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Original article

Measuring senescence rates of patients with end-stage renal disease while accounting for population heterogeneity: an analysis of data from the ERA-EDTA Registry

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ABSTRACT

Purpose: Although a population's senescence rate is classically measured as the increase in mortality rate with age on a logarithmic scale, it may be more accurately measured as the increase on a linear scale. Patients on dialysis, who suffer from accelerated senescence, exhibit a smaller increase in their mortality rate on a logarithmic scale, but a larger increase on a linear scale than patients with a functioning kidney transplant. However, this comparison may be biased by population heterogeneity.
Methods: Follow-up data on 323,308 patients on dialysis and 91,679 patients with a functioning kidney transplant were derived from the ERA-EDTA Registry. We measured the increases in their mortality rates using Gompertz frailty models that allow individual variation in this increase.
Results: According to these models, the senescence rate measured as the increase in mortality rate on a logarithmic scale was smaller in patients on dialysis, while the senescence rate measured as the increase on a linear scale was larger in patients on dialysis than patients with a functioning kidney transplant.
Conclusions: Also when accounting for population heterogeneity, a population's senescence rate is more accurately measured as the increase in mortality rate on a linear scale than a logarithmic scale.

The authors declare no conflicts of interest.

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Introduction

Senescence is constituted by a complex of biological mechanisms that lead to an increase in vulnerability to death from adolescence onward. A population's senescence rate can consequently be measured as an increase in mortality rate with age [1–3]. Classically, increases in mortality rates are measured on a logarithmic scale, which can be done using the Gompertz model [1–3]. However, it has been argued that the increase in mortality rate on a logarithmic scale is an inaccurate measure of a population's senescence rate [4]. Instead, it has been proposed that the senescence rate should be measured as the increase in mortality rate on a linear scale, which can also be determined using the Gompertz model [5]. This proposition has been empirically tested in patients with end-stage renal disease on dialysis and with a functioning kidney transplant [6]. Patients on dialysis are generally acknowledged to suffer both clinically and biologically from accelerated senescence. They exhibit higher prevalences and more rapid progression of various age-related disorders as compared with the general population. After kidney transplantation, these phenomena of accelerated senescence improve [6–9]. When measured as the increases in their mortality rates on a logarithmic scale, patients on dialysis have a lower senescence rate than patients with a functioning transplant. By contrast, when measured as the increases in their mortality rates on a linear scale, patients on dialysis have a higher senescence rate than patients with a functioning transplant [6]. These findings support the proposition that a senescence rate measured as the increase in mortality rate on a linear scale corresponds more accurately with clinical and biological knowledge than a senescence rate measured as the increase in mortality rate on a logarithmic scale.

Previous comparisons of both methods may have been biased because they have not accounted for population heterogeneity. Most populations are heterogeneous as they consist of individuals with different levels of frailty [10–12]. Distinctive from the clinical diagnosis of frailty, all individuals can be attributed a level of frailty in this statistical–epidemiological sense. At any age, individuals with higher levels of frailty suffer from an elevated mortality rate as compared with less frail individuals. In patients with end-stage renal disease, differences in frailty may result from varieties in primary renal disease, treatment modality, quality of care, ethnicity, and country [13–17]. Heterogeneity among patients on dialysis is likely greater than among patients with a functioning transplant because the more healthy patients are considered eligible for transplantation [13–15]. Subpopulations with different levels of frailty may display age-dependent increases in mortality rates that are different as well as different from the increase observed in the population as a whole [10–12]. Consequently, a senescence rate measured as the increase in mortality rate with age in a population as a whole may not correctly represent the senescence rates of the different subpopulations.

Extensions of models like the Gompertz model have been developed to account for population heterogeneity [10–12], but these models have not yet been used for comparing both methods to measure senescence rates. These models contain a frailty parameter that allows individual variation in the age-dependent increase in mortality rate. Here, we use such Gompertz frailty models to measure the senescence rates of patients with end-stage renal disease on dialysis and with a functioning kidney transplant while accounting for population heterogeneity. Now uncovering the possible bias due to population heterogeneity, we aim to compare the senescence rates measured as the increases in their mortality rates on a logarithmic scale, according to the classical method, and measured as the increases in their mortality rates on a linear scale, according to the alternative method.

Methods

Study population

This study included data from 27 national and regional registries (see Appendix A) participating in the Registry of the European Renal Association–European Dialysis and Transplant Association. These registries record the treatment and survival history of European patients receiving renal replacement therapy, either dialysis or kidney transplantation [15]. Patients were included if renal replacement therapy was started in or after 1985; follow-up ended on January 1, 2013. At baseline, the country or region of origin, birth date, sex, and primary renal disease were registered for each patient. Countries or regions of origin were grouped into four categories: Western Europe, Northern Europe, Southeastern Europe, and Southwestern Europe (see Appendix A). Primary renal diseases were also grouped into four categories: glomerular diseases including glomerulonephritis and glomerulosclerosis, pyelonephritis, vascular diseases including renal diseases due to diabetes mellitus, hypertension, and vascular disease and other or unknown diseases.

Follow-up and crude mortality rates

During follow-up, the dates and modalities of renal replacement therapy and the date of death were collected for each patient from the age of 20 years onward. For patients on dialysis, follow-up started 6 months after initiation of dialysis, excluding early mortality related to dialysis treatment or preceding transplantation, and lasted until death, transplantation, recovery of renal function, loss to follow-up, or January 1, 2013. The type of dialysis was categorized as hemodialysis or peritoneal dialysis. For patients with a functioning transplant, follow-up started 6 months after transplantation, excluding early mortality related to surgery or preceding dialysis treatment, and lasted until death, transfer to dialysis due to transplant failure, loss to follow-up, or January 1, 2013. Each transplantation was categorized according to the type of donor, being a deceased donor, living donor, or unknown donor.

Crude age-specific mortality rates were calculated from the follow-up data of the individual patients without using the Gompertz model by dividing the number of deaths by the number of person-years of follow-up per 5-year age group. Confidence intervals of the mortality rates were calculated using Byar's formula [18].

Mortality rates determined by the Gompertz models

The Gompertz model is described by $m(t) = \alpha\, e^{\gamma t}$, where $m(t)$ is the mortality rate at age t and α and γ the model's parameters. We used two Gompertz models that accounted for population heterogeneity. Both models were adjusted for covariates that affect the mortality rates, including the patient's sex, country of origin, primary renal disease, type of dialysis, and type of kidney donor. In addition, each model contained a random frailty parameter z that allowed further individual variation in the mortality rates through variation in either of the Gompertz model's parameters α and γ. Variation in α multiplies mortality rates at all ages by an age-independent factor; variation in γ multiplies mortality rates by a factor that increases with age. The Gompertz frailty models were fitted to the follow-up data by numerically integrating the frailty parameter z and numerically maximizing the log-likelihood with respect to α, γ, and z, as explained in more detail in Appendix A.

Senescence rates determined by the Gompertz models

We determined the senescence rates of the patients using the two Gompertz frailty models. The senescence rates measured as the