The 49th parallel: Does geographic position affect longevity of patients with cystic fibrosis?

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Feature Editor’s Introduction—Previous studies have reported a 10-year decrease in survival between people living with cystic fibrosis treated in the United States compared with Canada. A recent article published by Stephenson and colleagues in the Journal of Heart and Lung Transplantation investigated the contribution of lung transplant outcomes in Canada and the United States and found that significant differences in waitlist and posttransplant survival could explain up to one-third of this difference. In the Invited Expert Opinion article that follows, an expert group of pulmonologists and thoracic surgeons specializing in the treatment of cystic fibrosis from both countries address the possible reasons for this variation in outcomes, including differences in health care delivery, transplant allocation, access to lung transplantation, and waitlist and posttransplant outcomes. Although there is no single reason for the difference in outcomes, this Invited Expert Opinion article will likely increase discussion around current thoracic surgery and pulmonary care of patients living with cystic fibrosis and highlight efforts to improve survival by increasing referrals and access to lung transplantation and improving posttransplant survival. Treatment for patients with cystic fibrosis continues to evolve, and it remains to be seen how the development of new therapies like cystic fibrosis transmembrane conductance regulator modulators will influence the management and long-term survival of these patients.

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Recent publications1,2 have demonstrated inferior survival for people living with cystic fibrosis (CF) in the United States compared with Canada, both in general1 and after receiving a lung transplant.1 During 2017, Stephenson and colleagues2 conducted a population-based cohort study using prospectively collected data from 42 Canadian and 110 US CF centers from 1990 to 2013 captured by the comprehensive CF registries in each country. They demonstrated a 10.8-year survival gap for people living with CF in the United States compared with their counterparts in Canada. During 2021, these investigators combined the US and Canadian CF registries with the US transplant registry to better understand the influence of transplant on the observed survival gap.1 The authors used a modeling algorithm that suggested some of the difference in survival observed between the 2 countries could be mitigated if more transplants for CF occurred in the United States and if US lung transplant recipients lived as long as those in Canada.
We consider whether the consideration of the counterfactual scenarios posed by these investigators as a remedy for the observed survival gap between people living with CF in the United States compared with those living in Canada is plausible. Foremost in our analysis is the long-accepted concept that the health of populations reflects the cascade of interactions of the individual or class of individuals with society and its institutions—of which the health care system is a very small part. This observation is especially relevant when comparing epidemiologic observations in populations across different countries where societal structures vary, making it even more difficult to make firm conclusions on the causes of differing survival and where interventions may be most impactful.

HEALTH CARE DELIVERY IS DIFFERENT IN THE UNITED STATES VERSUS CANADA

Perhaps the key difference between the United States and Canada is the economy of their respective health care systems and the models of delivery of care. Canada administers universal health care coverage that is managed by 10 provinces, compared with the complex US system that includes a mixture of public, private, and no health insurance. One form of health insurance is Medicaid, which is reserved for low income or disabled individual and is administered by its 50 states. The terms of health coverage vary state by state. Medicare, also a public health insurance that serves individuals older than age 65 years or individuals with disability is administered nationally. Finally, private health insurance is administered by a wide range of insurance companies and is often secured through one’s employer. Among persons with CF in the United States, 41% have Medicaid, 11% have Medicare, 59% have private health insurance, and 1% are uninsured (these categories are not mutually exclusive). This is important enough that differences in survival between the United States and Canada disappear for people living with CF in the United States with private insurance.

TRANSPANT ALLOCATION SYSTEMS ARE DIFFERENT IN THE UNITED STATES VERSUS CANADA

The next major consideration is the structure and size of the respective transplant systems and the number of patients they serve. There were 4 lung transplant programs in Canada with a fifth performing a small number of transplants during the study period compared with the United States with approximately 64 lung transplant programs during the study period. Two thousand ninety-six lung transplants were performed in Canada and 20,995 in United States during the study periods. In Canada, there is no more than a single center in every transplant area, and they are usually divided by provinces. In the United States, most organ procurement occurs in areas where there is more than 1 center.

In Canada, the allocation of donor organs occurs within the center, whereas in the United States a national, predominantly disease severity-based allocation system is utilized; that is, the Lung Allocation Score (LAS), which prioritizes survival benefit and prevention of death on the waiting list. In the United States, if an organ is not utilized locally for a specific candidate, it is incrementally offered to the next candidate with the highest LAS in widening geographic concentric circles nationally. The LAS system does not allocate donor lungs based on likelihood of long-term survival and does not account for key variables that are known predictors of waitlist mortality in the population of persons living with CF—both of which result in underestimation of survival benefit in CF population.

LACK OF ACCESS TO TRANSPLANT IS EQUALLY PROBLEMATIC IN THE UNITED STATES AND CANADA BUT HAS DIFFERENT CHARACTERISTICS

A remarkable finding by the authors is the percentage of those with CF who died without being referred for transplant were similar in the 2 countries at approximately 50%. This remarkably high nonreferral rate is an opportunity for improvement that could improve survival in both countries. In the United States, it has been shown that people living with CF are less likely to be referred for transplant if they are infected with Burkholderia cepacia or have Medicaid insurance. However, in Canada, the reasons for this lack of referral are not known. We can speculate, given that only 4 transplant centers are available to patients, that those who live far from transplant centers may be less likely to be referred for transplant. A possible reason might be the need of relocation, for at least some period of time, to be closer to the transplant center. The different population density and distribution in the 2 countries might play a role too, although we do not have enough information to know the exact effect. Another possibility is less familiarity about the transplant process among CF centers that do not routinely interact with transplant centers, leading to fewer referrals. Socioeconomic factors are documented to play a role in nonreferral in the United States and their mitigation is an opportunity to reduce the number of those who die without being referred for transplant in the United States. In Canada, identification of the causes of nonreferral could lead to interventions that may ultimately resulting in fewer deaths in this population.

OUTCOMES OF TRANSPLANT WAITING LIST IS DIFFERENT IN THE UNITED STATES VERSUS CANADA

There are also differences on the waiting list in the 2 countries. Death rate on the waiting list was higher in the United States than in Canada (15.8% vs 6.5%). US transplant candidates who received a transplant spent less time
on the waiting list before transplant, whereas patients who died spent a longer time on the list.1 This may reflect the current LAS national allocation system that does not incorporate some special circumstances (eg, resistant organisms) that are unique to CF candidates resulting in underestimation of the risk of mortality on the waiting list. Although these numbers seem contradictory, they may be explained by regional differences or the effect of difficult to match donor recipients (eg, smaller size, presence of human leukocyte antigen antibodies).7 At the same time, broadening geographic sharing of donor lungs in the United States could lead to shorter waiting times for easier-to-match candidates in the United States.3 In addition, techniques that increase the ability to bridge to transplant, like extracorporeal life support are more common in larger centers.12,13 This is also true for techniques to maximize organ procurement like donation after cardiac death or ex vivo lung perfusion. All Canadian centers tend to be larger and maybe more likely to have access and utilize these techniques. ex vivo lung perfusion was also developed in Toronto and was not available to other centers in Canada or the United States for the first few years of the study.12 Even to date, Toronto has very high transplant rates due to use of this technique, the extensive use of donation after cardiac death donors, and the use of lobar transplants (for low stature persons living with CF) bringing overall transplant rates to be higher in Canada compared with the United States (10.7 per million vs 7.85 per million). Finally, heavy scrutiny of programs in the United States might lead to very careful management of the waiting list in terms of listing time (because time on the waiting list and death on the waiting list are significant evaluation parameters). In any case, increase in the number of suitable donor lungs and ways to improve bridging to lung transplant would further benefit people living with CF and other diagnoses in both countries.7

Another interesting finding is the small number of programs in Canada, which results in every program performing a relatively large volume of transplants, whereas in the United States there is a much higher variability in number of performed transplants among transplant centers. Program volume correlates with outcomes and the difference between the 2 countries may decrease significantly if only larger-volume programs are compared.1 The criterion of 26 lung transplants per year has been utilized before as a threshold for large versus smaller programs, leading to differences in outcomes.14 The effect appears to be linear, with larger programs having better survival, albeit with less of an effect with increasing volume. Consistent with these findings, larger programs in the United States have survival rates closer to those observed in Canada. Within Canada, the largest program has shown excellent survival rates, especially for patients without B cepacia infection before transplant.12 It would be interesting to know if differences in survival follow the same pattern for programs in Canada with respect to volume and outcomes (via personal communication lung transplants for CF recipients at each center during the study period were as follows: Toronto, 46%; Montreal, 29%; Edmonton, 16%; Vancouver, 7%; and other, 2%). These results are intriguing, but the quick reaction of restricting lung transplants for people living with CF to larger programs might lead to unintended consequence of excluding patients who cannot access these programs for a variety of reasons (eg, insurance or geographic reasons). However, this is an area that further policy interventions may be worth considering.

A finding that has been replicated in studies of people living with CF, but also elsewhere, is the worse outcome in people living with CF with Medicare or Medicaid insurance. In contrast, people living with CF who have US private insurance have similar survival to people living with CF in Canada.1 Worse survival for patients with public insurance has been shown in CF, cancer care, and other diseases.2,15,16 We still do not know whether it is related to the form of insurance itself, or more likely this is a marker for poor socioeconomic position and correlate factors such as food insecurity. As we stipulated at the outset, health reflects the interaction of individuals with every facet of society, and to tackle this would require a commitment to the study and design of interventions to mitigate the influence of socioeconomic position on survival.

**POSTTRANSPLANT SURVIVAL IS DIFFERENT IN THE US VERSUS CANADA**

Another interesting finding is the timing of worsening survival among CF lung transplant recipients. Although survival for the first year is approximately the same in both countries, a steady stepwise decline is seen for patients in the United States compared with Canada. This is an area where more study is needed and probably where interventions could be attempted. There are many possible explanations for the findings. The LAS, which is used for organ allocation in the United States, is calibrated in such a way to give the highest priority to candidates who are most likely to die on the waiting list, utilizing a 1-year window. Although the system has reduced waiting list deaths, it has led to sicker patients being considered, listed, and ultimately undergoing transplant.17 Modern technology and advanced care can mitigate that influence during the first year, but sicker patients have lower long-term survival. Another possibility is the way care is organized in the United States, where not all transplant centers have an affiliated CF center and insurance may dictate access to a limited number of health systems for patients (which might not include an accredited CF center). In addition, unlike Canada, US transplant centers are not directly accredited by the Cystic Fibrosis Foundation. Therefore, issues in fragmentation of care and difficulties in coordination of care could be leading to these differences in survival. Finally, socioeconomic differences may be playing a role here as well.
Transplant is a big event and transplant teams make great efforts to ensure there is adequate psychosocial support for the transplant candidates. This is also true for patients and their families. Although these efforts lead to adequate support early after transplant, it might not be possible to sustain these efforts in the long run, leading to worse survival. These are all areas that require more careful study because our comments are speculative in nature.

CONCLUSIONS

There is no single or simple explanation for the demonstrated heterogeneity in survival. These studies 1,2 provide further information on recent efforts spearheaded by the Cystic Fibrosis Foundation, Cystic Fibrosis Canada, and other organizations worldwide to improve survival and quality of life of people living with CF. A current effort by the Cystic Fibrosis Foundation is attempting to improve referral, access to transplant, and posttransplant survival in people living with CF, via the CF Lung Transplant Consortium, which is made up of 15 lung transplant programs in the United States and Canada. We hope that future studies will dive deeper into all the issues raised that lead to interventions that can improve survival for people living with CF both in the United States and Canada, as well as other countries.

Conflict of Interest Statement

The authors reported no conflicts of interest.

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