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Original Article

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Confounding effect of comorbidity in survival studies in patients on renal replacement therapy

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Abstract

Background. After taking other confounding factors into account, the impact of comorbidity on mortality was investigated when comparing mortality between five European countries, dialysis modalities and renal disease groups.

Methods. The study included 15 571 incident patients on renal replacement therapy (RRT) from five national or regional registries participating in the European Renal Association—European Dialysis and Transplant Association Registry that collect comorbidity data. The presence of diabetes mellitus, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and malignancy was recorded at the start of RRT.

Results. The comorbidities were each independently associated with mortality, with hazard ratios (HRs) ranging from 1.40 (95% CI: 1.30–1.51) for peripheral vascular disease to 1.65 (95% CI: 1.48–1.83) for diabetes. Age, gender, primary renal disease, modality and country together explained 14.4% of the variance in mortality; the comorbidities explained an additional 1.9%. In the comparison of renal vascular disease with glomerulonephritis, the crude HR of 2.40 (95% CI: 2.12–2.72) changed to 1.24 (95% CI: 1.09–1.41) after adjustment for age, gender, primary renal disease, treatment modality and country and to 1.06 (95% CI: 0.93–1.22) after further adjustment for the comorbidities. For the comparison between countries and other patient groups, the change in the survival estimate after adjustment for comorbidity was less.

Conclusion. Comorbidity is an important predictor for mortality. However, after adjustment for age, gender, primary renal disease, treatment modality and country, when comparing outcomes between patient groups the influence of comorbidity may be less important than expected.

Keywords: comorbidity; confounding; renal replacement therapy; survival

Introduction

In clinical research among patients on renal replacement therapy, it is often investigated whether certain variables have an effect on mortality. In order to estimate the true effect of a single variable—like country, dialysis modality or primary renal disease—it is essential that the results are adjusted for the potential confounding effect of other variables—such as age—that are known to be highly predictive of mortality. If groups differ with respect to age, this may hamper a fair comparison of mortality between those groups. Adjustment for confounding by age will remove this effect.

Most of the time, group comparison will be adjusted for (possible) differences in age. Depending on the variable under study, adjustment for other potential confounders—like gender or primary renal disease—on top of age may be required. For many comparisons, adjustment for comorbidity is thought to be essential, since comorbidity has been shown to be predictive of mortality [1–11]. Consequently, many papers have

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stressed the need to collect data on comorbidity. However, collecting data on comorbidity is relatively difficult and time-consuming when comparing patient characteristics such as age or primary renal disease. As age and comorbidity are related, it may be that adjustment for comorbidity on top of age—and other potential confounders—may have limited value. The question was therefore raised, whether adjustment for comorbidity is always necessary.

Although many studies have reported on the association between comorbidity and mortality, very few of them have quantified the actual bias resulting from lack of adjustment for comorbidity in survival comparisons. More importantly, the bias resulting from lack of adjustment for comorbidity, on top of other characteristics, has not been the object of study so far.

To our knowledge, the Dialysis Outcomes and Practice Patterns Study (DOPPS) is the only study that has evaluated how much the observed differences in mortality between dialysis centres and countries can be attributed to case-mix factors including comorbidity [12]. It was found that the variability in demographic factors and comorbid conditions explained a rather small part of the differences in mortality, indicating that the importance of adjustment for these factors may be limited in practice. Within DOPPS the differences in case-mix between the countries may not have been large enough to induce substantial confounding. Possibly, the adjustment for case-mix, therefore, resulted in only a limited change of relative risks of deaths. In addition, the separate contribution of comorbidity to these results was not presented; e.g. it may be that it is far more important to adjust for comorbidity than for gender.

In the present study, our aim was to quantify the confounding effect of comorbidity when studying differences in survival between countries, dialysis modalities or renal disease groups. The study was performed in incident patients on renal replacement therapy for end-stage renal disease participating in the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Registry.

Subjects and methods

Subjects

Data were collected from the five national and regional renal registries participating in the ERA-EDTA Registry that were able to provide data on comorbidity for the purpose of the present study. Comorbidity is not routinely registered in many countries participating in the ERA-EDTA Registry. Participating registries were as follows: Austrian Dialysis and Transplant Registry (OEDTR) (1998–2001), Catalan Renal Registry (Registre de Malalts Renals de Catalunya—RMRC) (Catalonia, Spain) (1995–2001), Lombardy Registry of Dialysis and Transplantation (Registro Lombardo Dialisi e Trapianto) (Lombardy, Italy) (1994–1997), Norwegian Renal Registry (1999–2001), Renal Association UK Renal Registry (United Kingdom, England/Wales) (selected sample of the database 1999–2001). Numbers in brackets indicate the time period of the incident cohort used. Incident patients >18 years of age at the start of renal replacement therapy (RRT) and surviving the first 91 days since start of RRT were included. For inclusion of patient data into the national and regional registries, these organizations complied with their national data protection legislation.

Classification of comorbid conditions

The definitions used by each participating registry for diabetes mellitus (both as a renal disease and as a comorbidity in addition to another renal disease), ischaemic heart disease, peripheral vascular disease, cerebro-vascular disease and malignancy are shown in Appendix 1. Data collection on comorbidity was performed by a doctor or high-skilled nurse. Although detailed descriptions of diagnostic criteria for each comorbidity were often lacking, in all the cases the comorbid conditions were indicated as being present or absent in the medical history at the start of RRT. Sometimes they were further specified by providing subcategories of the disease involved. In all registries it was possible to distinguish between 'no comorbidity' or 'missing data on comorbidity', with the exception of Norway. In Norway, all patients without any data were considered to have no comorbidity.

Data analyses

To examine the association between the presence of comorbid conditions and survival time, Cox proportional hazards regression analysis was used. A Cox regression analysis provides a hazard ratio (HR) that indicates the instantaneous chance of death for a risk group compared with a reference group. For example, an HR of 2.0 for men compared with women means that men have a risk of death that is twice as high as that of women. If men and women differ with respect to age in a study population, a Cox regression analysis would provide the opportunity to adjust for the confounding effect of age. Instead of using only gender in such a Cox model, one would also include the confounder age in order to yield an HR for gender that is adjusted for age, i.e. indicating the risk of death for men *vs* women irrespective of their age.

The predictive values of comorbidity and other patient characteristics were expressed as the percentage of explained variance in survival (R^2) and was calculated according to Nagelkerke [13]. R^2 expresses the extent to which the variables included in a Cox regression model explain the variance in survival time. The higher the percentage the better, with 0% indicating no prediction at all and 100% indicating perfect prediction. In this study, the effect of additional adjustment for comorbidity was investigated by studying (i) the increase in R^2 for Cox regression models including an increasing number of (demographic or clinical) variables, and finally, including comorbidity, and (ii) the HRs of Cox models investigating the relationship of country, treatment modality and renal disease on the one hand with mortality on the other hand. For the latter purpose, the crude as well as the adjusted HRs were calculated and three models were built: (i) the crude model, only including the one variable of interest—i.e. country, dialysis modality or primary renal disease, (ii) the adjusted model,

including the variable of interest and the relevant potential confounders—i.e. age, gender, primary renal disease, treatment modality and country (the relevant potential confounders that were adjusted for did of course not include the variable of interest in a particular model, see Table 1), (iii) the adjusted model, including the variable of interest, the relevant potential confounders and the comorbidities.

In the crude analysis of the relationship between diabetes and mortality (Table 2), the comorbidity variable 'diabetes' also included diabetes as the cause of renal failure. In the multivariate analyses (concerning the adjusted models), 'diabetes' as a comorbidity did not include diabetes as the cause of renal failure, since diabetes as the cause of renal failure was already included in the variable 'primary renal disease'. Thus it was investigated to what extent comorbidity adds to adjustment for primary renal disease and other characteristics

In the Cox regression analysis, death was the event of interest and follow-up time was censored at recovery of renal function, loss of follow-up, at the end of the observation period [31 December 2001 for Austria, Norway, Spain (Catalonia) and United Kingdom (England/Wales); 31 December 1997 for Italy (Lombardy)], and when patients were still alive and on RRT after 4 years.

There was no uniform follow-up period for the countries because the follow-up time that was registered was different for each country. In order to avoid reduction of informative data it was decided not to censor follow-up time after 2 years (available follow-up time for each country); as the proportional hazard assumption was checked and appeared to be valid for the data of our study, this does not invalidate the analysis.

All analyses were performed using SPSS 11.0.1.

Results

In the study, 15 571 patients from five renal registries were included (Table 3). The mean age of the patients was 61.6 years, 61.5% were males and 20.0% had diabetes as primary renal disease. Of the study patients, 78.8% were on haemodialysis (HD), 18.8% on peritoneal dialysis (PD) and 2.5% were living on a functioning graft.

The most common comorbidity was diabetes (27.0%); in 7.0% diabetes was not the cause of renal failure. Malignancies were the least common (10.1%). The prevalence of each comorbidity strongly increased with increasing age. For example, the prevalence of ischaemic heart disease was 2.4% for patients aged 18–40 years, 14.1% in patients aged 40–60 years and 29.0% in patients over 60. The prevalence of comorbidities differed somewhat between countries, especially with regard to diabetes, which varied from 20.2% in Lombardy (Italy) to 39.8% in Austria, and with regard to peripheral vascular disease, which varied from 13.3% in England/Wales (UK) to 34.1% in Austria. As expected, the prevalence of heart disease and peripheral disease was higher in countries with a high prevalence of diabetes mellitus.

In Table 2 the association between each comorbidity and mortality is shown. The crude HRs ranged from 1.99 (95% CI: 1.86–2.12) for diabetes to 2.24 (95% CI: 2.05–2.44) for malignancies. The HRs when adjusted for age, gender, primary kidney disease, modality and country were lower and ranged from 1.40 (95% CI: 1.30–1.51) for peripheral vascular disease to 1.65 (95% CI: 1.48–1.83) for diabetes.

It was investigated to what extent the comorbidities were predictive of mortality after adjustment for other general characteristics. It appeared that age alone explained 11.2% of the variance (Figure 1). Subsequent addition of gender, primary renal disease, treatment modality and country to the model showed that these explained 0, 2.7, 0.2 and 0.3% in addition to age, respectively, resulted in a total explained variance of 14.4%. On top of these factors, the five comorbidities explained an additional 1.9% variance, resulting in 16.3% explained variance by all factors. The same patterns were found in each country (data not shown). Also, for the three age classes the patterns were rather similar, except that within each age class the percentage explained variance by age was much smaller.

In Figure 1, the percentage of explained variance is given for the five comorbidities together. The total amount of explained variance by all comorbidities is relatively small and there is no consistency in the importance of comorbidities across countries and age groups. Thus there is no apparent hierarchy in the comorbidities.

Finally, it was investigated to what extent adjustment for comorbidity in survival analyses actually influences HRs for three different predictor variables of interest (country, dialysis modality and primary renal disease) after correcting for other differences in case-mix. The differences in case-mix between the countries can be seen in Table 3. The differences in case-mix between the dialysis modalities HD and PD were mean age, 63 and 60; percentage males, 62 and 61; percentage diabetes, 20 and 19; percentage with at least one comorbidity, 50 and 42. The differences in case-mix between the primary renal diseases, renal vascular disease and glomerulonephritis were mean age, 68 and 55; percentage males, 70 and 70; percentage HD, 81 and 77; percentage with at least one comorbidity, 65 and 30. Thus, the differences in case-mix were relatively large between patients with glomerulonephritis and patients with renal vascular disease, especially with respect to age and comorbidity.

The HRs of the different classes of the predictor variables of interest were compared (Table 1). The crude HRs of the countries ranged from 0.99 (95% CI: 0.86–1.14) for Lombardy (Italy) to 1.49 (95% CI: 1.30–1.71) for Austria, when compared with the UK (England/Wales). Adjusting the HRs for age, gender, primary renal disease and treatment modality reduced the differences between countries, now ranging from 0.97 (95% CI: 0.84–1.12) for Lombardy (Italy) to 1.39 (95% CI: 1.15–1.68) for Norway. The differences between the HRs were only slightly further reduced when the analysis was additionally adjusted

Table 1. Effect of adjustment for comorbidity on survival effect estimates on top of other relevant potential confounders. Comparison by predictor variables—i.e. country, dialysis modality and two primary renal diseases

Predictor variable of interest	HR (95% CI)		
	Crude	Adjustment for general characteristics	Additional adjustment for comorbidity
Model I. Comparison of countries			
Country			
England/Wales (UK)	1	1	1
Austria	1.49 (1.30–1.71)	1.33 (1.15–1.53)	1.20 (1.04–1.39)
Catalonia (Spain)	1.21 (1.06–1.38)	1.02 (0.90–1.17)	1.04 (0.91–1.19)
Lombardy (Italy)	0.99 (0.86–1.14)	0.97 (0.84–1.12)	0.99 (0.86–1.14)
Norway	1.35 (1.12–1.62)	1.39 (1.15–1.68)	1.37 (1.14–1.66)
Potential confounders			
Age	–	1.05 (1.05–1.06)	1.05 (1.05–1.05)
Gender			
Male	–	1	1
Female	–	0.91 (0.85–0.97)	0.99 (0.93–1.06)
Primary renal disease			
Glomerulonephritis	–	1	1
Interstitial nephritis	–	1.15 (0.99–1.33)	1.13 (0.97–1.30)
Cystic kidney disease	–	0.71 (0.58–0.86)	0.74 (0.60–0.90)
Renal vascular disease	–	1.33 (1.18–1.51)	1.18 (1.04–1.35)
Diabetes	–	2.13 (1.89–2.40)	1.97 (1.74–2.23)
Multisystem disease	–	2.72 (2.33–3.16)	2.55 (2.18–2.97)
Other	–	1.32 (1.16–1.49)	1.24 (1.10–1.41)
Modality			
Tx	–	1	1
HD	–	4.98 (2.48–10.0)	4.58 (2.28–9.20)
PD	–	4.98 (2.47–10.0)	4.70 (2.33–9.47)
Diabetes	–	–	1.49 (1.34–1.66)
Ischaemic heart disease	–	–	1.31 (1.22–1.41)
Peripheral vasculor disease	–	–	1.25 (1.16–1.34)
Cerebrovascular disease	–	–	1.29 (1.18–1.40)
Malignancies	–	–	1.64 (1.50–1.80)
Model II. Comparison of dialysis modalities			
Dialysis modality			
PD	1	1	1
HD	1.18 (1.08–1.29)	0.99 (0.90–1.08)	0.96 (0.88–1.06)
Potential confounders			
Age	–	1.05 (1.04–1.05)	1.04 (1.04–1.04)
Gender			
Male	–	1	1
Female	–	0.92 (0.86–0.98)	1.00 (0.93–1.06)
Primary renal disease			
Glomerulonephritis	–	1	1
Interstitial nephritis	–	1.11 (0.96–1.28)	1.09 (0.94–1.26)
Cystic kidney disease	–	0.73 (0.60–0.89)	0.76 (0.63–0.93)
Renal vascular disease	–	1.28 (1.12–1.45)	1.14 (1.01–1.30)
Diabetes	–	1.97 (1.75–2.22)	1.84 (1.63–2.08)
Multisystem disease	–	2.52 (2.17–2.94)	2.37 (2.03–2.77)
Other	–	1.28 (1.13–1.45)	1.21 (1.07–1.37)
Country			
Engl/Wales (UK)	–	1	1
Austria	–	1.39 (1.20–1.60)	1.26 (1.09–1.46)
Catalonia (Spain)	–	1.10 (0.96–1.26)	1.11 (0.97–1.28)
Lombardy (Italy)	–	0.96 (0.84–1.11)	0.98 (0.85–1.13)
Norway	–	1.63 (1.35–1.97)	1.59 (1.32–1.93)
Diabetes	–	–	1.47 (1.32–1.63)
Ischaemic heart disease.	–	–	1.29 (1.20–1.39)
Peripheral vascular disease	–	–	1.22 (1.13–1.31)
Cerebrovascular disease	–	–	1.26 (1.16–1.37)
Malignancies	–	–	1.61 (1.47–1.76)
Model III. Comparison of primary renal diseases			
Primary renal disease			
Glomerulonephritis	1	1	1
Renal vascular disease	2.40 (2.12–2.72)	1.24 (1.09–1.41)	1.06 (0.93–1.22)
Potential confounders			
Age	–	1.07 (1.06–1.07)	1.06 (1.05–1.07)

(Continued)

Table 1. Continued

Predictor variable of interest	HR (95% CI)		
	Crude	Adjustment for general characteristics	Additional adjustment for comorbidity
Gender			
Male	–	1	1
Female	–	0.74 (0.65–0.84)	0.85 (0.74–0.97)
Modality			
Tx	–	1	1
HD	–	3.77 (1.21–11.8)	3.52 (1.12–11.01)
PD	–	3.80 (1.21–11.9)	3.64 (1.16–11.45)
Country			
Engl/Wales (UK)	–	1	1
Austria	–	1.39 (1.06–1.84)	1.27 (0.96–1.68)
Catalonia (Spain)	–	1.12 (0.86–1.45)	1.12 (0.86–1.46)
Lombardy (Italy)	–	0.99 (0.76–1.30)	1.05 (0.80–1.37)
Norway	–	1.10 (0.79–1.52)	1.07 (0.77–1.49)
Diabetes	–	–	1.51 (1.29–1.77)
Ischaemic heart disease	–	–	1.37 (1.21–1.56)
Peripheral vascular disease	–	–	1.40 (1.22–1.60)
Cerebrovascular disease	–	–	1.26 (1.09–1.46)
Malignancies	–	–	1.46 (1.22–1.76)

Table 2. Influence of each comorbidity on survival

	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Diabetes[b]	1.99 (1.86–2.12)	1.65 (1.48–1.83)
Ischaemic heart disease	2.06 (1.93–2.21)	1.43 (1.33–1.53)
Peripheral vascular disease	2.16 (2.03–2.31)	1.40 (1.30–1.51)
Cerebrovascular disease	2.09 (1.93–2.26)	1.41 (1.30–1.53)
Malignancies	2.24 (2.05–2.44)	1.64 (1.50–1.79)

[a]Adjustments are made for age, gender, primary renal disease, modality and country.
[b]Includes diabetes as cause of renal failure and diabetes not as cause of renal failure.

for the five comorbidities: the HRs ranged from 0.99 (95% CI: 0.86–1.14) for Lombardy (Italy) to 1.37 (1.14–1.66) for Norway.

The same adjustments were made for the comparison of the two major treatment modalities: HD and PD. The crude HR for HD compared with PD was 1.18 (95% CI: 1.08–1.29). This HR decreased to 0.99 (95% CI: 0.90–1.08) after adjustment for general characteristics. Additional adjustment for comorbidity revealed an HR of 0.96 (95% CI: 0.88–1.06).

This procedure was also followed for the comparison of mortality between patients with two different causes of renal failure with a large difference in prognosis, i.e. glomerulonephritis and renal vascular disease. The crude HR was 2.40 (95% CI: 2.12–2.72) and decreased to 1.24 (95% CI: 1.09–1.41) after adjustment for general characteristics and further decreased to 1.06 (95% CI: 0.93–1.22) after further adjustment for comorbidity.

Discussion

This study among 15 571 patients on renal replacement therapy from five European countries confirms that comorbidity is an important predictor for survival and is thus of prognostic importance for the individual patient. The data of the present study also show that in the comparison of survival between five European countries, two dialysis modalities, and two primary renal disease groups, the estimate of the HRs changed importantly after adjustment for general characteristics like age or gender, but very little after further adjustment for comorbidity.

Since the present study as well as many other studies have shown that comorbidity is clearly associated with mortality, it is initially surprising that adjustment for comorbidity—on top of other characteristics—has a limited effect on mortality comparisons. It may simply be that age and comorbidity are highly correlated—as is well known and was also demonstrated in this study. The same holds true for primary renal disease. Adjusting for age (or primary renal disease), therefore, already (partly) removes the effect of comorbidity. Additional adjustment for comorbidity on top of age or primary renal disease will then have a limited effect. Age is effectively a proxy for comorbidity. Additional analyses revealed that comorbidity alone indeed explained a larger part of the variance (6.9%) than it did on top of age and other characteristics (1.9%). Age alone explained 11.2% of the variance.

A second reason for the limited effect of additional adjustment for comorbidity may be the limited number of comorbidities available from all five registries, variation in definitions and absence of severity grading of the comorbidities. Adjustment for a larger number of comorbidities and for the severity of comorbidity

Table 3. General characteristics of the study population

	Total $n=15\,571$	Austria $n=3169$	Catalonia (Spain) $n=5405$	England/Wales (UK) $n=2146$	Lombardy (Italy) $n=3844$	Norway $n=1007$
Mean age (SD)	61.6 (15.1)	61.1 (14.6)	63.1 (14.8)	59.6 (15.7)	61.3 (15.1)	60.4 (15.8)
Male (%)	61.5	60.4	62.2	61.3	60.5	66.2
Primary renal disease						
Diabetes (%)	20.0	32.9	19.2	16.7	13.9	13.8
Renal vascular disease (%)	17.3	16.1	17.2	13.8	17.8	27.2
Glomerulonephritis (%)	17.4	15.0	15.0	16.9	21.9	21.7
Therapy						
HD (%)	78.7	88.6	90.6	61.4	65.5	70.3
PD (%)	18.8	9.7	8.1	37.2	31.6	16.9
Functioning graft (%)	2.5	1.7	1.3	1.4	2.9	12.8
Diabetes[a] (%)						
All	27.0	39.8	27.1	23.0	20.2	21.4
18–40	15.6	18.9	13.9	17.3	10.0	28.8
40–60	24.6	35.3	22.3	25.9	17.1	23.4
>60	30.1	45.7	30.7	22.8	23.5	18.4
Ischaemic heart disease (%)						
All	21.9	28.7	19.0	25.3	17.8	25.0
18–40	2.4	5.8	1.6	2.0	1.2	2.3
40–60	14.1	22.4	9.7	17	10.0	14.4
>60	29.0	36.0	25.0	36.0	24.5	36.6
Peripheral vascular disease (%)						
All	22.6	34.1	26.3	13.3	14.3	18.3
18–40	3.4	7.1	5.0	0.7	1.2	2.3
40–60	14.9	25.5	15.8	10.2	7.8	11.9
>60	29.6	43.4	33.3	18.3	19.6	25.8
Cerebrovascular disease (%)						
All	13.4	23.2	11.2	12.1	10.2	10.2
18–40	2.3	5.2	1.6	2.0	1.4	2.3
40–60	8.6	15.3	6.0	9.2	5.9	6.6
>60	17.6	30.5	14.5	16.3	13.7	14.2
Malignancies (%)						
All	10.1	10.1	8.1	10.0	12.0	13.7
18–40	1.9	2.6	2.0	1.3	2.1	0.8
40–60	6.8	6.8	5.2	7.4	8.1	7.8
>60	13.1	13.2	10.0	13.7	15.6	20.2

[a]Includes diabetes as cause of renal failure and diabetes not as cause of renal failure.

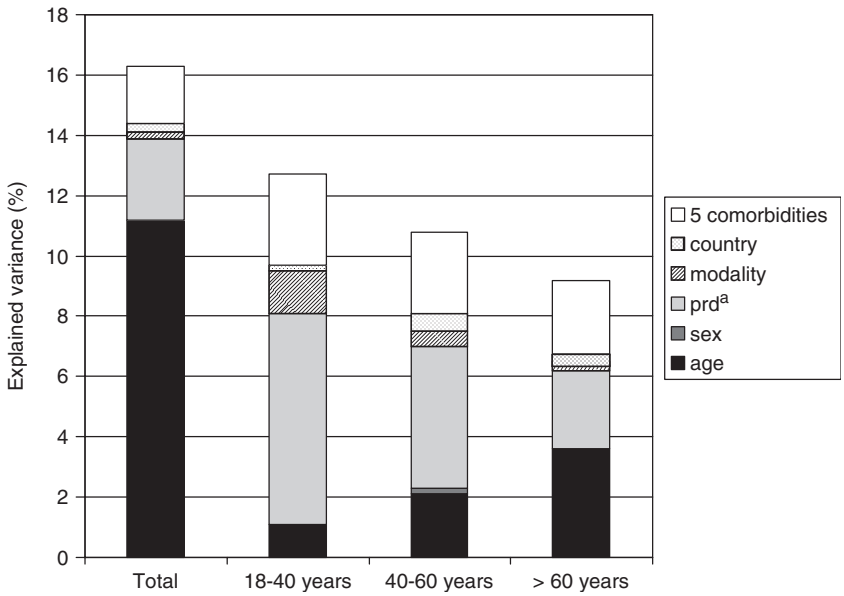

Fig. 1. Prediction of survival by general characteristics and comorbidity. $n=15376$ (195 missing cases due to one or more missing variables). Age, gender, primary renal disease, treatment modality, country and five comorbidities were consecutively entered into the model. The amount of variance explained by a factor reflects additional explained variance on top of the factors already included in the model. [a]prd, primary renal disease.

could have had a larger effect on HR. To investigate these possibilities the data from the Necosad study were analysed.

The Necosad study is a multi-centre study on 1489 incident dialysis patients treated in the Netherlands for which 12 comorbidities and severity grading are recorded [5], of which seven were not recorded in the five European countries. These additional seven comorbidities explained an additional 2.6% of the variance in survival, on top of the 19% that was explained by general characteristics and the five comorbidities. However, additional adjustment for these seven comorbidities in the comparisons of survival between renal vascular disease and glomerulonephritis—the two groups that differed most with respect to comorbidity—only slightly changed the estimate of the HRs [HR changed from 2.18 (95% CI: 1.40–3.39) when adjusting for general characteristics and five comorbidities to 2.34 (95%CI: 1.49–3.67) when adjusting for general characteristics and 12 comorbidities]. Thus there was little additional benefit for the effort of collecting the additional seven comorbidities, and grading severity. These analyses on Necosad, a carefully conducted observational study, support the findings of this study.

It is well known that data based on the clinical diagnosis of a disease are subject to misclassification and lack sensitivity [14]. It may be that with better recording and grading of comorbidity there would be larger effects on the estimate of the HR, but in practical terms for registries and most clinical studies this is not practicable. This study shows that the effect of adjustment for comorbidity—in the way that it is recorded in actual practice—is relatively limited.

The comorbidities were not recorded completely uniformly in all countries participating in the study. Due to the resulting statistical noise, the real effect of adjustment for comorbidity may have been slightly underestimated. However, this study investigated the effect of adjustment for comorbidity in the way it is recorded in daily practice.

The maximum percentage of variance that could be explained by comorbidity and other covariates together was low and did not exceed 22%. This may be interpreted as a sign of low data quality. However, other studies have shown that the ability to predict survival time is relatively limited [15,16], even when the number of variables to adjust for is very large. This low percentage of explained variance seems inherent to the Cox regression analysis used in this and other studies. Experts on survival analysis state that values of about 40% can be reached, but that—depending on the methods of calculation—studies of survival often have much lower estimates of explained variation [17]. Moreover, the purpose of studies is not to accurately predict survival in individuals but to detect clinically meaningful differences in survival time of months or years between groups. Consequently, the low percentage of explained variance found in this study is probably not an indicator of limitations in data.

In theory it will be possible that adjustment for comorbidity has a larger effect on the survival estimates when comparing other groups than those presented in this study. For example, in this study population the prevalence of comorbidity was similar between groups within different age strata. If comorbidity differed more between groups within different age strata, additional adjustment for comorbidity might have had a stronger effect.

Since there was only one country with a longer follow-up period than 4 years, we censored the follow-up for the patients of this country at 4 years. Censoring earlier in follow-up, i.e. 2 years for all countries, did not change the results of the study. Consequently, we may assume that the results are not influenced by follow-up time.

This appears to be the first study showing the actual influence of adjustment for comorbidity on HR estimates on all patients starting RRT. Recently, DOPPS on 16 720 prevalent patients in the US, Europe and Japan selected for HD only showed that the majority of the 22 recorded comorbidities were associated with mortality, and that adjustment for these comorbidities together with other case-mix factors decreased differences in mortality between countries to some extent [12]. However, the additional value of comorbidity in the prediction of survival was not investigated separately from the effects of the other case-mix factors.

In conclusion, this study confirms that comorbidity is common in dialysis patients and that comorbidities are clearly associated with survival. However, after adjustment for age, gender, primary renal disease, treatment modality and country, when comparing outcomes between patient groups the influence of comorbidity, may be less important than expected. Thus studies that are not able to record comorbidity may already account for a large part of the confounding effect of comorbidity by adjusting for age and primary renal disease. Some residual confounding may be inevitable since it is difficult—and maybe impossible—to record comorbidity in a way that does justice to its complexity. Furthermore, if comorbidity differs between groups within different age strata, its confounding effect will be less adequately removed by adjustment for age, and in those cases additional adjustment for comorbidity might be required. Nevertheless, collection of comorbidity data where possible is desirable in order to obtain the most valid effect estimate possible in RRT survival studies, and for other reasons such as estimation of disease burden or defining patient groups for research purposes.

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Appendix 1. Classification of comorbid conditions used by renal registries

	Classification of co-morbidity	Definition or more detailed description of the classification of comorbidity
Diabetes mellitus		
Austria	Diabetes mellitus type I	Insulin needed within year after diagnosis
	Diabetes mellitus type II	Age at start of diabetes mellitus >40 years, treatment with oral antidiabetics or diet possible for longer period of time
	Secondary diabetes mellitus	Caused by other conditions (pancreatic diseases, hormonal imbalance, drug or chemically induced, insulin receptor abnormality, genetic syndrome)
	Unspecified diabetes mellitus	Note: Transitory steroid-induced diabetes mellitus should not be classified as diabetes mellitus
Catalonia (Spain)	Diabetes mellitus type I	
	Diabetes mellitus type II	
	Secondary or unspecified diabetes mellitus	
England/Wales (UK)	Diabetes mellitus	Including diet controlled and drug induced diabetes mellitus
Lombardy (Italy)	Diabetes mellitus type I	
	Diabetes mellitus type II	
	Secondary or unspecified diabetes mellitus	
Norway	Diabetes mellitus type I	Insulin dependency from debut (not secondary)
	Diabetes mellitus type II	
	Secondary diabetes mellitus	
	Unspecified diabetes mellitus	
Ischaemic heart disease		
Austria	Coronary heart disease	Documented by angiography, stress echo, thallium scintigraphy, etc.
	Myocardial infarction	
	Angina pectoris	

(Continued)

Appendix 1. Continued

	Classification of co-morbidity	Definition or more detailed description of the classification of comorbidity
Catalonia (Spain)	ICD-9-CM[a] code 410-414 410:Acute myocardial infarction; 411:Other forms of subacute ischaemic heart disease; 412:Old myocardial infarction; 413:Angina pectoris; 414:Other forms of chronic ischaemic heart disease	
England/Wales (UK)	CABG or coronary angioplasty	
	Myocardial infarction	Diagnosed by ST segment evaluation, Q waves in relevant leads, enzyme rise > 2x upper limit of normal (or rise in creatinine kinase-MB above local reference range)
	Angina pectoris	History of chest pain on exercise with or without ECG changes, exercise tolerance test, radionucleotide imaging or angiography
Lombardy (Italy)	Coronary heart disease Myocardial infarction Angina pectoris	
Norway	Myocardial infarction Angina pectoris	
Peripheral vascular disease		
Austria	Peripheral vascular disease	Included aortic aneurysm, diffuse vascular calcifications, documented vascular stenosis
Catalonia (Spain)	ICD-9-CM[a] code 440-441, 443 440:Atherosclerosis; 441:Aortic aneurysm and dissection; 443:Other peripheral vascular disease	
England/Wales (UK)	Claudication	Current claudication based on a history, with or without Doppler or angiographic evidence
	Angioplasty, stenting vascular graft (non coronary)	Includes vascular grafts (e.g. aortic bifurcation grafts) and renal artery stents
	Amputation for peripheral vascular disease	
Lombardy (Italy)	Peripheral vascular disease	
Norway	Peripheral vascular disease	Including all arteries (except carotid/cerebrovascular and coronary) Should include both symptomatic disease and affection necessitating pre-transplant intervention
Cerebrovascular disease		
Austria	Cerebrovascular disease	
Catalonia (Spain)	ICD-9-CM[a] code 430-438, 342 430:Subarachnoid haemorrhage; 431:Intracerebral haemorrhage; 432:Other and unspecified intracranial haemorrhage; 433:Occlusion and stenosis of precerebral arteries; 434:Occlusion of cerebral arteries; 435:Transient cerebral ischaemia; 436:Acute but ill-defined cerebrovascular disease; 437:Other and ill-defined cerebrovascular disease; 438:Late effects of cerebrovascular disease; 342:Hemiplegia and hemiparesis	
England/Wales (UK)	Cerebrovascular disease	Any history of strokes (whatever cause) and including transient ischaemic attacks caused by carotid disease
Lombardy (Italy)	Cerebrovascular disease	
Norway	Cerebrovascular disease	
Malignancy		
Austria	Malignancy	Solid tumour and other malignancies, including basal cell carcinoma
Catalonia (Spain)	ICD-9-CM[a] code 140-208, 230-239	Including basal cell carcinoma
England/Wales (UK)	Malignancy	Any history of malignancy (even if curative) e.g. removal of melanoma, excluding basal cell carcinoma
Lombardy (Italy)	Malignancy	Including basal cell carcinoma
Norway	Malignancy	Including basal cell carcinoma

[a]United States National Center for Health Statistics. Annotated International Classification of Diseases, Ninth Revision, Clinical Modification. Ann Arbor: Edwards Brothers, Inc., 1987.