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The Netherlands

Measuring senescence in human populations

Koopman, J.J.E.

Citation

Koopman, J. J. E. (2015, October 8). *Measuring senescence in human populations*. Retrieved from <https://hdl.handle.net/1887/35764>

Version: Corrected Publisher's Version

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Downloaded from: <https://hdl.handle.net/1887/35764>

Note: To cite this publication please use the final published version (if applicable).



MEASURING SENESCENCE RATES USING THE GOMPERTZ MODEL

Published as:

J. J. E. Koopman, M. P. Rozing, A. Kramer, D. J. de Jager, D. Ansell,
J. M. J. De Meester, K. G. Prütz, P. Finne, J. G. Heaf, R. Palsson,
R. Kramar, K. J. Jager, F. W. Dekker, R. G. J. Westendorp.

Senescence rates in patients with end-stage renal disease:
a critical appraisal of the Gompertz model.

Aging Cell 2011; 10: 233-238

Background • The most frequently used model to describe the exponential increase in mortality rate with age is the Gompertz model. Logarithmically transformed, the model conforms to a straight curve, of which the slope is classically interpreted as a population's senescence rate. Earlier, it has been proposed that the derivative function of the Gompertz model is a superior measure of the senescence rate.

Methods • We tested both measures of the senescence rate in a population of patients with end-stage renal disease derived from the ERA-EDTA Registry. It is clinical dogma that patients on dialysis experience accelerated senescence, whereas those with a functional kidney transplant have mortality rates comparable to the general population. We calculated the age-specific mortality rates for European patients on dialysis ($n = 274\ 221$; follow-up = 594 767 person-years), for European patients with a functioning kidney transplant ($n = 61\ 286$; follow-up = 345 024 person-years), and for the general European population.

Results • We found a higher mortality rate, but a less steep slope of the logarithmic mortality curve in patients on dialysis compared with both patients with a functioning kidney transplant and the general population ($p < 0.001$). A classical interpretation of the Gompertz model would imply that the senescence rate in patients on dialysis is lower than in patients with a functioning transplant and lower than in the general population. In contrast, the derivative function of the Gompertz model yielded the highest senescence rate for patients on dialysis, whereas the senescence rate was similar in patients with a functioning transplant and the general population.

Conclusion • We conclude that a population's senescence rate is better measured by the derivative function of the Gompertz model than by the slope of the logarithmically transformed Gompertz model.

In 1825, Benjamin Gompertz observed that human mortality rates increase exponentially with age.¹ Since then, no other definition of senescence has gained so much common acceptance.² Mathematically, the model is known as the Gompertz model and has become the most frequently used model of senescence.^{3,4} The model describes the mortality rate at a given age with parameters α and γ . When transformed logarithmically, the model con-

forms to a straight curve. The slope of this straight curve represents the increase in mortality rate on a logarithmic scale and is determined by parameter γ .

The Gompertz model fits mortality data very firmly, but it is purely empirical. Still, many investigators have tried to attribute biological properties to the estimated parameters. Based on mortality data from animal experiments⁵⁻⁸ and historical

changes in human mortality patterns,⁹⁻¹¹ the slope of the logarithmically transformed mortality curve has classically been defined as the species-specific senescence rate.^{2,12} However, based on theoretical considerations, the validity of this slope as a measure of the senescence rate has been criticised.¹³⁻¹⁵ We have previously proposed to use the increase in mortality rate on an absolute scale instead, as described by the derivative function of the Gompertz model.¹⁶

This work aims to empirically test both the classical and the newly proposed measure of the senescence rate in patients with end-stage renal disease. For this, we have calculated the age-specific mortality rates of a very large population of European patients with end-stage renal disease, comprising both patients on dialysis and patients with a functioning kidney transplant, using the general European population as a reference. It has been widely recognised that patients on dialysis show accelerated senescence as compared with the general population.¹⁷⁻²⁰ Patients on dialysis have higher mortality rates.²¹⁻²³ Moreover, they suffer from age-related diseases with a higher frequency and more rapid progression, among which cardiovascular diseases,²²⁻²⁶ the metabolic syndrome and insulin resistance,^{27,28} cognitive impairment and dementia,²⁹ metabolic bone disease,³⁰ and dysfunction of the immune system.^{31,32} Many of these patients are classified as frail.³³⁻³⁵ Biologically, this clinically accelerated senescence is attributed to disturbed levels of metabolites and signalling molecules, such as urea, advanced glycosylation end products, homocysteine, and

endothelin.^{18,19,36-39} After transplantation, the age-related diseases in these patients improve and the age pattern of mortality of these patients converts toward the pattern of the general population.^{25,40,41} Therefore, these populations provide an excellent opportunity to assess different measures of the senescence rate, as a valid measure of senescence rate should reflect these differences in senescence rates by attributing the highest senescence rate to patients on dialysis and a lower senescence rate to patients with a functioning kidney transplant and the general population.

Methods

Study population

The study population of patients with end-stage renal disease was derived from the Registry of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA Registry),⁴² which records European patients who receive renal replacement therapy, either dialysis or kidney transplantation. Via national and regional registries, individual patient data were derived from Austria, the Flemish speaking region of Belgium, the French speaking region of Belgium, Denmark, Finland, Greece, Iceland, the Netherlands, Norway, Romania, Sweden, the United Kingdom, and from several regions in Italy and Spain. Data were gathered during a period beginning between 1985 and 2007, and ending at 1 January 2008 for four regions in Spain and Italy, and 1 January 2009 for the other regions and countries. For each individual patient, the following parameters were collected at baseline:

country or region of origin, date of birth, gender, primary cause of renal failure, and date and modality of first renal replacement therapy. Data on history of renal replacement therapy with dates and changes of modality and date were collected during follow-up. Primary renal diseases were classified according to the ERA-EDTA Registry's coding system.⁴²

Mortality rates were calculated based on the follow-up data contributed by each individual patient, separated for follow-up on dialysis treatment and follow-up with a functioning kidney transplant. In case of the dialysis group, follow-up began six months after initiation of dialysis treatment, to account for acute treatment-related mortality,⁴³ and lasted until death, transplantation, recovery of renal function, loss to follow-up, or censoring at 1 January 2008 or 2009. In case of the patients with a functioning transplant, follow-up began six months after transplantation, to account for acute surgery-related mortality,^{40,44} and lasted until death, transfer to dialysis due to transplant failure, loss to follow-up, or censoring at 1 January 2008 or 2009. For both treatment groups, per 5-year age group, the number of deaths was divided by the years of follow-up, yielding the age-specific mortality rates.

Reference population

Mortality data of the general European population were available through the Human Mortality Database (HMD)⁴⁵ and Eurostat.⁴⁶ For the countries in our study, the population and death figures were

retrieved from the HMD for each 5-year age category and for the years of data contribution. For Greece, Romania, and Spain, these mortality data were downloaded from Eurostat, as they were not available in the HMD. For the calculation of age-specific mortality rates of the general European population, per 5-year age groups and years of participation, the sum of all deaths was divided by the sum of all inhabitants of the participating countries.

Analyses

The application of the Gompertz model is limited to mortality data between the ages of approximately 20 and 80 to 90 years.⁴ Moreover, after the age of 85 years, available mortality data were scarce. Follow-up after this age comprised 15 638 person-years (2.52%) and 8360 deaths (5.83%) for the patients on dialysis and 175 person-years (0.05%) and 25 deaths (0.26%) for the patients with a functioning kidney transplant. Therefore, data on patients below the age of 20 years and from the age of 85 years onward were excluded from this study.

The Gompertz curves were characterised by estimating the values of the parameters of the Gompertz model on the age-specific mortality data as well as the statistical significance of the differences in the model parameters between the treatment groups. The parameters α and γ are mathematically described by the Gompertz model as $m(t) = \alpha e^{\gamma t}$, where $m(t)$ is the mortality rate and t is the age in years. The calculations were performed by fitting the parametric proportional hazards Gompertz

model⁴⁷ on the individual patient data and by linear regression on the aggregated data of the general European population.

The classical senescence rates were given by γ , of which the values were derived by the aforementioned determination of the model parameters. In addition, according to the newly proposed method that we have described earlier,¹⁶ the derivative function of the Gompertz model was applied to the mortality rates to estimate the senescence rates. For that, the values of the model parameters, determined as described above, were incorporated in the model's derivative function: $m'(t) = \alpha \gamma e^{\gamma t}$.

The management of the ERA-EDTA Registry database, the calculations of the age-group-specific mortality rates of the study population, and the linear regression analyses were carried out using PASW Statistics 17.0 (SPSS, Chicago, IL, USA). Linear regression was performed by the linear mixed model with the natural logarithms of the mortality rates as dependent variable, treatment group as factor, and age as covariate. All these calculations were repeated using Stata/SE 10.1 (StataCorp, College Station, TX, USA). The fitting of the Gompertz model was performed using Stata/SE 10.1.

Table 3.1 • General characteristics of the study population of patients with end-stage renal disease

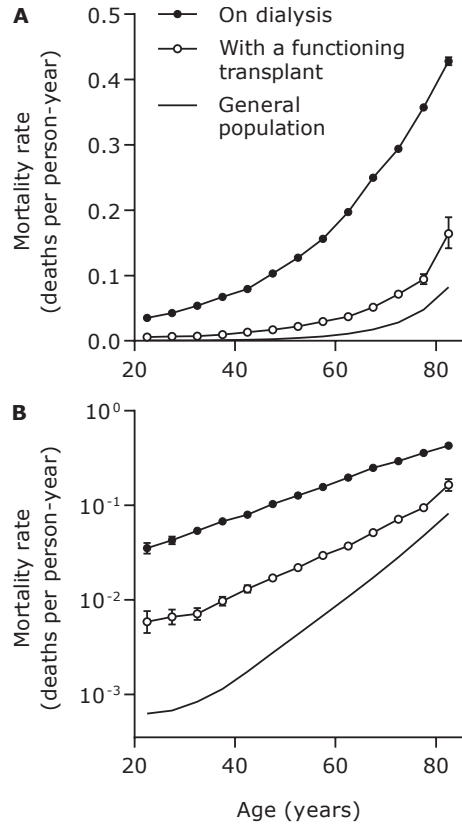
	All patients	Patients on dialysis	Patients with a functioning kidney transplant
By number of patients			
Total number of patients	290 510	274 221	61 286
Men, %	61.1	61.2	62.7
Age, median (iqr) years			
at first treatment	64.6 (52.0–73.3)	65.0 (52.7–73.5)	49.2 (38.3–58.6)
at death	71.0 (62.7–77.1)	71.1 (62.8–77.1)	60.5 (51.5–68.2)
Follow-up per patient, median (iqr) years	1.8 (0.3–4.7)	1.3 (0.2–3.1)	4.5 (1.4–8.7)
By years of follow-up			
Total years of follow-up, person-years (%)	942 458	594 767 (63.1)	345 024 (36.6)
Men, %	60.4	59.3	62.2

As patients could successively undergo dialysis treatment and kidney transplantation, patients can be represented in both the patient group on dialysis and the patient group with a functioning transplant. Iqr: interquartile range.

Results

Table 3.1 shows the basic characteristics of the study population, both presented as the total number of patients and by the number of years of follow-up. As starting dialysis treatment or receiving kidney transplantation occurred more than once in some patients, part of the population ($n = 58\,387$ or 20.1%) contributed follow-up to both treatment modalities. The number of these consecutive treatment modalities ranged between 1 and 11 per patient.

Figure 3.1A shows the mortality rates per 5-year age groups for patients on dialysis, for patients with a functioning kidney transplant, and for the general population. In all groups, mortality rates increased exponentially with age from adolescence onward. For each age group, the mortality rate of the dialysis patients was the highest, whereas the mortality rate of patients with a functioning transplant was higher than that of the general population. After transformation of the mortality rates to a logarithmic scale, the mortality rates of all three groups conformed to straight curves from the age of 20 years and onward (Figure 3.1B). The r^2 values of these straight curves, indicating the fit of the Gompertz model, were 0.998 for patients on dialysis, 0.992 for patients with a functioning transplant, and 0.986 for the general population. Again, for each age group, the mortality rate of the patients on dialysis was the highest, the mortality rate of the group with a functioning transplant was intermediate, and the mortality rate of the general population was the lowest.



Age	20-39	40-59	60-79	80-84
●	54 801	170 078	330 071	45 107
○	85 643	173 004	96 474	1 133

Figure 3.1 • Age patterns of mortality rates of patients on dialysis, patients with a functioning kidney transplant, and the general population on a linear scale (A) and a logarithmic scale (B). Logarithmic transformation of the mortality rates yields straight curves, of which the slopes have classically been interpreted as senescence rates. For the mortality rates of the patients on dialysis and with a functioning transplant, the estimates are given with 95% confidence intervals. The follow-up in person-years for each treatment modality is shown in a table.

Table 3.2 • Quantitative description of the Gompertz model's parameters

	Patients on dialysis	Patients with a functioning kidney transplant	General population
$\ln a$	-4.75 (-4.71 to -4.79)	-7.71 (-7.58 to -7.83)	9.55
$a \times 10^{-2}$	0.86 (0.83 to 0.90)	0.04 (0.04 to 0.05)	0.01
$\gamma \times 10^{-2}$	4.29 (4.23 to 4.35)	6.70 (6.49 to 6.90)	8.50
MRDT	16.17 (15.95 to 16.40)	10.35 (10.05 to 10.68)	8.16

Estimated values of the Gompertz model's parameters for the mortality rates of patients on dialysis, patients with a functioning kidney transplant, and the general population. The mortality rate doubling times (MRDT) are derived from γ as $MRDT = \ln 2 / \gamma$ and are given in years.⁴⁸ The values of a were derived from those of $\ln a$. The estimates are given with 95% confidence intervals. All estimates of the parameters were significantly different among the three groups and from zero ($p < 0.001$).

The quantitative description of the age patterns of the mortality rates by the Gompertz model's parameters is presented in Table 3.2. The intercept or basal mortality rate a was highest in patients on dialysis, intermediate in patients with a functioning kidney transplant, and lowest in the general population ($p < 0.001$). The slope γ of the straight curves was lowest in the patients on dialysis, intermediate in the patients with a functioning transplant, and highest in the general population ($p < 0.001$). The corresponding mortality rate doubling time was highest in the dialysis patients, intermediate in the patients with a functioning transplant, and lowest in the general population.

We performed various additional analyses. Stratification of the mortality rates of patients on renal replacement therapy by gender, primary renal disease, and country of origin yielded similar results. Stratification by calendar year, for which the data were divided into two periods from 1985 through 1996, and from 1997 through

2008, yielded similar results. Inclusion of only the first treatment period on dialysis or with a functioning transplant, did not affect the outcome. Furthermore, adjustment for duration of follow-up for different treatment modalities did not substantially influence the results (data not shown).

Next, we estimated the increase in the mortality rates on an absolute scale as described by the derivative function of the Gompertz model to determine the senescence rates for the various groups. The derivative function yielded estimates for the age-specific senescence rates as depicted in Figure 3.2. At every age, the senescence rate was highest in patients on dialysis as compared with the patients with a functioning kidney transplant and the general population. Contrary to a fixed senescence rate as determined by the Gompertz model's parameter γ , these senescence rates increased with age. This increase was greatest in patients on dialysis. Senescence rates estimated by the derivative function of the Gompertz model became similar to

those of the general population when the patients with end-stage renal disease had a functioning kidney transplant. These estimates do not preclude that age-specific mortality rates are higher in patients with a functioning transplant than in the general population for every age category.

Discussion

In this work, based on the commonly used Gompertz model, we have tested two measures of a population’s senescence rate using a population of patients with end-stage renal disease as a model of accelerated senescence. The Gompertz model describes the mortality rate $m(t)$ at a given age t with parameters α and γ as:

$$m(t) = \alpha e^{\gamma t} \tag{3.1}$$

The parameter α determines the mortality rate at the intercept, also referred to as the basal mortality rate, and is usually set at adolescence. The parameter γ determines the rate at which the mortality rate increases with age.^{4,48} On a logarithmic scale, the mortality rates conform to a straight curve, which is described as:

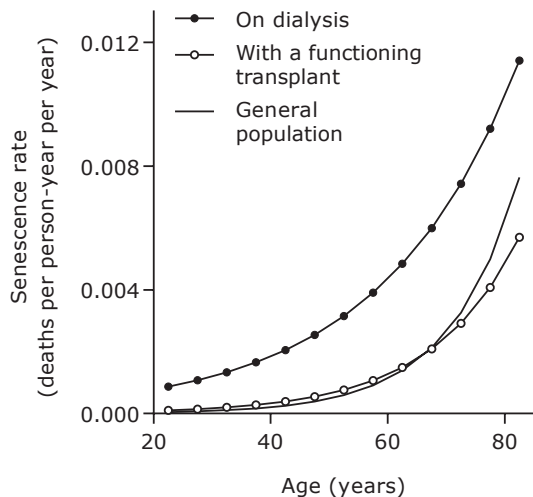
$$\ln m(t) = \ln \alpha + \gamma t \tag{3.2}$$

On the logarithmic scale, variation in α results in a parallel shift of the straight curve, whereas variation in γ results in a different slope. The slope of the curve has classically been regarded as an estimate of the senescence rate.^{2,12} As an alternative estimate of the senescence rate, we have proposed to use the derivative function of the Gompertz model,¹⁶ described as:

$$m'(t) = \alpha \gamma e^{\gamma t} \tag{3.3}$$

Using the mortality data of a unique and unprecedented large population of patients with end-stage renal disease, both the classical measure of the senescence rate, based on the slope of the straight curve determined by γ , and the newly proposed measure of the senescence rate, estimated by the derivative function of the Gompertz model, were obtained. We showed that the mortality rates were highest and the slope of the straight curve was lowest in patients

Figure 3.2 • Age patterns of senescence rates of patients on dialysis, patients with a functioning kidney transplant, and the general population. It is emphasised that, in contrast to the mortality rates in Figure 3.1, these curves depict senescence rates. According to the newly proposed method, the senescence rates were calculated using the derivative function of the Gompertz model. Values of the Gompertz model’s parameters, as presented in Table 3.2, were incorporated into this function.



on dialysis. In patients with a functioning transplant, the mortality rates and the slope were intermediate. In the general population, the mortality rates were lowest, but the slope was highest compared with both patient groups. The classical interpretation of the parameters of the Gompertz model should lead to the conclusion that the senescence rate in patients on dialysis is lower than the senescence rates in patients with a functioning transplant and the general population. Moreover, successful kidney transplantation lowered the mortality rates, but would increase the senescence rate. This interpretation of the parameter estimates is in sharp contrast with the clinical notion that patients on dialysis experience an accelerated senescence, whereas after transplantation, their age pattern of the mortality rates shifts toward the pattern of the general population.

We have presented the derivative function of the Gompertz model as an alternative measure of the senescence rate. This measure yielded senescence rates that were highest in patients on dialysis compared with patients with a functioning transplant and the general population. The senescence rates in the patients with a functioning transplant and the general population were similar, although the mortality rates were higher in patients with a functional transplant than in the general population for every age category. Only at the highest ages, the senescence rate of patients with a functioning transplant slightly lagged behind that of the general population, probably due to preferential selection of healthy patients for transplantation. In contrast to the classical interpretation of parameter γ

as a measure of the senescence rate, this result is consistent with the higher senescence rates observed in patients on dialysis compared with the general population and with the presumed return to normal mortality patterns after successful kidney transplantation.

From literature, it is well known that α and γ are inversely related.^{10,49} Mathematical calculations show that this relationship between both parameters is necessary, called the Strehler-Mildvan correlation.⁵⁰ This correlation is in conflict with the classical interpretation of the Gompertz model. Accepting γ to represent the senescence rate and α to represent non-senescent mortality, both parameters should not be interdependent. This paradox is solved when using the derivative function as a measure for senescence rate: it relates both parameters to the senescence rate (Equation 3).

The interpretation of the Gompertz model has been subject to scrutiny of other scholars.^{2,51,52} The critical difference between their analyses and ours is the logarithmic transformation. Until now, measures for the senescence rate have been relative, which is an immediate consequence of any logarithmic transformation. In contrast, the approach we have applied here is based on the non-transformed mortality rates, rendering a measure for the absolute senescence rate, as we have proposed in our earlier paper.¹⁶

It has to be noted that a distinction must be made between the clinical senescence rate on individual level and the demographic senescence rate on the population level.

The Gompertz model, based on aggregated mortality data, is used to estimate the senescence rate on the population level. Whether classical or novel, its interpretation provides the demographic senescence rate. Unlike implied by some studies, the individual senescence rate cannot be directly inferred from the demographically determined senescence rate.^{50,53}

While Benjamin Gompertz was the first to introduce a mortality model, many alternative models have since been proposed that fit human mortality rates even better.^{3,54-56} The quest here is not to arrive at the best statistical fit of the data, but to obtain parameters that can be estimated empirically and represent biological phenomena. The approach that is presented to estimate the senescence rate using the derivative function of the Gompertz model is such an attempt. This model is applicable to any model that fits mortality patterns. It is solely based on the definition of senescence as an increase in mortality rate with age and is independent of any biological interpretation of the model from which it is derived, as long as the model fits the mortality data. Other models may even be preferred over the Gompertz model, as the Gompertz model is limited to fit mortality data between adolescence and the age of 80 to 90 years.⁴ Similarly, the approach presented here is applicable to the determination of senescence rates of non-human species, among which often used experimental animal models in which the effects of environmental factors and genotype could be assessed. It would, therefore, be worthwhile to test empirically the validity of this interpretation of the derivative

function for alternative models and alternative species as well.

In conclusion, this study shows that empirical testing of parameter γ of the Gompertz curve as a measure of a population's senescence rate failed to identify the high senescence rate in patients with end-stage renal disease on dialysis and did not identify the improvement when these patients underwent kidney transplantation. In contrast, the recently proposed alternative measure of the senescence rate, determined by the derivative function of the Gompertz model, estimated the highest senescence rates for dialysis patients, and recognised the improved prognosis of patients with a functioning kidney transplant. Thus, we propose to use the derivative function of the Gompertz model to estimate the senescence rate.

Acknowledgements

We are grateful for the valuable comments of dr. S. le Cessie, dr. A.J.M. de Craen, K. Meilgaard, and prof. dr. T. Stijnen. We thank the dialysis and transplantation centres for the contribution of data via their national and regional renal registries. We thank the following registries for the contribution of these data: Austrian Dialysis and Transplant Registry (OEDTR) (R. Kramar); Dutch speaking Belgian Society of Nephrology (NBVN) (B. De Moor, J.M.J. De Meester, and H. Augustijn); French speaking Belgian Society of Nephrology (GNFB) (J.M. des Grottes and F. Collart); Danish Nephrology Registry (DNS) (J.G. Heaf); Finnish Registry for Kidney Diseases (P. Finne and C. Grönhagen-Riska);

Greek Renal Registry (G.A. Ioannidis); Icelandic Renal Registry (R. Palsson); Italian Registry of Dialysis and Transplantation (RIDT) (A. Rustici, M. Nichelatti, A. Limido, A. Molino, M. Salomone, G. Cappelli, F. Antonucci, A. Santoro, E. Mancini, M. Standoli, M. Bonomini, L. DiLiberato, A. DiNapoli, F. Casino, C. Zoccali, M. Postorino, and A.M. Pinna); Norwegian Renal Registry (T. Leivestad); Romanian Renal Registry (RRR) (G. Mircescu, L. Garneata, and E. Podgoreanu); Swedish Kidney Registry (SNR) (K.G. Prütz, L. Bäckman, M. Evans, S. Schön, M. Stendahl, and B. Rippe); Dutch End-Stage Renal Disease Registry (RENINE) (A. Hoitsma and A. Hemke); UK Renal Registry; and the regional registries of Andalusia (SICATA) (P. Castro de la Nuez and M.A. Pérez Valdivia), Asturias (J.R. Quirós and R. Alonso de la Torre), Basque country (UNIPAR) (Á. Magaz, J. Aranzabal, M. Rodrigo, and I. Moina), Cantabria (C Piñera and M. Arias Rodríguez), Castile and León (R. González and C. García-Renedo), Castile-La Mancha (G. Gutiérrez Ávila and I. Moreno Alía), Catalonia (RMRC) (E. Arcos, J. Comas, and P.A. Montserrat), Extremadura (J.M. Ramos Aceitero and M.A. García Bazaga), and Valencian region (REMRENAL) (O. Zurriaga Llorens and M. Ferrer Alamar); and the other ERA-EDTA Registry committee members for their advice in the analysis and the drafting of the manuscript: R. Vanholder, C. Wanner, D. Ansell, C. Combe, L. Garneata, F Jarraya, P. Ravani, R. Saracho, F. Schaefer, S. Schön and E. Verrina. The ERA-EDTA Registry is funded by the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA).

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