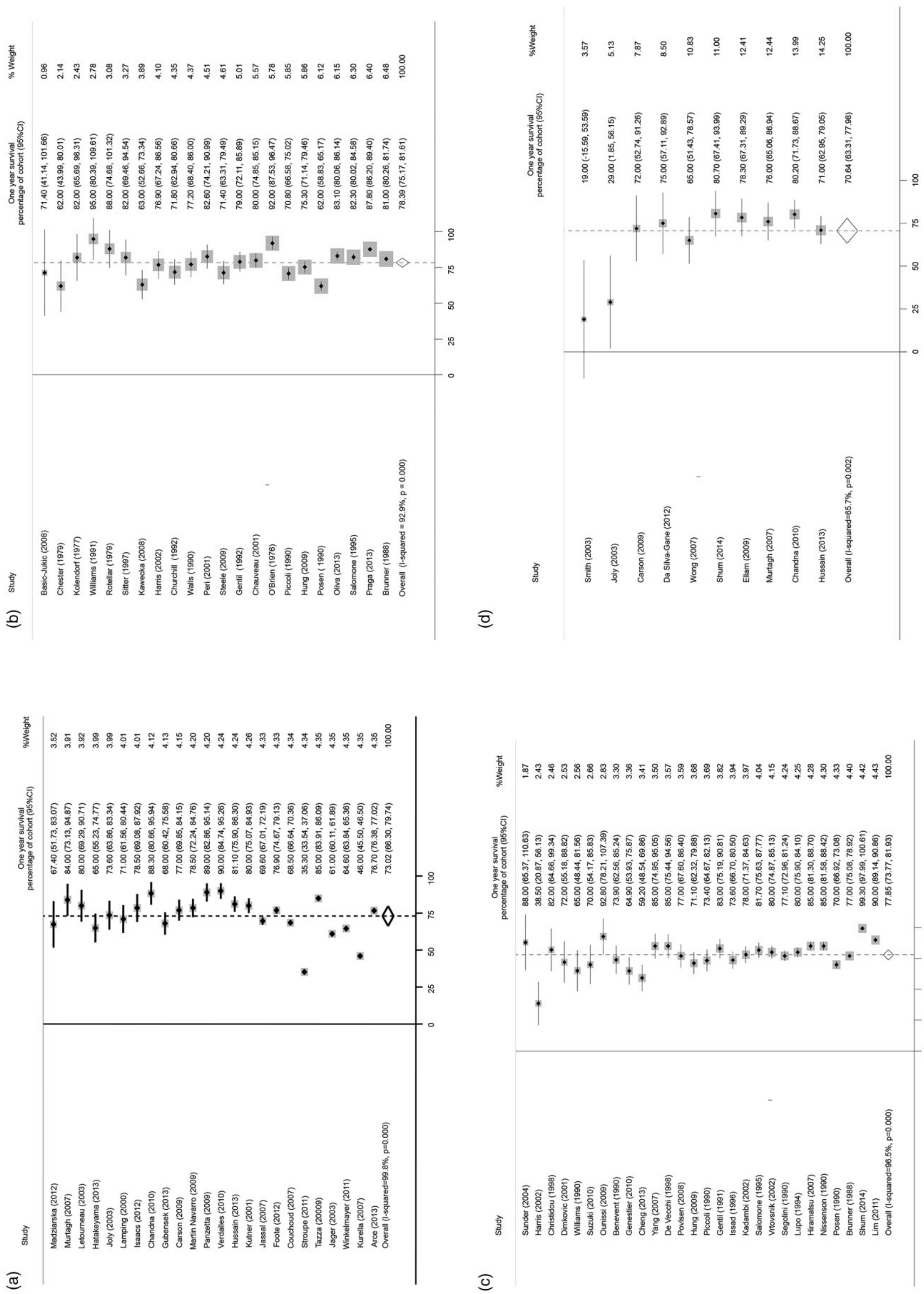

Fig. 3 One-year survival of elderly patients with different treatment modalities.
(a) undifferentiated dialysis, (b) haemodialysis, (c) peritoneal dialysis, (d) supportive care. Individual study characteristics are listed in Table 1.

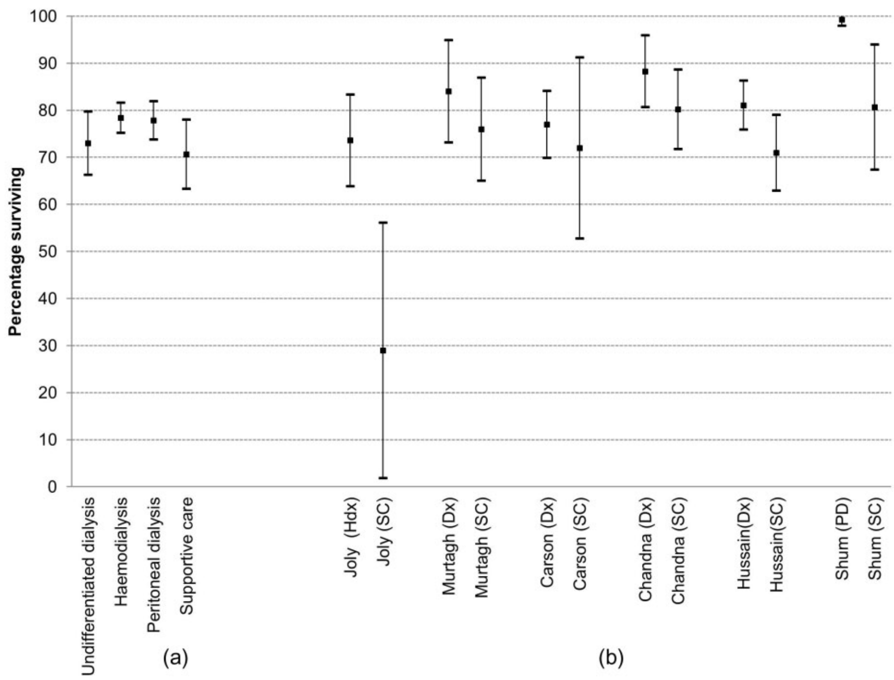

Fig. 4 Comparative 1-year survival (95% (confidence interval (CI)) of elderly patients treated with undifferentiated dialysis, haemodialysis, peritoneal dialysis and supportive care in (a) all studies and (b) in studies directly comparing survival for supportive (non-dialysis) and dialysis management. Individual study characteristics are listed in Table 1.

impaired functional status[S1,S6] and age older than 80[S1] were associated with loss of survival advantage. Interestingly, despite overall comorbidity being identified as an important factor in ascertaining benefit, such a measure was only reported in 26% of studies. In addition, higher levels of comorbidity were not always present in supportive care patients when compared with dialysis groups[S23,S36,S49]. This could be explained by comorbidity in elderly ESKD patients being uniformly high, resulting in it losing any discriminating capability. A further difficulty in comparing the comorbidity impact between studies was the use of different assessments (Table 3) including the Davies score[S36], Charlson comorbidity index[S23], Stokes comorbidity grade[S44] or author-devised scales[S19] with varying capacity to capture severity of conditions. The lack of comorbid data and its lack of uniformity meant that adjustment for levels of comorbidity were not possible in our analysis. Studies that have explored the impact of individual comorbid conditions on mortality of dialysis patients report variable effects. Cancer is independently associated with decreased survival in some studies[21,22] and not others;[5,23] and other conditions such as dementia[22,23] and peripheral vascular disease[23] also differ in their predictive capacity. While it appears intuitive to suppose that differences in the type and severity of comorbidities will influence survival, the studies generally characterized comorbidities as simply present or absent making comparative analysis difficult. Studies which delineate the effect of specific, well defined comorbid conditions on survival of elderly patients treated with both dialysis and supportive care are greatly needed to better inform decision-making with individual patients.

Regardless of treatment modality, considerable variability still exists around survival estimates manifested by the high heterogeneity present within each treatment modalities following meta-analysis. We explored potential reasons for this including patient age, study size, study design and cohort era but found that heterogeneity remained. This difference in survival estimates between studies may be explained by a number of other factors. The studies in this review were conducted between 1976 and 2014 and included considerable variability in age definitions which are likely to reflect broader medical and social context changes, such as overall increased dialysis availability and increasing acceptance onto dialysis particularly in high-income countries[24] that cannot be explored as sources of variability. Other factors that may account for variability between studies include 'centre effects',[25] a likelihood for smaller studies to reflect units with specialized interests, variations in health service structure, diversities in primary care referral policy and in patient expectations leading to differential dialysis uptake. Importantly, treatment components of supportive care may have varied between centres and the different start points for survival measurement may also have contributed to diversity. The differences in survival estimates make it important to present all the available evidence and to be mindful of the variability when prognosticating for elderly ESKD patients.

No RCTs were identified which allocated elderly patients to either dialysis or supportive care. This signifies that no high quality data on the survival benefits of one treatment pathway over another is available. Randomizing is likely to be difficult as the lack of supportive care outcomes makes powering problematic and the willingness of patients to engage in such an approach is questionable. The difference in baseline characteristics between dialysis and supportive care patients detected in this systematic review of observational studies is likely to continue and will remain a challenge, so multi-centre, international observational studies that adjust for these differences and, ideally, randomized trials should be considered as a matter of importance.

Qualitative research of elderly patients contemplating dialysis reveals patients consider the impact of dialysis on autonomy,[8] quality of life, potential survival advantages and impact on families.[26] Concerns about autonomy may be well-founded with evidence that dialysis initiation in the elderly is associated with substantial rates of functional and/or cognitive decline.[27] Furthermore, elderly haemodialysis patients may spend half of the days survived at or in the hospital *versus* 4% for supportive care patients.[28] As many as 61% of patients regret starting dialysis with treatment decisions instead reflecting physician and family preferences, further highlighting the need to improve counselling.[29] A qualitative systematic review examined patient end-of-life decisions and included supportive care patients.[30] They highlighted that patients were willing to sacrifice survival for freedom and QOL and also emphasized patients experiences' of 'being a burden' to their families.[30] Rigorous research into outcomes other than survival that are important to elderly patients such as quality of life, symptom burden, hospitalizations and impact on carers needs to take place.

The strength of this review are that it is comprehensive. We used broad search terms and included all cohort study types as well as RCTs in order to collate all relevant data. The findings, however, are limited by the size and quality of the underlying studies, especially those examining elderly supportive care patients, resulting in differentially greater uncertainty around survival estimates for these patients. A further major issue in assessing supportive care survival was the potential for lead-time bias. Lead-time bias results from incorrect estimation of survival due to varying definitions of the 'starting point' for survival assessment. Global differences in practice with respect to early or late dialysis start affect dialysis survival time when it is measured from initiation. The issue of lead-time bias is much more problematic for supportive care studies which had widely variable starting points from which survival was measured. It was not possible to assess the effect of this upon survival estimates, and it may be considerable. The generalizability of these findings is limited by the fact that all studies reported only on patients referred to specialist care; few studies overall were from resource poor settings and studies reporting on supportive care originated in Europe and Developed Asia only.

Our systematic review demonstrated that substantial uncertainty around survival estimates remains due to the lack of precision for survival with supportive care as a result of paucity of reports and potential for lead-time bias as well as residual heterogeneity within treatment modalities. One-year survival of elderly ESKD patients treated with either supportive care or dialysis was generally comparable on the available observational data. There is an urgent need for research of elderly patients treated with supportive care or dialysis that avoids the limitations of the existing literature and that better outlines the full impacts of these treatments upon patients and their carers.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Global distribution of studies in elderly end-stage kidney disease patients (size of dots represents size of studies)

Fig. S2 Comparative 1-year survival (95% CI) of elderly patients treated with undifferentiated dialysis, haemodialysis, peritoneal dialysis and supportive care in all studies, b) studies with mean study age 65–79 and c) studies with mean study age >80

Fig. S3 Comparative 1-year survival (95% CI) of elderly patients treated with undifferentiated dialysis, haemodialysis, peritoneal dialysis and supportive care by study size tertiles

Fig. S4 Comparative 1-year survival (95% CI) of elderly patients treated with undifferentiated dialysis, haemodialysis, peritoneal dialysis and supportive care by study design

Fig. S5 Comparative 1-year survival (95% CI) of elderly patients treated with undifferentiated dialysis, haemodialysis, peritoneal dialysis and supportive care by cohort era