Chapter 13: Senescence rates in patients with end-stage renal disease: a critical appraisal of the Gompertz model

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Abstract

The most frequently used model to describe the exponential increase in mortality rate over age is the Gompertz equation. Logarithmically transformed, the equation conforms to a straight line, of which the slope has been interpreted as the rate of senescence. Earlier, we proposed the derivative function of the Gompertz equation as a superior descriptor of senescence rate. Here, we tested both measures of the rate of senescence in a population of patients with end-stage renal disease. It is a clinical dogma that patients on dialysis experience accelerated senescence, whereas those with a functional kidney transplant have mortality rates comparable to the general population. Therefore, 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. We found higher mortality rates, but a smaller slope of logarithmical mortality curve for patients on dialysis compared to 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 rate of senescence 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 equation yielded highest senescence rates for patients on dialysis, whereas the rate was similar in patients with a functioning transplant and the general population. We conclude that the rate of senescence is better described by the derivative function of the Gompertz equation.

Introduction

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 equation 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 semilogarithmically, the formula conforms to a straight curve, hereinafter referred to as the Gompertz curve. The slope of this straight curve 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 experiments [5-8] and historical changes in human mortality patterns [9-12], the slope of the logarithmically transformed Gompertz curve has classically been defined as the species-specific senescence rate [2, 13]. However, based on theoretical considerations, the validity of the slope of the Gompertz curve as a measure of the senescence rate has been criticized [14-16]. We have previously proposed to use the tangent of the mortality curve instead, as described by the derivative of the Gompertz equation [17].

This work aims to empirically test both the classical and the newly proposed measure of senescence rate in end-stage renal disease patients. Hereto, 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 with a functioning kidney transplant, using the general European population as a reference. It has been widely recognized that renal disease patients on dialysis show accelerated senescence when compared to the general population [18, 19]. Furthermore, after transplantation, the mortality pattern of these patients converts toward the mortality pattern of the general population [20, 21], although this effect might also partly be due to selection of healthy subjects for transplantation. Therefore, these populations provide an excellent opportunity to assess different measures of the rate of senescence, 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.

Materials and methods

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 [22](ERA-EDTA Registry), 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, sex, primary cause of renal failure, and date and modality of first renal replacement therapy. 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 coding system (ERA-EDTA Registry Annual Report 2008, 2010).

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 [23], 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 [20, 24], 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 five-year age group the number of deaths was divided by the years of follow-up, yielding the age-specific mortality rates.

The application of the Gompertz model is limited to mortality data between the ages of approximately 20 and 80 to 90 years [3]. Moreover, after the age of 85 years, available mortality data was scarce. Follow-up after this age comprised 15,638 person-years (2.52%) and 8,360 deaths (5.83%) for the patient group on dialysis and 175 person-years (0.05%) and 25 deaths (0.26%) for the patient group 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.

Mortality data of the general European population were available through the Human Mortality Database [25] and Eurostat [26]. For the countries in our study, the population and death figures were retrieved from the HMD for each five-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 through the HMD. For the calculation of age-specific mortality rates of the

general European population, per five-year age groups and years of participation, the sum of all deaths was divided by the sum of all inhabitants of the participating countries.

The Gompertz curves were characterized 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 model [27] 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 analytical method that we have described earlier [17], the derivative function of the Gompertz equation was applied to the mortality curves of this study to determine the senescence rates. Hereto, the values of the model parameters, determined as described above, were incorporated in the derivative equation: $m(t) = \alpha \gamma e^{\gamma t}$.

The management of the ERA-EDTA Registry database, the calculations of the age-group-specific mortality rates of the patient population, and the linear regression analyses were carried out using PASW Statistics 17.0 (IBM SPSS Statistics). 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 LP). The fitting of the Gompertz model was performed using Stata/SE 10.1.

Results

Table 1 shows the basic characteristics of the patient 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 occured 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 1a shows the mortality rates per five-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 over age from adolescence onward. For each age group, the mortality rate of the dialysis patients was 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 semilogarithmical scale, the mortality curves of all three groups conformed to straight Gompertz curves from the age of 20 years and onward (**figure 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 highest, the mortality rate of the group with a functioning transplant was intermediate, and the mortality rate of the general population was lowest.

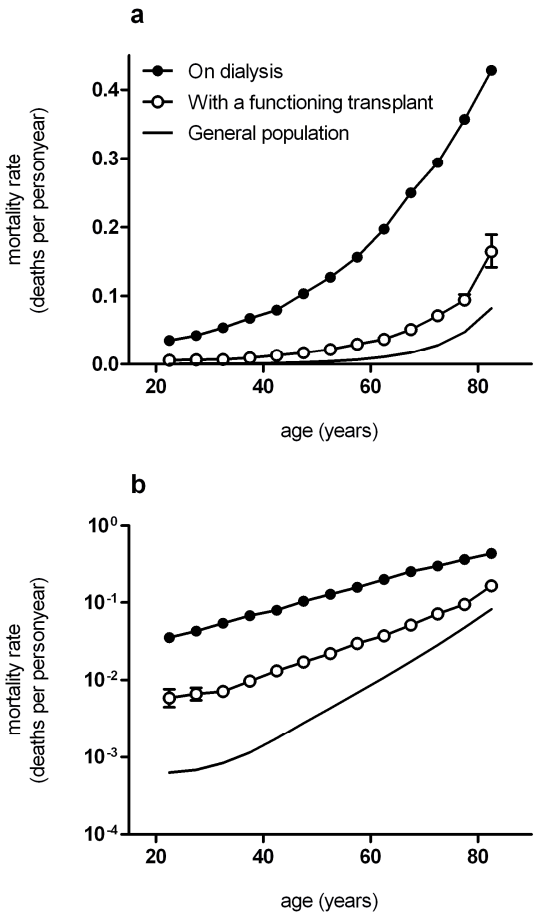
Table 1. General characteristics of the end-stage renal disease patient population

Characteristic	Total	On dialysis	With a functioning transplant
By number of patients			
Total amount of patients *n*	290,510	274,221	61,286
Sex *% male*	61.1	61.2	62.7
Age *median (iqr)*			
- 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 years (iqr)*	1.8 (0.3-4.7)	1.3 (0.2-3.1)	4.5 (1.4-8.7)
By contributed years of follow-up			
Total years of follow-up *person-years (%)*	942,458	594,767 (63.1)	345,024 (36.6)
Sex *% male*	60.4	59.3	62.2

General characteristics of the patients with end-stage renal disease, presented by the number of patients and by contributed years of follow-up. *iqr*: interquartile range.

The quantitative description of the Gompertz curves by the model parameters is presented in **table 2**. The intercept or basal mortality rate α of the Gompertz curve of patients with a functioning kidney transplant was higher than that of the general population (p<0.001), while α for the patients on dialysis was higher than that of both other groups (p<0.001). The slope γ of the Gompertz curve of the patients with a functioning transplant was lowest for the patients on dialysis, intermediate for the patients with a functioning transplant, and highest for the general

population (p<0.001). The corresponding mortality rate doubling time was highest for the dialysis patients, intermediate for the patients with a functioning transplant, and lowest for the general population. We performed various additional analyses. Stratification of the mortality rates of patients on renal replacement therapy by sex, primary renal disease, and country of origin yielded similar results. Stratification by calendar year, for which the data were divided in 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).



Follow-up in person-years per age group

Age group	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 1. Age-specific mortality rates of patients on dialysis, patients with a functioning kidney transplant, and the general population on a linear scale (a) and on a semilogarithmical scale (b). *Logarithmical transformation of the mortality curves yields straight Gompertz curves, of which the slopes have classically been interpreted as the senescence rate. 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 the table at the bottom of this figure.*

Next, we estimated the tangent of the mortality curve as described by the derivative of the Gompertz equation to determine the senescence rates for the various groups. The derivative function yielded estimates for the age-specific senescence rates as depicted in **figure 2**. At every age, the senescence rate was highest in patients on dialysis when compared to patients with a functioning kidney transplant and to the general population. Contrary to a fixed senescence rate as determined by parameter γ in the Gompertz equation, senescence rates accelerated over age. This acceleration was fastest in patients on

dialysis. Senescence rates estimated by the derivative of the Gompertz equation became similar to those of the general population when the patients with end-stage renal disease had a functioning kidney transplant (**figure 2**). 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.

Table 2. Quantitative description of the Gompertz model parameters

Parameter	On dialysis	With a functioning transplant	General pop.
ln α	-4.75 (-4.71; -4.79)	-7.71 (-7.58; -7.83)	-9.55
$\alpha \times 10^{-2}$	0.86 (0.83; 0.90)	0.04 (0.04; 0.05)	0.01
$\gamma \times 10^{-2}$	4.29 (4.23; 4.35)	6.70 (6.49; 6.90)	8.50
MRDT	16.17 (15.95; 16.40)	10.35 (10.05; 10.68)	8.16

Estimated values of the Gompertz model parameters for the mortality curves of patients on dialysis, patients with a functioning kidney transplant, and the general population. The mortality rate doubling times (MRDT) are given in years, derived from γ by MRDT = ln 2 / γ (Ricklefs and Scheuerlein, 2002). The values for α were derived from those for ln α. The estimates are given with 95% confidence intervals. All estimates of the parameters were significantly different between the three groups and from zero (p<0.001).

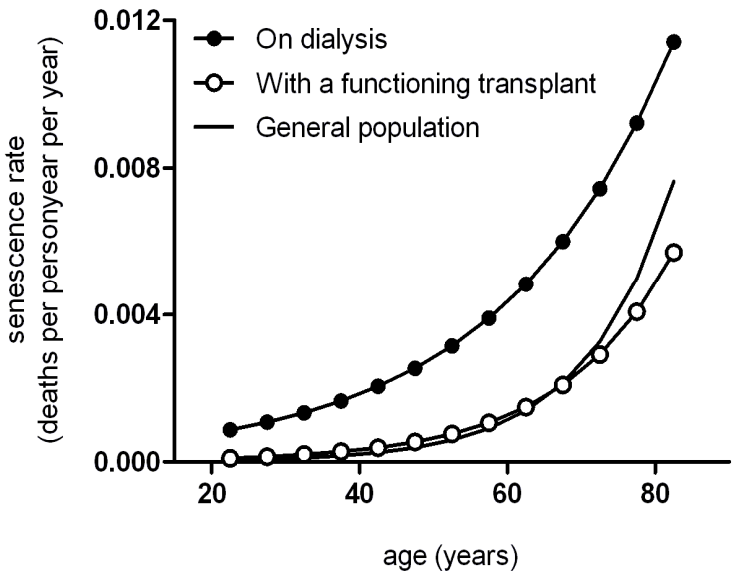


Figure 2. Age-specific senescence rates of patients on dialysis, patients with a functioning kidney transplant, and the general population. *It is emphasized that, in contrast to the mortality rates in Figure 1, these curves depict senescence rates. According to the newly proposed method, these senescence rates were calculated using the derivative of the Gompertz equation. Values of the Gompertz model parameters, as presented in Table 2, were incorporated into this equation.*

Discussion

In this work, we have tested two estimates of senescence rate using a population of end-stage renal disease patients as a model of accelerated senescence. When compared to the general population, patients on dialysis have higher mortality rates[19, 28]. Moreover, they suffer from age-related diseases with a higher frequency and more rapid progression, among which there are cardiovascular diseases [21, 28, 29], cognitive impairment and dementia [29], metabolic bone disease [30], and dysfunction of the immune system. After successful kidney transplantation, the accelerated rate of senescence in the end-stage renal disease patients approaches the senescence rate of the general population [20, 21]. These populations therefore provide an excellent opportunity to assess different measures of the rate of senescence.

The commonly used Gompertz model describes the mortality rate $m(t)$ at a given age t with parameters α and γ as:

$$m(t) = \alpha\, e^{\gamma t} \quad \text{(Eq. 1)}$$

The parameter α determines the intercept of the curve, also referred to as the basal mortality rate, and is usually set at adolescence. The parameter γ determines the extent of the age-dependent increase in the mortality rate [3, 31]. On a semilogarithmical scale, the curve conforms to a straight line, the Gompertz curve, which is described as:

$$\ln m(t) = \ln \alpha + \gamma t \quad \text{(Eq. 2)}$$

On the semilogarithmical scale, variation in α results in a parallel shift of the Gompertz curve, whereas variation in γ results in a different slope. The slope of the Gompertz curve has classically been regarded as the best estimate of the senescence rate [2, 13]. As an alternative estimate of the senescence rate, we have proposed to use the derivative of the Gompertz equation [17], described as:

$$m'(t) = \alpha\, \gamma\, e^{\gamma t} \quad \text{(Eq. 3)}$$

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 γ of the Gompertz curve and the newly proposed measure of the senescence rate, estimated by the derivative of the Gompertz equation, we have obtained the following results. We showed that the mortality rates of patients on dialysis were highest and the slope of their Gompertz curve was

lowest when compared to patients with a functioning kidney transplant and the general population. 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 to 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 rate in patients with a functioning transplant as well as the general population. Moreover, a successful kidney transplantation lowers the mortality rates, but would increase the senescence rate. This interpretation of the parameter estimates is in sharp contrast to the clinical notion that patients on dialysis experience an accelerated senescence, whereas after transplantation the mortality pattern of patients shifts toward the mortality pattern of the general population. We have presented the first derivative of the Gompertz equation as an alternative measure of the senescence rate. This measure yields senescence rates that are highest for patients on dialysis compared to patients with a functioning transplant and the general population. The senescence rates of the group with a functioning transplant and the general population are similar, although the age-specific mortality rates are higher in patients with a functional transplant than in the general population for every age category. Only at the highest ages, the senescence rates of patients with a functioning transplant slightly lag behind those of the general population. In contrast to the classical interpretation of parameter γ as a measure of the rate of senescence, 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. It should be noted however that the post transplant mortality conversion might partly be due selection bias of the transplanted cohort rather than a conversion in the mortality rate.

While Benjamin Gompertz was the first to introduce a mortality model, many alternative models that fit human mortality data have since been proposed that fit human mortality data even better [4, 32-34]. 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 here, to estimate the senescence rate using the derivative function of the Gompertz equation is such an attempt. This model is likely to be applicable to any model that fits mortality patterns. The approach presented here is solely based on the definition of senescence as an increase in mortality rate over 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 [3]. It would, therefore, be worthwhile to

empirically test the validity of this interpretation of the derivative for alternative models as well [35].

In conclusion, this study shows that empirically testing of parameter γ of the Gompertz curve as a measure of 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 undergo kidney transplantation. In contrast, the recently proposed alternative measure of senescence rate, determined by the derivative function of the Gompertz equation, estimates the highest senescence rates for dialysis patients and recognizes the improved prognosis of patients with a functioning kidney transplant. Thus, we propose to use the derivative of the Gompertz equation to estimate the rate of senescence.

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