OPEN

Demographic Trends in Liver Transplant Survivors After 3 Decades of Program Implementation: The Impact of Cohort and Period Effects on Life Expectancy

Mario Romero-Cristóbal, MD,[1,2] Fernando Díaz-Fontenla, MD,[1,2] Ainhoa Fernández-Yunquera, MD,[1,2] Aranzazu Caballero-Marcos, MD,[1,2] Andrés Conthe, MD,[1,2] Enrique Velasco, MD,[3] José Pérez-Peña, MD,[4] José-Ángel López-Baena, MD,[3] Diego Rincón, MD,[1,2,5] Rafael Bañares, MD, PhD,[1,2,5] and Magdalena Salcedo, MD[1,2,5]

Background. Demographic analyses may reveal current patterns of change in the outcomes of rapidly developing medical procedures because they incorporate the period perspective. **Methods.** We analyzed the changes in size, age structure, and hospitalizations in the population of liver transplantation (LT) survivors in our center during the last 30 y (n = 1114 patients) and generated projections, including life expectancy (LE), considering cohort and period effects. Life tables were used to project the complete LE (overall 1990–2020 experience), the cohort LE (according to the decade of surgery: 1990–2000, 2000–2010, and 2010–2020), and the period LE (current 2015–2020 experience). **Results.** The population of LT recipients in follow-up continued to experience progressive growth and aging since 1990 (492 patients [41.9% >65 y] in 2020), and the magnitude of these phenomena may double in the next 30 y. However, the number of admissions and days of admission has been decreasing. The complete LE at LT was 12.4 y, whereas the period LE was 15.8 y. The cohort LE (limited to 10 y) was 5.3, 6.3, and 7.3 y for the 1990–2000, 2000–2010, and 2010–2020 cohorts, respectively. **Conclusions.** The target population of our medical care after LT is growing and aging. The prevalence of both of these phenomena is expected to increase in the coming years and is associated with a current improvement in LE. However, the hospitalization burden associated with LT survivors is declining. The period effect should be considered for generating up-to-date information on these current trends, which are crucial when designing health policies for LT survivors.

(*Transplantation Direct* 2024;10: e1684; doi: 10.1097/TXD.0000000000001684.)

Many factors that influence patient outcomes after liver transplantation (LT), including immunosuppressive regimens,[1] antiviral therapies,[2,3] organ allocation policies,[4] and surgical and organ procurement techniques,[5] are rapidly changing. Moreover, the baseline characteristics of LT candidates have also markedly varied, especially concerning age, cardiovascular risk, metabolic comorbidity, etc. Consequently, the appropriate care after LT and the burden on health systems requirements may also undergo relevant changes, with influencing trends or magnitudes that are difficult to anticipate without specific data analysis. Consideration of these demographic trends, as well as the evolving variations in the

Received 7 May 2024.

Accepted 27 May 2024.

[1] Liver Unit, Digestive Department, H.G.U. Gregorio Marañón, Madrid. Spain.

[2] CIBEREHD. Instituto de Salud Carlos III, Madrid, Spain.

[3] Liver Transplant and Hepatobiliary Surgery Unit, H.G.U. Gregorio Marañón, Madrid. Spain.

[4] Department of Anesthesiology, H.G.U. Gregorio Marañón, Madrid.

[5] School of Medicine, Universidad Complutense, Madrid. Spain.

The authors declare no funding or conflicts of interest.

R.B. and M.S. share senior authorship.

All authors have contributed significantly to the research and preparation of this article and approve the final version. M.R.-C. and M.S. participated in research design, writing the article, performing the research, contributed new reagents or analytic tools, and participated in data analysis. F.D.-F., A.F.-Y., A.C.-M., A.C., J.-A.L.-B., and D.R. participated in research design, performing the research, and data analysis. R.B. participated in research design, writing the article, performing the research, contributed new reagents or analytic tools, and participated in data analysis.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Rafael Bañares, MD, PhD, Hospital General Universitario Gregorio Marañón. Liver Unit, Doctor Esquerdo 46, Madrid 28007, Spain. (rbanares@ucm.es).

The submitted article is original and has not been published previously, nor is it currently under consideration for publication elsewhere.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001684

hospital requirements generated by LT recipients, may be important to maintain the current results and organization of LT programs.

Demography is defined as the statistical study of the size and structure of populations over space and time. One of the advantages of this methodological approach is the incorporation of the calendar period as one of the timelines to be used as a relevant source for data analysis. The traditional survival analysis methods, mostly based on the classic Kaplan-Meier test,[6,7] do not discriminate among different calendar times and thus fail to accurately analyze data from patients who have received LT recently or many years ago. Other temporal-trend studies estimate survival from different historical cohorts that have been followed for a determinate number of years (eg, 5 or 10 y),[8-10] according to the date of surgery. This approach does not recapitulate the potential survival influence of recent medical advances, which may differently impact outcomes of the diverse cohorts defined according to time since LT. In contrast, period analysis methodology can provide more accurate survival estimates. This approach incorporates the survival probabilities observed in current generations obtained through left truncation of the follow-up of contributing past cohorts.[11] Although period analysis has been widely validated in other rapidly developing fields, such as cancer,[12,13] this methodology has been scarcely used in the transplantation field.

Therefore, a demographic approach may account for the cumulative changes in LT populations over calendar time, has the possibility to identify current survival trends, and may provide more accurate projections. Importantly, the goal of a projection is not to make predictions about the probability of future events but rather to reveal current patterns of change. In this context, life expectancy (LE) is a projection that allows the comparison among mortality of different populations although they have a diverse composition. LE can be calculated from data of complete cohorts generated and followed-up until the present moment (complete analysis), from historical cohorts with different follow-ups (cohort analysis), or from the most recent left-truncated data (period analysis).[14] Using this methodology, it is possible to consider age, cohort, and period effects, thus providing valuable and updated data on recent trends in the size, age composition, and survival of current LT populations.

Thus, the aims of our study were (1) to analyze the demographic and hospitalization trends of LT recipients in our center after 30 y of program implementation; (2) to project the size, age composition, and mortality experience (LE) of this population; and (3) to explore the age, cohort, and period effects on LE calculation.

PATIENTS AND METHODS

Patients

We included all patients who underwent LT in our center (Hospital General Universitario Gregorio Marañón, Madrid, Spain) from the beginning of the program in 1990 to the end of 2020 (n = 1114). Patients who received a second LT, either urgent or elective, (121/1114; 10.86%) were included in the population corresponding to the first transplant date. Demographic and clinical characteristics were extracted from a prospectively recorded local database in which follow-up information was updated every 6 mo. Hospital admissions (including admissions corresponding to the LT procedure) were retrospectively analyzed by reviewing individual medical records. Hospital admissions that occurred over 2 different calendar years were considered 2 different admissions (1 corresponding to each year).

The protocol of our hospital includes at least 2 scheduled visits per year during the first 3 y on an outpatient basis and 1 annual visit thereafter. Additional visits were performed when needed by patients' clinical needs.

For the purpose of demographic estimations, 1114 patients entered the population at the time of the LT and left it when they died or were lost to follow-up. Patients were considered lost to follow-up when scheduled medical visits were missed for ≥1 y (42/1114; 3.77%). In these cases, we considered that they abandoned the population at the date of the last available visit. Pediatric recipients transferred to our center in adulthood (20 patients during the 30-y study period) were not considered part of the study population.

Temporal Perspectives

The age that the patients would reach their anniversary was considered as the patients' age for the whole calendar year. To explore cohort effects, the total sample was arbitrarily segmented into 3 historical cohorts according to the date of surgery (1990–1999, 2000–2009, and 2010–2020). To evaluate period effects, we considered 5-y period, with the most recent being between 2015 and 2020.

Statistics

Quantitative variables are expressed as the mean (SD). Categorical variables are shown as proportions (percentages). For the comparison of the baseline characteristics in the 3 historical cohorts, Royston chi-square trend statistic for proportions[15] and Cuzick test (an extension of the Wilcoxon rank-sum test)[16] for quantitative variables were used. Annual rates were calculated according to the number of living patients in the middle of the corresponding year.

To anticipate the future characteristics of the overall cohort of patients under medical care in our center, we projected its size, the number of patients older than 65 y and the LE, considering that the observed current trends remained stable. The projections of the total population size and the population older than 65 y were calculated by the mathematical function (linear, exponential, or logarithmic), which best fitted the observed data according to the least squares method.

LE was obtained from the life tables with the observed risks of death for each time window since LT (**Tables S1–S7, SDC,** http://links.lww.com/TXD/A682). Depending on the chosen timeline, we calculated different survival projections at the time of LT, as previously described[12,14]:

- Complete LE was defined as follows: projection based on the mortality experience observed in the total sample from 1990 to 2020.
- Cohort LE was defined as follows: projection based on the mortality experience observed for each historical cohort: 1990–1999, 2000–2009, and 2010–2020. To obtain comparable results, each cohort LE was limited to 10 y.

- Period LE was defined as follows: projection based on the mortality experience observed during the most recent calendar period (2015–2020). This period analysis implies the left truncation of the sample data, indicating that the results observed before 2015 did not contribute to generating the reference mortality risks. Therefore, the sample was constituted by the overlapping of the current survivors of the successive cohorts.

The different data sources used to calculate survival projections are depicted in Figure 1. **Figure S1** (**SDC,** http://links.lww.com/TXD/A682) shows the different life tables used for these analyses.

As chronological age by itself is a risk factor for dying, we also calculated the following survival projections for each of the previous temporal frames:

- LE at LT depending on the chronological age at the time of surgery (younger than 40 y, 40–60 y, and older than 60 y).
- LE at different chronological ages (regardless of the age that the patients had at LT). The LE for LT survivors was compared with that observed in the general Spanish population of the same chronological age (data from *Instituto Nacional de Estadística* of Spain).[17]

Ethics

The study was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón (dated February 21, 2022).

RESULTS

General Results

Table 1 summarizes the baseline characteristics of the overall cohort at the time of LT and the comparison among the 3 historical cohorts. As shown, the most recent cohorts showed a significant trend to include older recipients and donors, fewer patients with alcoholic disease, and more patients with metabolic dysfunction–associated fatty liver disease, as well as a relevant increase in patients diagnosed with hepatocellular carcinoma.

Figure 2 shows the evolution of the total population under follow-up, the transplant and mortality rates, the age of the patients at the moment of LT and death, and the mean age of survivors over calendar time. The transplant rate was systematically greater than the mortality rate, and consequently, the population of LT recipients has been growing since the beginning of the program (Figure 2A). Not surprisingly, the mean age of the total population and the proportion of survivors older than 65 y progressively increased (Figure 2B). The population pyramids of the LT population at different time points are shown in Figure 3. Overall, these results indicate that the population of LT recipients in our unit is not stabilized, progressively increasing the number of patients and their age.

Trends in the number of hospital admissions and the number of days of hospitalization generated by the LT survivors in each calendar year are summarized in Figure 4. The total number of hospital admissions and the cumulative days of admission tended to increase until 2013–2014 and constantly

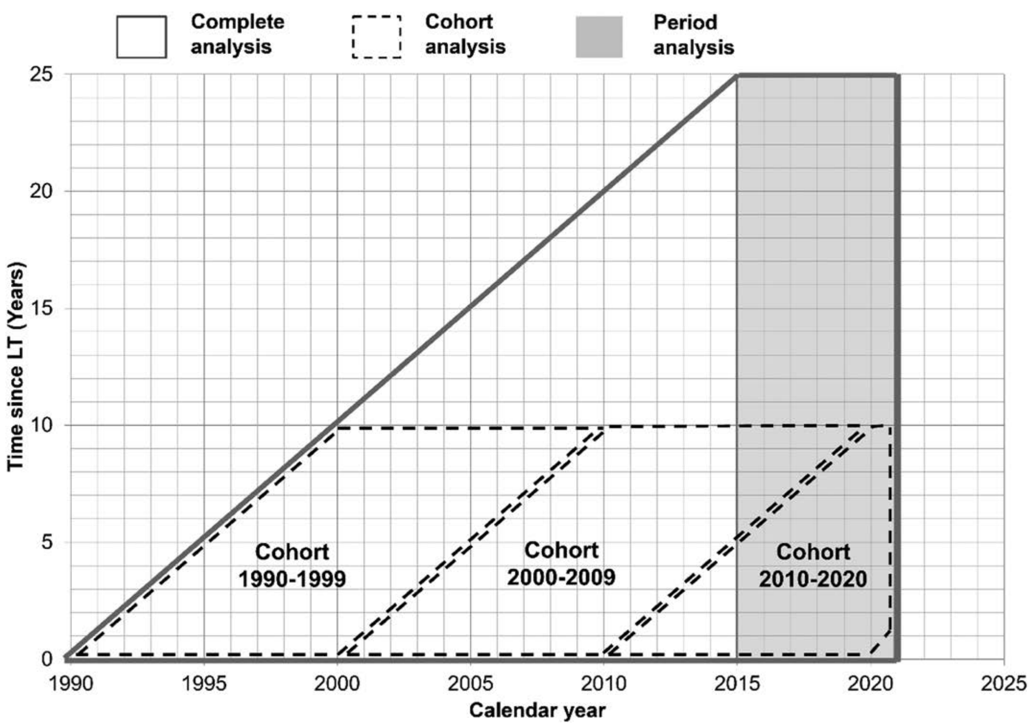

FIGURE 1. Illustration of the baseline and follow-up data to calculate life expectancy from the complete cohort (complete life expectancy), the 3 historical cohorts (cohort life expectancy), and the most recent experience (period life expectancy). For the complete life expectancy, all the LT recipients contribute to generating the mortality risk observed at different time intervals after LT, regardless of the date of the surgery and the follow-up time. For the cohort life expectancy, only those patients who received LT at a specific previous period and who were followed-up during a determinate time generated the mortality risk observed. To obtain comparable results, the life expectancy of each cohort was limited to 10 y. For the period life expectancy, only the LT recipients who transit the most recent calendar period, regardless of the date of surgery, generate the mortality risk observed at different time intervals since LT. LT, liver transplantation.

TABLE 1.

Basal characteristic of the total cohort and trend comparison over the 3 historical cohorts

	Total population (1990–2020)	Cohort 1 (1990–1999)	Cohort 2 (2000–2009)	Cohort 3 (2010–2020)	
	N = 1114	N = 339	N = 371	N = 404	*P*
Age at LT, y	51.33 (10.52)	47.91 (11.42)	51.88 (9.52)	53.69 (9.96)	<0.001
Male	834/1114 (74.87)	242/339 (71.39)	283/371 (76.28)	309/404 (76.49)	0.120
Donor age, y	51.07 (19.45)	39 (17)	51 (18)	61 (18)	<0.001
Cause					
Hepatitis C virus	427/1114 (38.33)	118/339 (34.81)	163/371 (43.94)	146/404 (36.14)	0.815
Alcohol	331/1114 (29.71)	148/339 (43.66)	105/371 (28.30)	78/404 (19.31)	<0.001
MAFLD	68/1114 (6.10)	9/339 (2.65)	7/371 (1.89)	52/404 (12.87)	<0.001
Immune or cholestasic	86/1114 (7.72)	30/339 (8.85)	22/371 (5.93)	34/404 (8.42)	0.888
HCC	348/1114 (31.24)	39/339 (11.50)	114/371 (30.73)	195/404 (48.27)	<0.001
Acute liver failure	81/1114 (7.27)	33/339 (9.73)	21/371 (5.66)	27/404 (6.68)	0.129
MELD score	16.95 (7.57)	18.45 (7.90)	17.26 (6.55)	15.21 (7.50)	<0.001

Data are expressed as mean (SD) or proportion (%).
HCC, hepatocellular carcinoma; LT, liver transplantation; MAFLD, metabolic dysfunction-associated fatty liver disease; MELD, model for end-stage liver disease.

decreased thereafter. Considering that the total number of patients under follow-up increased every calendar year, the mean days of hospitalization per patient under follow-up decreased progressively.

Projections of the Population Size and Their Age Composition

The logarithmic function best fits the observed data (adjusted R^2 = 0.9966 and 0.9949 for the total number of survivors and the survivors older than 65 y, respectively). Figure 5 shows the projections for the next 30 y if the observed trends for age and population growth were maintained. As shown, the projection of the total number of LT recipients under follow-up indicates a continuous increase in the number of patients, approximately doubling the current population by 2050. Additionally, the number of patients older than 65 y would continue to increase, from 41.3% in 2020 to >80% in 2050.

Life Expectancy

Complete LE

Table 2 shows the overall LE and LE according to different chronological age ranges at the time of LT. As shown, overall and age-stratified LE projection improved 2 y after LT compared with the projected LE at the moment of LT, indicating the impact of early mortality related to the procedure. Interestingly, LE was greater for patients who received LT before the age of 40 y, whereas the projection was similar for recipients who underwent LT between 40–60 y and after 60 y of age.

The comparison between LE in LT survivors according to their different chronological ages (regardless of the age at LT) and LE for the general population of the same age is shown in Table 3. As expected, the LE of LT recipients was reduced in all age ranges.

Cohort LE

LE at the time of LT (limited to 10 y of follow-up) increased over the successive historical cohorts, being 5.3, 6.3, and 7.3 y for LT recipients who underwent surgery during 1990–1999, 2000–2009, and 2010–2020, respectively.

The limited sample size precluded the evaluation of the age effect on the cohort LE (ie, age at transplantation and chronological age regardless of the age at surgery).

Period LE

Figure 6 shows LE corresponding to the observed mortality risks during the last analyzed period (2015–2020, period LE) in comparison with the complete LE (1990–2020). As shown, LE improved in the most recent period. In contrast with the complete LE, there was virtually no reduction in the period LE at the time of LT compared with the projection obtained 2 y later. These changes are because of recent improvements in early mortality. In fact, the percentages of patients who died in the first year after LT were 30.1%, 32.7%, 19.2%, 13.2%, 13.1%, and 6.5% for the successive 5-y period (χ^2 for trend = 65.13; *P* trend < 0.001; **Figure S2, SDC,** http://links.lww.com/TXD/A682).

As in the case of cohort LE, the sample size was insufficient to accurately estimate the age effect on period LE.

DISCUSSION

The use of demographic approaches to evaluate many complex health problems has clearly increased in recent

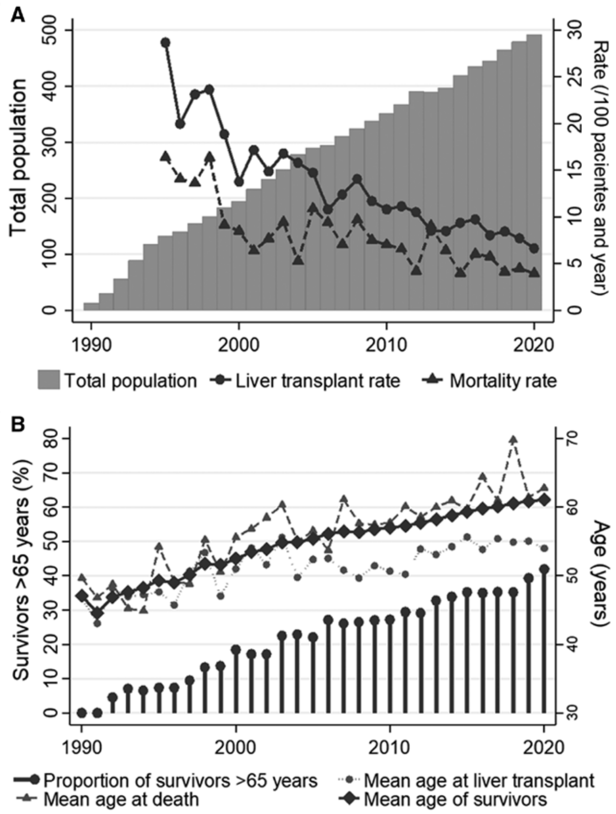

FIGURE 2. Evolution of the different demographic indicators according to calendar year. A, LT rate, mortality rate, and total population of survivors in follow-up in each calendar year. The LT rate and the mortality rate are calculated by dividing the number of new transplants or the number of patients who died during the calendar year by the total population of survivors in follow-up at half of the corresponding calendar year (expressed as total number/100 people and year, units in the right y-axis). The total population is the total number of LT survivors under follow-up at the end of each calendar year (units in the left y-axis). As the total number of patients followed-up is progressively increasing since the beginning of the program, the transplant and mortality rates are progressively lower. B, Mean age at transplant, mean age at death, mean age of survivors, and proportion of survivors older than 65 y in each calendar year. The mean age at transplant and the mean age at death are calculated as the mean age of all the patients who received a new transplant and all the patients who died during the corresponding calendar year (right y-axis), respectively. The mean age of survivors is calculated as the mean age of all the LT survivors who are under follow-up during any time along the corresponding calendar year (right y-axis). The age that the patients would reach at their anniversary was considered as the patients' age for the whole calendar year. The proportion of patients older than 65 y is calculated by dividing the number of patients in follow-up during the calendar year older than 65 y by the total number of patients in follow-up at the end of the corresponding calendar year (expressed as % in the left y-axis). LT, liver transplantation.

years. However, knowledge of demographic trends after LT, a paradigm of medical complexity, is still scarce. Thus, we aimed to evaluate some demographic aspects in a large cohort of LT patients followed up in our unit within the last 30 y. Our study revealed several relevant demographic trends in this population. First, we revealed that the LT population is markedly dynamic, showing a progressive growth in the total number of patients in follow-up with a sustained increase in their age. Furthermore, the projections suggested that both phenomena will continue to progress in the following years. Finally, LE at LT progressively improved despite the increasing age of both recipients and donors. In fact, LE had a continuous favorable trend along the 3 historical cohorts (increasing approximately 10% in each of them), and the survival projection based on the most recent mortality risks (period LE) showed better results than the projection based on the historical and outdated risks of the total cohort (complete LE).

Another important piece of information is that despite the increasing number of LT recipients, hospital admissions in this population showed a marked downward trend, probably reflecting the improvement in outpatient facilities and the overall health status of this population.

Our analysis offers novel insights that, to the best of our knowledge, have not been previously reported. The main point supporting this comment is that we have applied a methodology based on demographic analyses, which significantly differ from classical survival analyses that do not consider the period effect. Thus, we have incorporated the period effect into survival estimates, highlighting the disparity with estimates derived from complete cohorts. Moreover, our findings suggest that, given the rapid changes in prognostic factors, the results from traditional analyses in the field of LT may be, at least partially, inaccurate and outdated. Our study offers absolute results across various calendar years, as opposed to other studies that emphasize relative changes between different groups of patients, which are commonly reported in cohort studies. One of these absolute changes is the dynamics of the global and real population of individuals living with an LT throughout each calendar year (which is very different from the demographic changes of patients receiving an LT each calendar year).

Another relevant fact from our study is that LE at the time of transplant in the recent period (period LE) is better than the historical one (complete LE). This information is novel, highly relevant, and not obvious. The main fact here is that, despite the increasing age and comorbidity of donors and recipients, the overall impact of the program (ie, the number of years of life we expect to achieve with a transplant on average) continues to improve.

Our findings (greater number of patients in follow-up, better health outcomes, and fewer hospital admissions) are similar to those observed in other settings, such as cancer or cardiovascular diseases.[18-20] Overall, our results provide valuable information for patients, clinicians, researchers, and policymakers. We suggest that some new models of assistance (more closely interconnected with primary care or geriatrics and with an enhanced nursing role) would help to address the expected increase in the burden of disease generated for LT survivors.

It should be emphasized that demographic projections do not aim to predict events but rather to offer representations of future phenomena, provided their conditioning factors remained stable. Therefore, projections are intrinsically biased, considering their influencing factors are constantly change.[14] Thus, it is possible that the herein-reported data in LE were excessively optimistic because of the impact of the recent reduction in early mortality in modern cohorts and the lower mortality risk in the survivors of the oldest cohorts, who received LT when the comorbidity and age criteria were stricter and donors were younger. Moreover, it could be argued that these favorable long-term probabilities would not be reproduced in the most recent, oldest recipients with more

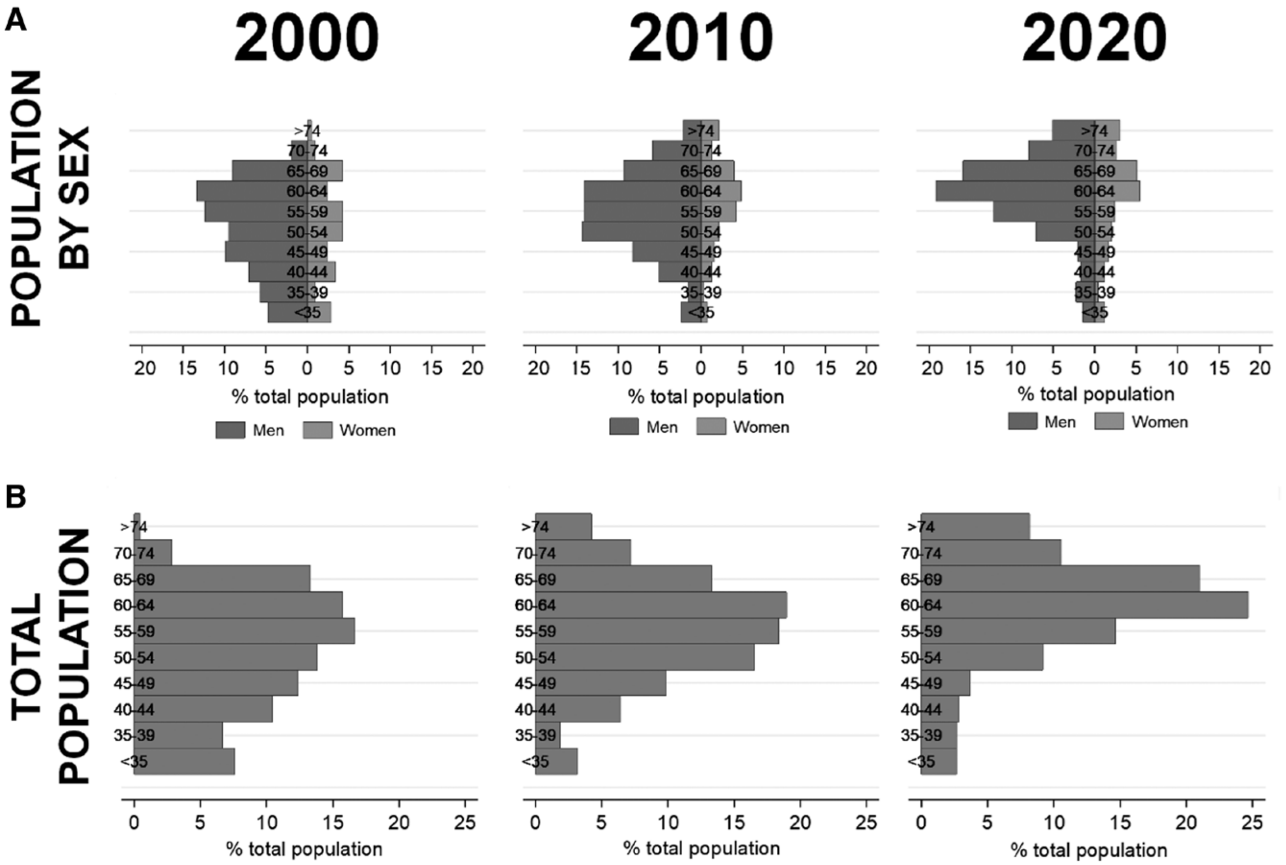

FIGURE 3. Population pyramids of liver transplant survivors in follow-up at different calendar times. Each pyramid shows the proportion of patients in each age range with respect to the total number of survivors in follow-up at the end of the years 2000, 2010, and 2020, overall (bottom row) and segregated by sex (top row).

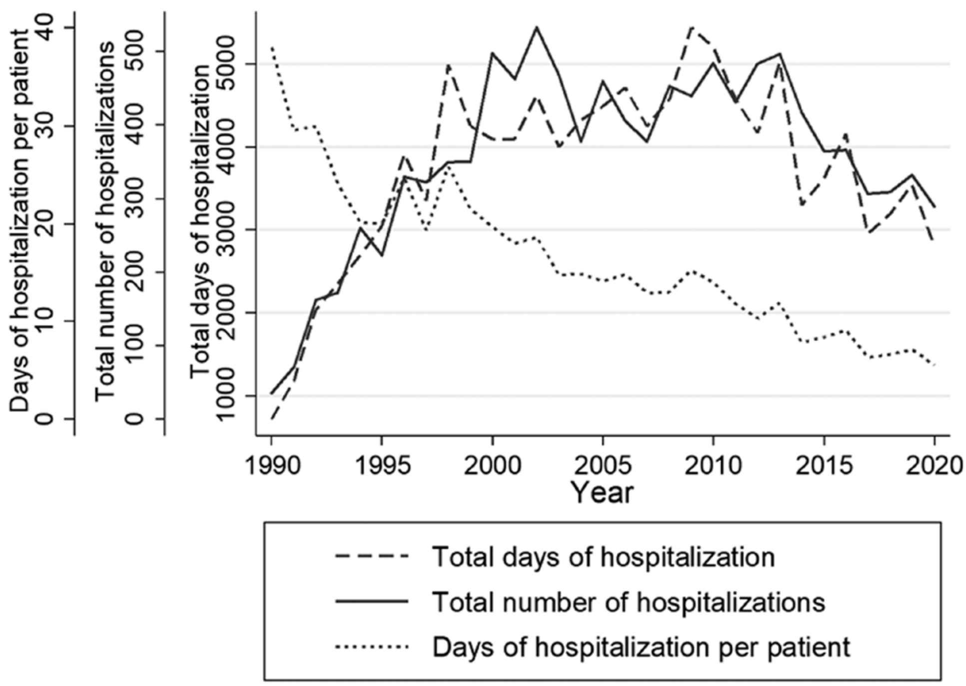

FIGURE 4. Hospital care indicators in the population of liver transplant survivors according to calendar year. Total days of hospitalization and total number of stays generated by the liver transplant survivors in follow-up during each calendar year. The days of hospitalization per patient were calculated as the total number of days of hospitalization in the year divided by all the patients in follow-up during that year.

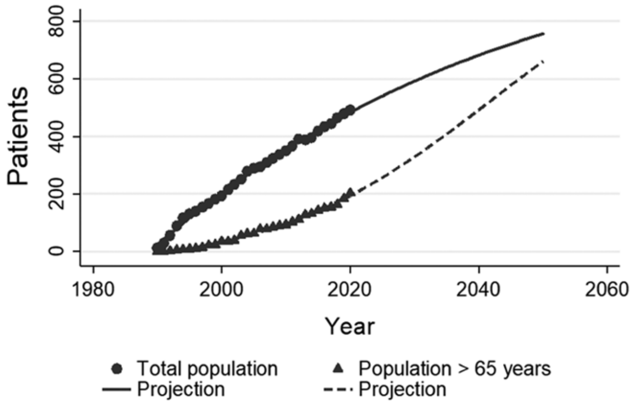

FIGURE 5. Total liver transplant survivors in follow-up and survivors older than 65 y at the end of each calendar year (period 1990–2020) and possible future projections for the next 30 y. Dots are the total number of survivors observed at the end of each calendar year, triangles are the number of survivors older than 65 y at the end of the calendar year, the continuous line illustrates the projection for the total number of survivors, and the dashed line is the projection for the number of survivors older than 65 y. Nonlinear (logarithmic) least squares estimations (adjust R^2=0.9966 and 0.9949 for total survivors and for survivors older than 65 y, respectively).

comorbidities. Consequently, the progressive improvement in LE would decrease, and therefore, a slowdown in the growth and aging of our LT populations would occur. In contrast, our data suggest that these trends (longer LE, larger and older populations) may continue or even increase in the upcoming years. These findings are not surprising; first, they would be concordant with changes experienced by the general population.[21,22] Moreover, the mortality of LT patients is increasingly conditioned by nonhepatic complications,[23] which are progressively better diagnosed and treated; finally, it is conceivable that the expected improvement in the overall process of LT can also positively affect LE.

Considering that the age criteria for transplant eligibility have become more flexible in recent years, there is increasing concern regarding LT outcomes in older patients.[24,25] It is generally accepted that age at LT, considered an isolated factor, does not impact early mortality.[26] However, the majority of studies have shown that 5-y survival in patients older than 65–70 y shows a 10% to 20% decrease.[27-29] In our study, the complete sample projection showed that recipients younger than 40 y who underwent LT presented higher survival expectancy than those patients older than 40 y. Unfortunately, because of the limited sample size, we could not explore whether there was a trend in LE improvements according to the different age ranges at LT in the cohort and period analysis. Despite this, and based on our results, increased age at LT does not seem to reduce the overall results of the LT program, as the most recent LE is improving, although the mean age at surgery is progressively higher.

Our study also clearly shows that the increase in survival expectancy and older age at the time of LT lead to progressive aging of the population of LT survivors. This fact is extremely important considering that age is a well-known risk factor for most of the expected complications after LT.[26] Therefore, to mitigate the impact of aging on overall long-term survival, the specific management of immunosuppressive regimens and the prevention of malignancy and cardiovascular and metabolic bone diseases should be intensified in the future.

A common method to study temporal trends after LT is to include the transplantation cohort as a covariate. However, the period analyses, which represent the current mortality experience observed in the different time intervals since the surgery, could provide a more reliable approach. In fact, period analysis simultaneously summarizes the most recent advances in the treatment of recently transplanted patients (eg, the development of preservation techniques or organ selection) and of those recipients who underwent surgery years ago (such as the optimization of immunosuppression strategies or the prevention of cardiovascular risk factors). Thus, period analysis (represented by the period LE in our study) provides survival information closer to the global technical and scientific states of the art at each time point. There are several studies, mainly involving cancer populations[12,30-32] but also some with solid organ recipients,[33,34] that empirically corroborate these data.

Our study offers other relevant results. According to our data, the LE of LT recipients is systematically lower than that observed in the general population of the same chronological age (even at 70 or 80 y). This observation is in agreement with what has been reported in other studies.[29] This finding is probably associated with the fact that patients with advanced liver disease are a selected population with relevant nonhepatic comorbidities and with the deleterious cumulative effects of chronic immunosuppression that persist even at advanced ages. Reducing this "survival gap" between LT recipients and

TABLE 2.

Life expectancy at liver transplantation and thereafter, globally and according to the chronological age at surgery

Years since LT	Global	Age at LT <40 y	Age at LT 40–60 y	Age at LT >60 y
At LT	12.4	16.3	11.9	11.1
2	13.9	18.0	13.4	12.1
4	13.2	17.4	12.7	11.5
6	12.4	15.9	11.8	10.9
8	11.4	15.0	10.7	9.9
10	10.3	13.6	9.7	8.7
12	8.9	12.1	8.2	7.9
14	7.6	10.5	7.0	6.4
16	6.6	9.6	5.9	5.5
18	5.3	8.3	4.6	4.3
20	3.7	6.5	2.9	3

These projections correspond to the complete life expectancy (survival experience of the total cohort 1990–2020).
LT, liver transplantation.

TABLE 3.

Comparison of life expectancy of liver transplant patients and the general population according to their chronological age (regardless of the age at surgery of liver transplant patients)

	Life expectancy, y	
Age, y	**Liver transplant recipients**	**General population**
17–25	49.3	63.5
25–30	41.5	57.0
30–35	36.7	51.6
35–40	32.0	46.7
40–45	27.6	42.4
45–50	23.4	37.6
50–55	19.9	32.9
55–60	16.6	28.0
60–65	13.9	24.1
65–70	11.8	19.9
70–75	8.8	16.0
75–80	5.9	12.2
≥80	2.1	5.4

The projections about liver transplant recipients correspond to the complete life expectancy (survival experience of the total cohort 1990–2020). Data of life expectancy for the general population from INE (Instituto Nacional de Estadística) available at https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736177004&menu=ultiDatos&idp=1254735573002.

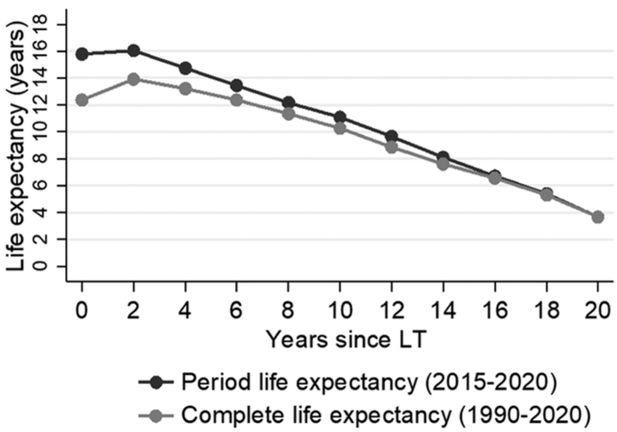

FIGURE 6. Comparison of life expectancy of LT patients at surgery and thereafter, calculated from the total cohort (1990–2020, complete life expectancy) and from the most recent experience (2015–2020, period life expectancy). The survival projection improved in the period analysis (mortality experience observed in the recent period 2015–2020) compared with the projection with the total sample (1990–2020). In the period analysis, life expectancy at LT and after 2 y was virtually the same, in contrast with the lower life expectancy at the moment of surgery than after 2 y in the complete analysis. This is because of recent improvements in early mortality. Both projections become progressively equal after 15 y of surgery because the mortality risks on which they are based come from virtually the same individual patients at later time periods (see **Figure S1, SDC,** http://links.lww.com/TXD/A682). LT, liver transplantation.

the general population is a formidable research challenge for transplant medicine.

Finally, it is important to highlight the recent decrease in the hospital burden associated with the LT population observed in our study. Although there are studies that explore hospitalization trends in patients with other digestive and liver diseases[19,35,36] or hepatocellular carcinoma,[37] there are no data about the temporal changes in LT recipients. There are several possible explanations for this finding. First, there was a substantial progression in the experience of the LT team. Second, the development of direct-acting antivirals for hepatitis C treatment has probably contributed to a lower incidence of complications requiring hospitalization. Finally, the progressive development of outpatient management is also a major contributor. As previously mentioned, our data are parallel to the trending healthcare policies in other common diseases affecting the nontransplant population.[38,39]

Our study has several limitations. First, our results are based on a single center and, thus, a single country. Therefore, it can be argued that the population trends in other LT programs may be different. However, our LT program is one of the oldest; thus, our data were indicative of the different changes that occurred in the LT field, and we included a representative number of patients.[40] Moreover, patient management has followed the general recommendations issued by international societies.[41-43] Therefore, our general conclusions are expected to be mostly valid for other LT populations. Second, regarding hospitalization data, it is possible that some admissions were missed if the patients had been admitted to other centers. However, the current policy in Spain implies that LT recipients are usually referred to the transplant center, regardless of the cause of admission. Therefore, the number of undocumented admissions is probably not significant. Importantly, it is possible that the different policies of each health system regarding hospital admission could modify the current estimations, especially considering that other transplant centers that accumulate long-term survivors will devolve care to district hospitals. Finally, the limited sample size precluded the exploration of the effect of age at LT on the cohort and period LE projections. Nevertheless, the results of this single-center proof-of-concept study warrant a demographic analysis in more comprehensive transplant populations (ie, at a national level), which could overcome some of these limitations.

In conclusion, the improvement of LE after LT was observed in recent years, and its consequent increase in the number of LT survivors implies significant growth and aging of the LT population. Moreover, these 2 demographic processes are expected to continue to increase in the coming years. However, healthcare for this population tends to be less dependent on hospital admissions. Our results suggest that the use of a demographic approach, including the period perspective, may improve the evaluation of the healthcare requirements of LT programs.

REFERENCES

1. Meier-Kriesche HU, Li S, Gruessner RW, et al. Immunosuppression: evolution in practice and trends, 1994-2004. *Am J of Transplant*. 2006;6:1111–1131.
2. Orfanidou A, Papatheodoridis GV, Cholangitas E. Antiviral prophylaxis against hepatitis B recurrence after liver transplantation: current concepts. *Liver Int*. 2021;41:1448–1461.
3. Burra P, De Martin E, Zanetto A, et al. Hepatitis C virus and liver transplantation: where do we stand? *Transpl Int*. 2016;29:135–152.
4. Sass DA, Doyle AM. Liver and kidney transplantation: a half-century historical perspective. *Med Clin N Am*. 2016;100:435–448.
5. Bodzin AS, Baker TB. Liver transplantation today: where we are now and where we are going. *Liver Transpl*. 2018;24:1470–1475.
6. Elisofon SA, Magee JC, Ng VL, et al. Society of pediatric liver transplantation: current registry status 2011-2018. *Pediatr Transplant*. 2020;24:e13605.

7. Mousa OY, Nguyen JH, Ma Y, et al. Evolving role of liver transplantation in elderly recipients. *Liver Transpl*. 2019;25:1363–1374.
8. Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol*. 2012;57:675–688.
9. Barber K, Blackwell J, Collett D, et al; on behalf of the UK Transplant Liver Advisory Group. Life expectancy of adult liver allograft recipients in the UK. *Gut*. 2007;56:279–282.
10. Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR). *OPTN/SRTR 2019. Annual Data Report*. US Department of Health and Human Services; 2019.
11. Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet*. 2002;360:1131–1135.
12. Brenner H, Gefeller O, Hakulinen T. Period analysis for “up-to-date” cancer survival data: theory, empirical evaluation, computational realisation and applications. *Eur J Cancer*. 2004;40:326–335.
13. Ellison FL. An empirical evaluation of period survival analysis using data from the Canadian Cancer Registry. *Ann Epidemiol*. 2006;16:191–196.
14. Luy M, Di Giulio P, Di Lego V, et al. Life expectancy: frequently used, but hardly understood. *Gerontology*. 2020;66:95–104.
15. Royston P. PTREND: Stata module for trend analysis for proportions. Available at http://ideas.repec.org/c/boc/bocode/s426101.html. Accessed February 1, 2024.
16. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4:87–90.
17. INEbase. Instituto Nacional de Estadística. Demografía y población. Available at https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736177004&menu=ultiDatos&idp=1254735573002. Accessed February 1, 2024.
18. Gondos A, Brenner H. Period analysis for more up-to-date graft and patient survival estimates in transplantation: an evaluation using United Network for Organ Sharing Data. *Transplantation*. 2010;89:580–588.
19. Gondos A, Doehler B, Opelz G, et al. From cancer to transplantation: an evaluation of period analysis for calculating up-to-date long-term survival estimates. *Am J Epidemiol*. 2010;172:613–620.
20. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level results from the global burden of disease study 2015. *JAMA Oncol*. 2017;3:1683–1691.
21. Rodríguez Fernández CM, Fernández Pérez C, Bernal JL, et al. RECALAD. patient care at national health system digestive care units—a pilot study, 2015. *Rev Esp Enferm Dig*. 2017;110:44–50.
22. Zapatero-Gaviria A, Gomez-Huelgas R, Diez-Manglano J, et al. RECALMIN. Four years of growth of the internal medicine units of the Spanish National Health System (2013–2016). *Rev Clin Esp (Barc)*. 2019;219:171–176.
23. Khaw KT. How many, how old, how soon? *BMJ*. 1999;319:1350–1352.
24. Arai H, Ouchi Y, Toba K, et al. Japan as the front-runner of super-aged societies: perspectives from medicine and medical care in Japan. *Geriatr Gerontol Int*. 2015;15:673–687.
25. Aberg F, Gissler M, Karlsen TH, et al. Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic Study. *Hepatology*. 2015;61:668–677.
26. Cottone C, Pena Polanco NA, Bhamidimarri KR. Transplant of elderly patients: is there an upper age cutoff? *Clin Liver Dis*. 2021;25:209–227.
27. Durand F, Levitsky J, Cauchy F, et al. Age and liver transplantation. *J Hepatol*. 2019;70:745–758.
28. Cross TJ, Antoniades CG, Muiesan P, et al. Liver transplantation in patients over 60 and 65 years: an evaluation of long-term outcomes and survival. *Liver Transpl*. 2007;13:1382–1388.
29. Bilbao I, Dopazo C, Lazaro JL, et al. Our experience in liver transplantation in patients over 65 yr of age. *Clin Transplant*. 2008;22:82–88.
30. Schwartz JJ, Pappas L, Thiesset HF, et al. Liver transplantation in septuagenarians receiving model for end-stage liver disease exception points for hepatocellular carcinoma: the national experience. *Liver Transpl*. 2012;18:423–433.
31. Su F, Yu L, Berry K, et al. Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, post-transplantation outcomes, and transplant-related survival benefit. *Gastroenterology*. 2016;150:441–453.e6.
32. Smith LK, Lambert PC, Botha JL, et al. Providing more up-to-date estimates of patient survival: a comparison of standard survival analysis with period analysis using life-table methods and proportional hazards models. *J Clin Epidemiol*. 2004;57:14–20.
33. Brenner H, Hakulinen T. Advanced detection of time trends in long-term cancer patient survival: experience from 50 years of cancer registration in Finland. *Am J Epidemiol*. 2002;156:566–577.
34. Brenner H, Hakulinen T. Period estimates of cancer patient survival are more up-to-date than complete estimates even at comparable levels of precision. *J Clin Epidemiol*. 2006;59:570–575.
35. Shahab O, Sayiner M, Paik J, et al. Burden of primary biliary cholangitis among inpatient population in the United States. *Hepatol Commun*. 2019;3:356–364.
36. Hirode G, Saab S, Wong RJ. Trends in the burden of chronic liver disease among hospitalized US adults. *JAMA Netw Open*. 2020;3:e201997.
37. Mullangi S, Keesari PR, Zaher A, et al. Epidemiology and outcomes of hospitalizations due to hepatocellular carcinoma. *Cereus*. 2021;13:e20089.
38. Huntley AL, Thomas R, Mann M, et al. Is case management effective in reducing the risk of unplanned hospital admissions for older people? A systematic review and meta-analysis. *Fam Pract*. 2013;30:266–275.
39. Fox MT, Persaud M, Maimets I, et al. Effectiveness of early discharge planning in acutely ill or injured hospitalized older adults: a systematic review and meta-analysis. *BMC Geriatr*. 2013;13:70.
40. ONT. Organización Nacional de Trasplante. *Memoria de actividad y donación de trasplante*. 2020. https://www.ont.es/wp-content/uploads/2023/06/Actividad-de-Donacion-y-Trasplante-Hepatico-en-Espana-2021.pdf. Accessed February 1, 2024.
41. Belli LS, Duvoux C, Berenguer M, et al. ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients. *J Hepatol*. 2017;67:585–602.
42. Charlton M, Levitsky J, Aqel B, et al. International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients. *Transplantation*. 2018;102:727–743.
43. Mehta N, Bhangui P, Yao FY, et al. Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS Transplant Oncology Consensus Conference. *Transplantation*. 2020;104:1136–1142.