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VIEWPOINT

Assessment of long-term outcomes post living liver donation highlights the importance of scientific integrity when presenting transplant registry data

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Living donor liver transplantation has expanded in recent years, particularly in North America. As experience with this procedure has matured over the last 25 years, centers are increasingly faced with potential living donors who are more medically complex. As donors move through the evaluation process, completing the informed consent process continues to be challenged by a paucity of granular data demonstrating long-term outcomes and overall safety specifically in the otherwise "healthy" living liver donor population. Two recently published studies examined long-term outcomes post-living liver donation using Korean registry data and reported similar results, with excellent overall survival when compared to appropriately matched controls. However, the authors of these studies were presented differently, with one reporting an alarmist view based on one aspect of a suboptimal analysis approach using an inappropriate comparator group. Herein, the North American Living Liver Donor Innovation Group (NALLDIG) consortium discusses these two studies and their potential impact on living liver donation in North America, ultimately highlighting the importance of scientific integrity in data presentation and dissemination when using transplant registry data.

KEYWORDS
living donation, living donor liver transplantation

Abbreviations: NALLDIG, North American Living Liver Donor Innovation Group.

*Please see Appendix for list of members and institutions.

Summary sentence: The North American Living Liver Donor Innovation Group discusses the critical importance of accurate analysis and reporting of transplant registry-based studies; in particular, in living donation, where the potential for negative impact on donor understanding of risk and willingness to donate is high.

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With a persistent shortage of deceased organ donors leading to 25%–30% waitlist mortality, living donor liver transplantation activity has increased by more than 25% in the United States, representing >5% of adults and >15% of pediatric liver transplants performed in 2021.[1] In Canada, it represents an even larger cohort, with living donation making up almost 30% of adult and up to 80% of all pediatric liver transplantation. Central to the growth and success of a living donor program is careful evaluation of the potential donor, including medical, surgical, and psychosocial history to ensure safety of these donors. Critically important to the evaluation process is conveying the potential short and long-term impact of undergoing a surgical procedure that is not needed for their own health, but instead for the benefit of another. Estimating the risks of a procedure in an otherwise healthy individual can be challenging, especially as programs begin to consider donors with comorbidities including advanced age, mild obesity, or hypertension. Our understanding of donor risk is challenged by the infrequency of the events necessitating large data sources to estimate risk, thus making it difficult to derive a valid control population. As members of the liver transplant community, we have a responsibility to understand the inherent limitations of existing data that inform donor risk while enabling the safe expansion of living donor liver transplantation.

To create lasting collaborations to address contemporary issues related to living donor liver transplantation, the North American Living Liver Donor Innovation Group (NALLDIG) was formed in 2018. By early 2022, 31 centers across the United States and Canada representing >95% of all living donor liver transplant activity in the region voluntarily participate in NALLDIG (see Appendix for list of centers). In reviewing the latest data related to long-term outcomes following living liver donation, we have identified a pair of recently published studies using Korean registry data.[2,3] Despite observing similar excellent long-term outcomes compared with a reference group of matched patients, the discordant messaging in the title and abstracts between these two studies highlights the importance of study design when using transplant registry data, as well as the need for clear and accurate representation of results to avoid public misconception and fear of living donation surgery for donors and their families.

Recently, in the *Journal of Hepatology*, Choi and colleagues published a noteworthy study of long-term outcomes of Korean living liver donors, titled "Outcomes of living liver donors are worse than those of matched healthy controls."[2] In their analysis, which used the Korean National Health Insurance Services database for donors who donated between 2002 and 2018, the authors examined outcomes for 12,372 living liver donors which were compared to three separate control groups who were also drawn from the NHIS database. Matching was performed 10:1 based on sex and 5-year age ranges, comprising a total of 123,710 individuals which they divided into healthy population (Group I, excluding all medical comorbidities and with ALT and AST <40, SBP<140 mmHg, and fasting blood glucose <125 mg/dL), general population without comorbidities that would make them ineligible to donate (Group II), and general population with comorbidities (Group III). Although careful examination of long-term outcomes for living liver donors is essential, and the South Korean population is an excellent population in which to conduct these analyses given the relative frequency of living donor liver transplantation, the current study suffers from a serious design flaw which makes interpretation of the data very challenging, as highlighted in detail in the letter to the editor from the Toronto group.[4] Indeed, the Control Group I "heathy population" is actually *healthier* than the living liver donors given that "the proportion of individuals with Charlson Comorbidity Index ≥1, diabetes, hypertension, or depression in the living liver donor group was higher than that in the matched healthy group (Control Group I)." They then use this heavily weighted (10:1 match) heathier group to demonstrate, unsurprisingly, a subtle but statistically worse outcome in the living liver donor group, hence the title of the paper. Depression (an exclusion criteria for both Control Group I or II) and income grades I to IV (the lowest income grade 1 was more common in the donor group) were risk factors for adjusted mortality. As it would not be anticipated that liver donation would improve long-term health, it would have been far better to use a control group who was matched for comorbidities (i.e., Control Group II), rather than a group with no comorbid medical conditions. Reassuringly, the living liver donors in this study had better outcomes than Control Groups II or III, and most importantly, as noted by the authors, the overall risk of death was very low. Unfortunately, both the manuscript title, "Outcomes of living liver donors are worse than those of matched healthy controls" and the lay summary, which is intended for the public at large are highly misleading, given this lack of a matched control group. This leads to confusion and uncertainty not only for those within the medical community but also for prior donors as well as for future potential living donors and their recipients. One may wonder whether these choices were made to drive the sensationalism of the media on this topic particularly in some European countries where practice of LDLT is no longer pursued for a variety of reasons including overall skepticism that the procedure is truly safe for living donors.

This confusion is further extended due to conflicting results reported in an analysis published in *Annals of Surgery* in 2021 of a similar Korean study cohort from patients who donated between 2000–2015, with a 3:1 matching based on sex and 5-year age range, selected from the whole population (Control 1) as well as second group (Control 2) who had undergone health examination and did not have any medical contraindications to donation or laboratory abnormalities (creatinine, ALT, AST, GGT >2 times the upper limits of normal range).[3] These authors observed a similar low incidence of death in prior living liver donors, which was lower than the general population (Control 1) but higher than the population without contraindication to organ donation (Control 2). In contrast to the article published by Choi et al., this manuscript is titled "Long-term Survival of 10,116 Korean Live Liver Donors" and concludes that "although mortality of donors was lower than the general population (Control 1), our findings revealed that live liver donors have a higher long-term mortality risk than healthy controls (Control 2)." By taking this approach, these authors have accurately reflected their study outcomes without taking the

further step to create unnecessary controversy surrounding living liver donation. Instead, they have highlighted areas of potential further study, which will enable our group and others to appropriately design prospective studies aimed at understanding and optimizing long-term outcomes post-donation. Even within the context of appropriate study design, it is important to note that analysis of observational registry data can lead to errors related to causal inference, the concept that a specific exposure results in a causal effect on an outcome being analyzed.[5] Studies using observational data can only compare the risk of the outcome in those who were exposed to the risk of the outcome in the unexposed population. In the context of the studies compared in this Viewpoint, the survival of the "healthy" group does not represent the counterfactual outcome of the living liver group had they not proceeded with donation. These studies rely on the assumption that all unaccounted for variables that can impact outcome are randomly dispersed between the control group and the donor group. This is clearly an untenable assumption since there is clear selection of the donor for those very same variables that affect outcomes.

The use of living liver donation continues to provide a safe opportunity to access life-saving liver transplantation for waiting recipients, with excellent short and long-term outcomes. The practice of living donor liver transplantation has matured and is on the rise both in Western countries and worldwide.[6] Several studies have shown improved post-transplant survival with living donor compared to waiting for a deceased donor.[7-12] Moreover, studies examining outcomes of living liver donors in the United States have shown excellent results with low rates of Clavien-Dindo grade III or higher complications, excellent long-term quality of life, and very low mortality that is comparable with living kidney donors.[10,13-15] Due to the rising utilization of living liver donation in the West, we wholeheartedly agree that ongoing efforts to monitor and optimize long-term donor outcomes are paramount. However, the study by Choi et al. does not provide an accurate assessment of the long-term risks attributable to donation due to the lack of an appropriately matched control group. This lack of an appropriate comparator group can over inflate the risks to the donor and in fact may make it almost impossible to truly quantify the attributable risk. We recognize that compared with the parallel study by Hong et al., it may not actually be feasible to extrapolate long-term outcomes from a relatively homogeneous population of Korean living liver donors to potential donors in North America, where centers are actually more conservative in their choices of donors than those in South Korea.[6] Even accounting for differences in practice patterns, the living liver donor population between the United States and Korea are substantially different, with US donors more often being >55 years at donation (10% in the United States vs. <1% in Korea), less often of male (49% in the United States vs. 65% in Korea), and higher BMI (43% of the US donors with BMI >25 kg/m^2 vs. only 21.8% of Korean donors).[2,13] Thus, moving forward, ongoing efforts from consortiums such as NALLDIG, and other multicenter national or international registries, will be paramount to determine appropriate risk stratification algorithms for potential living liver donors in the West.

Comparison of these two studies emphasizes several key principles of academic publishing. Journal editorial boards bear the responsibility of arranging high-quality, expert peer review. The dramatic increase in the volume of manuscripts submissions during COVID-19 pandemic has strained many editorial board members and reviewers, likely resulting in publication of studies of variable rigor.[16] In parallel, careful assessment of statistical techniques and interpretation of analyses has become an integral part of the review process. Many journals now employ full-time statistical editors, which has enabled identification of serious flaws in experimental design including insufficient study power, missing data, or inappropriate use of statistical tests or models.[17] Editors must also critically assess the power of a provocative manuscript title, as initially it may grab the reader's attention and can bias the reader's interpretation and impression. Journals also must be willing to publish studies even when results are disappointing and/or controversial. The transplant community should continue to carefully assess and respond to any work that may dampen enthusiasm for living donation or living donor liver transplantation.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

Involved in the conception or design of the work: All contributing authors. Literature screen and review: All contributing authors. Analysis and interpretation of data: All contributing authors. Drafted the article: All contributing authors. Critically revised the article: All contributing authors. Finally approved the version to be published: All contributing authors.

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APPENDIX

The North American Living Liver Donation Innovation Group (NALLDIG) involves the voluntary participation of the following centers and investigators: Baylor-Dallas (GTesta, AGupta, SLee); Cleveland Clinic (KHashimoto, DKwon); Columbia University (JEmond, AGriesemer, AFox, AKaplan); Cornell University (BSamstein, KHalazun, RBrown); Indiana University (AKubal); Intermountain Healthcare/Primary Children's Hospital (RGilroy, MRodriguez- Davalos); Johns Hopkins (EKing); Mayo Clinic (JHeimbach, T. Taner, KWatt); Mount Sinai School of Medicine (SFlorman, TSchiano); Northwestern University (JCaicedo, ZDietch, DGanger); Stanford University (M. Melcher, VKirchner); University of Alberta (BAnderson, JShapiro); University of California-San Francisco (JRoberts); University of Chicago (APillai, D. DiSabato); University of Colorado (E. Pomfret, W. Jackson); University of Maryland (DMaluf); University of Massachusetts (P.N. Martins); University of Michigan (CSonnenday); University of Minnesota (SChinnakotla); University of Pennsylvania/Children's Hospital of Philadelphia (KOlthoff, TBittermann, PAbt); University of Pittsburgh (AHumar, SGanesh); University of Rochester (RHernandez-Alejandro, KTomiyama, MLevstik); University of Southern California/Children's Hospital-Los Angeles (JEmamaullee, NKaur, H. Han, YGenyk); University of Texas-San Antonio (TKlair, SYamaguchi); University of Utah (TBaker, RKim), University of Virginia (NGoldaracena); University of Washington (KBambha, SBiggins, MSturdevant); University of Wisconsin (JGaronzik-Wang, DAl-Adra); Vanderbilt University (AShingina, M. Montenovo, SAlexopoulos); and Yale University (DMulligan, SEmre, ALiapakis, SRubman, RBatra).