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Perspective

Current status of liver transplantation in North America

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ABSTRACT

Liver transplantation is continuing to grow and evolve in North America. Changes in organ availability, recipient selection, indications and progressive approaches to oncologic treatment have occurred in the last five years. Despite increased activity in deceased and living donation in North America, there continues to be a high mortality on the waitlist as the recipient indications have changed over time which has led to new approaches to help patients with end-stage liver disease.

1. Increasing deceased donors

Over the last decade, there has been an overall growth in liver transplantation (LT) activity in North America (Fig. 1A and B) [1,2]. Although, pediatric deceased donor LT outcomes have improved over time, outcomes of adult deceased donor LT are challenged by older and sicker waitlist candidates and limited availability of high-quality organs [3–5]. The landscape of the LT has been shaped by several key factors. On one hand, the opioid crisis contributed significantly to the rise in the availability of the deceased donors [6]. On the other hand, the overall aging of the population, obesity epidemic, acceptance of HCV-positive organs and utilization of livers from donors following circulatory death (DCD) resulted in an increased number of extended criteria donors (ECD) [3,7–9].

The improved performance of the organ procurement organizations has been recognized, but recent data demonstrated that the tragic opioid epidemic is truly the driving force behind increased rates of deceased donation. In stark contrast to the decrease in the number of non-drug related donor deaths by 52%, there was 102% increase in the number of drug-related deaths over the past decade in the United States (US) [6]. The same phenomena is implicated in the significant increase of the deceased donors between the age of 18–34 years old and rise in donor deaths secondary to anoxic brain injury [3]. Another aspect of opioid crisis is the upsurge of the increased risk donors (IRDs), i.e. donors that are more likely to have HBV, HCV and HIV infection as established by the Centers for Disease Control and Prevention (CDC). The definition of IRDs evolved over time, but the proportion of IRDs based on current definition increased from 8.9% to 26.3% between 2010 and 2017 [10]. While it is important to convey the risks of IRD's, the use of nucleic acid testing has reduced the risks to recipients. The risk of undetected infection was < 1/1 000 000 for HIV after 14 days, for HBV after 35 days, and for HCV after 7 days from the time of most recent potential exposure to the day of a negative NAT. The period during which reported donor risk behaviors result in an "increased risk" designation can be safely shortened [11]. Increased risk donor organs are an important access for life saving transplants as a recent paper using machine learning showed the majority of patients are predicted to have higher 5-year survival accepting an IRD organ offer compared with waiting for a non-IRD organ [12].

Aging of the population, rise in the obesity with associated metabolic syndrome and non-alcoholic steatohepatitis present a challenging problem in donor selection and donor/recipient matching [13]. Although, the successful LT from older donors (≥60 years old) and donors with high percent of macrosteatosis (> 30%) have been reported, the transplantation of the grafts from these donors is associated with the increased risk of delayed graft function and primary non-function, necessitating a careful selection of the potential recipients with lower medical acuity for these livers [13]. Consequently, despite the early increase in utilization of livers from older donors between 1990 and 2009, the utilization of livers from older donors has leveled off over the past decade [14].

The introduction of direct acting antiviral (DAA) therapy, with sustained virological response rates nearing 100%, has changed the utilization patterns of livers from HCV-positive donors in the U.S [15]. The efficacy and low-side effect profile of DAAs encouraged many centers to accept livers from HCV-viremic donors (HCV-RNA-positive) and HCV Ab-positive donors for HCV-negative recipients [16]. In post-DAA era, early graft and patient outcomes appear to be similar between recipients receiving HCV-positive and HCV-negative graft [8].

The introduction of the HIV Organ Policy Equity (HOPE) Act in 2013 lifted the banned on utilization of HIV-positive organs in LT. To increase the access to the high quality organs, the HOPE ACT permits the transplantation of organs (under the research protocols) from HIV-positive donors into the HIV-positive recipients in the U.S [10]. As of right now, close to fifty HOPE LTs alone and HOPE simultaneous liver-kidneys have been performed [1].

North America witnessed a modest increase in the utilization rate of DCD livers with current rate nearing 6%; however, the inferior patient and graft survival following DCD LT contribute to the persistent reluctance by the centers to expand DCD acceptance criteria [17]. Not surprising the highest liver discard rates remain among DCD livers (~30%) followed by livers from older donors [3]. On the contrary, the discard rate of HCV-positive livers has significant dropped with the introduction of the DAA therapy [3,8].

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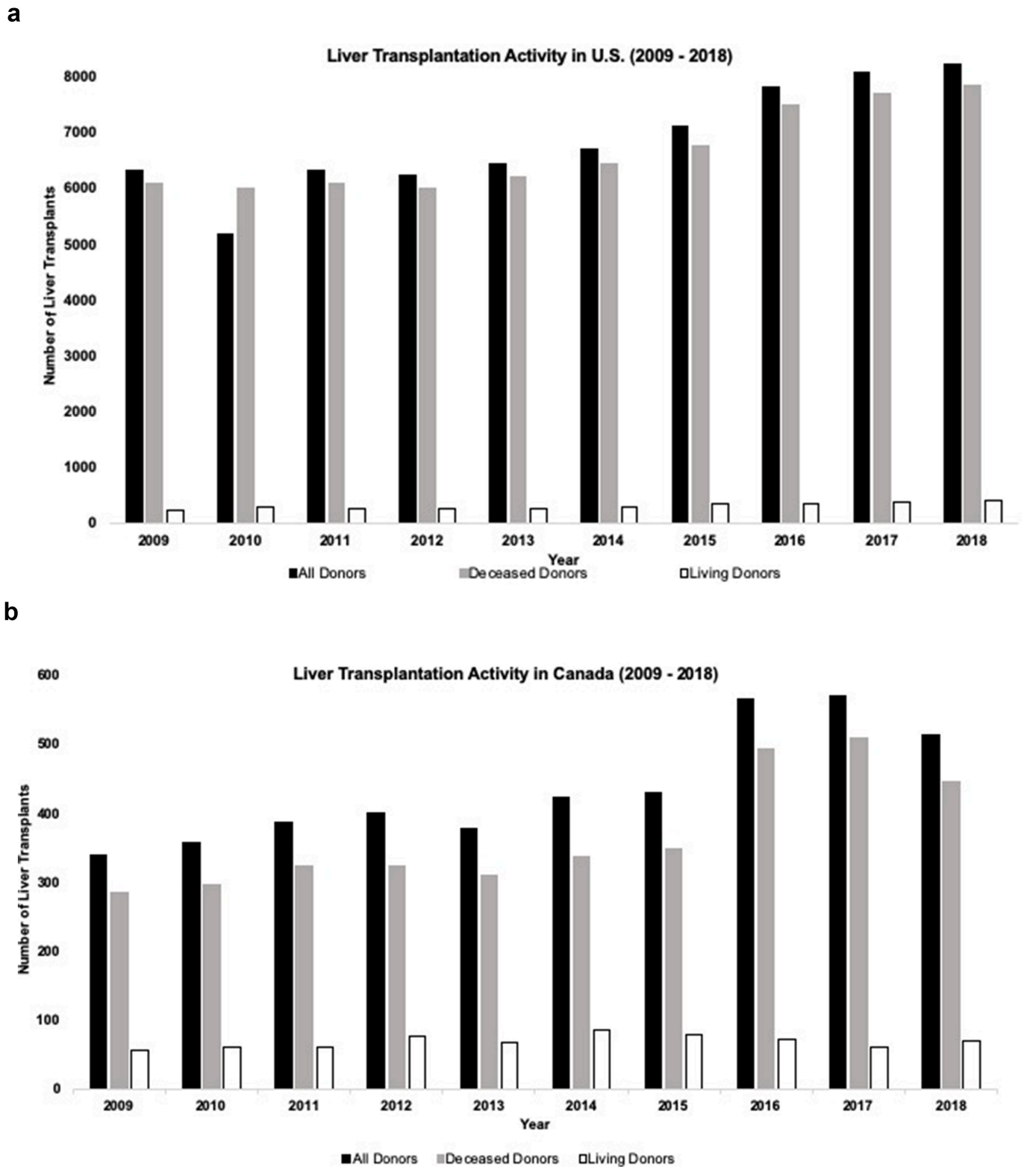

Fig. 1. A) Liver transplant activity in the United States. **B)** Liver transplant activity in Canada.

The opioid tragedy has attracted a significant attention from the public as well as the government, which will hopefully address the epidemic of the senseless loss of life. The organ transplantation community in the North America will continue to face the organ shortage and increasing number of marginal donors. In order to expand the potential donor pool, North American countries will need to adopt broader utilization of the older donors as has been the practice in Europe where over 50% of deceased donor livers come from the donors ≥ 50 years old compared to 35% in U.S.[14] The introduction of new methods in organ preservation and resuscitation of marginal organs as well as development of the novel organ replacement therapies will be key in addressing the growing need for treatment of patients with end-stage liver disease.

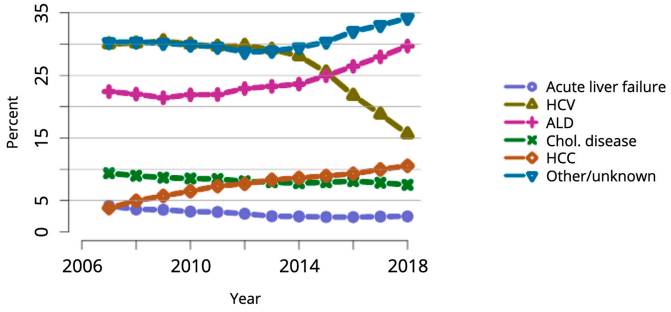

Fig. 2. Changing indications for liver transplantation over time.

1.1. Changing recipient indications

There has been a continued growth in the United States in waitlist registrants and transplants performed. There has been a significant decrease in registrations and transplants for hepatitis C (HCV)-related indications and increases in alcoholic liver disease and NASH (Fig. 2) [3]. It is suspected that alcoholic liver disease will surpass HCV in the coming year as an indication for LT. This is despite reports of the majority of alcoholic liver disease patients in North America do not get referred for LT that are seen in the community or rural areas due to lack of awareness and knowledge about transplant as a curative option [18]. Population studies suggest that rising alcohol-related liver disease death rates and was most recently found to have the highest risk of death among gastrointestinal diseases (6.8 per 10 000) [19].

A new and rising indication for LT has been acute alcoholic hepatitis (AAH). Indications for LT in this disease state are very specific [20]. A recent consensus statement has defined many of the parameters to make this possible. In the setting of AAH patients must have the following [1]: AAH patients presenting for the first time with decompensated liver disease that don't respond to medical therapy without severe medical or psychiatric comorbidities [2]; no fixed period of abstinence prior to transplantation and [3] assessment with a multidisciplinary psychosocial team. Supporting factors included lack of repeated unsuccessful attempts at addiction rehabilitation, no other substance use/dependency, acceptance of diagnosis/insight with a commitment to sobriety, and formalized agreement to adhere to total alcohol absentce. LT should be avoided in AH patients who are likely to spontaneously recover. Short-term and longterm survival comparable to other indications for LT must be achieved. Treatment of alcohol-use disorders should be incorporated into pre- and post-LT care [21]. Numerous studies have shown excellent results in this life saving indication when appropriately indicated with equivalent survival to other indications as well as similar recividism rates [20,22].

The incidence of nonalcoholic fatty liver disease (NAFLD) is continuing to rise in the Western world and especially North America, and it is estimated that this trend will continue for another 10–15 years. NAFLD is the hepatic manifestation of metabolic syndrome. As obesity, diabetes, and other lifestyle-related diseases continue to rise, the spectrum of NAFLD, e.g., nonalcoholic steatohepatitis, liver fibrosis, liver cirrhosis, liver-related morbidity, and mortality, will increase in parallel. Its widespread prevalence and associated economic burden have drawn significant attention and research in the area. Unfortunately, no targeted treatment exists to treat this condition, and therefore, emphasis has been on its prevention [23,24]. Its incidence and indication LT is rising at a similar rate to alcoholic liver disease. In many centers, NASH accounts for 30% of the liver transplant indications. These patient represent a unique sub-population in which cardiac comorbidities and complications of diabetes are prevalent and challenge the transplant physician and surgeon.

With the increase in deceased donors currently, the deceased donor transplant rate is at all time high of 51.4 per 100 waitlist-years and a downward trend in waitlist mortality across all groups including gender, race, diagnosis and urgency. In 2017, patients were also older as 22.9% were older than 65, almost double from ten years prior. The interesting trend is that waitlist mortality does differ by geography and does not reflect organ availability suggesting center behavior, referral and waitlist practices and patient management are varied around the country [3].

1.2. Increasing living donor liver transplantaiton

Living donor liver transplantation (LDLT) has emerged with the objective of mitigating deceased organ shortages and therefore, reduce mortality on LT waiting lists [25,26]. Although this technique was first described in the Western world, it has had a much greater impact in Asian countries where deceased donation rates are very low [27,28]. One of the main reasons why its growth has been quite limited in North America is probably related to a higher availability of cadaveric grafts compared to Asian countries and unfortunate events involving LDLT outcomes [29].

However, the high waiting list mortality in some regions, the current poor access to deceased donor grafts for patients with low MELD scores and the expanding indications for LT have pushed the North American community to reconsider LDLT as a valid and very useful alternative [30]. Such has been the case that in the United States LDLT annual number of adult-to-adult has shown a steady increase since 2013 [30–32]. For example, driven by organ shortage the University of Pittsburgh has dramatically increased their LT annual numbers at the expenses of LDLT, constituting now the main source of liver grafts at their institution [32]. On the other hand, in Canada, led by the University of Toronto's experience the number of LDLT for both adult and pediatric recipients have remained quite stable [33,34]. Moreover, this program's annual volume and experience has allowed the transplant community in North America to clarify and embark in the use of this technique to provide LDLT, with great results, for patients that wouldn't otherwise attract a deceased donor liver grafts (i.e. HCC with extended criteria, unresectable colorectal liver metastasis) [35].

1.3. Expanding transplant oncology

Following the oncologic benefits seen in hepatocellular carcinoma (HCC), there has been an expansion of cancer indications for LT in North America. Policies regarding cancer exceptions are similar between US and Canada. These indications vary geographically resulting from differences in organ availability and allocation policies. Nevertheless, through stringent selection criteria, multimodality treatment sequencing strategies, surgical innovations, and multidisciplinary management, liver transplantation has been recognized to offer many patients previously deemed unresectable longevity and even a chance for cure. Though this field is currently limited by the mismatch between the demand and availability of organs and reserved for patients deemed nonresectable, there is future potential for LT to enter the realm of

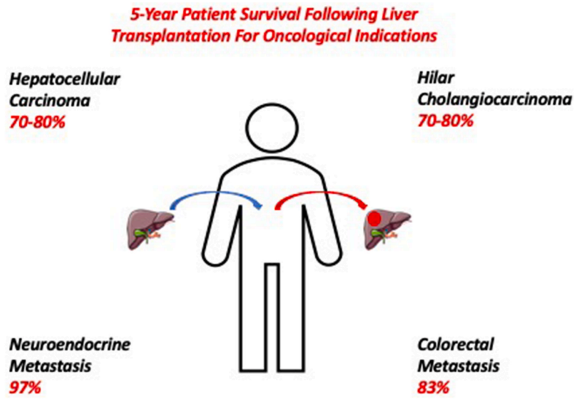

Fig. 3. Schematic of 5 year survival of different transplant oncology indications.

surgical oncology for earlier-stage disease. Consequently, LT may become an option for patients alongside liver resection, potentially with improved oncologic outcomes (Fig. 3).

Through rigorous neoadjuvant chemotherapy protocols, including high-dose intravenous neoadjuvant 5-FU based chemotherapy and external beam radiotherapy followed by iridium brachytherapy, and careful patient selection, outcomes for patients with hilar cholangiocarcinoma have improved from historic 5-year survival rates of 30–40% with resection to 70–80% with LT [36,37]. Recently, there has been a reappraisal of LT for intrahepatic cholangiocarcinoma – traditionally considered a contraindication for LT. This has stemmed not only from the success in hilar cholangiocarcinoma, but also with the recognition that some patients transplanted for other indications and who were found to have incidental intrahepatic cholangiocarcinoma on explant pathology could realize excellent long-term outcome [38–40]. Clinical trials are currently ongoing to define optimal selection criteria of these patients and their oncologic outcomes following LT in very early intrahepatic cholangiocarcinoma in cirrhotic patients. Further improvements in outcomes will likely come from the incorporation of circulating tumor DNA analysis in the selection process, which can identify aggressive tumor biology that would not benefit from surgical interventions [41]. Moreover, genomic analyses can identify actionable targets for therapeutic interventions, such as IDH-1 and 2, and thereby help tailor neoadjuvant and adjuvant therapies [42,43].

Favorable outcomes following LT for secondary malignancies such as neuroendocrine tumors metastatic to the liver and colorectal liver metastases have developed from a better understanding of tumor biology and improved chemotherapeutic regimens. In neuroendocrine liver metastases, 5- and 10-year survival of 97% and 89% was achieved in 42 patients using Milan criteria proposed by Mazzaferro et al. [44] In context, respective survival rates were 51% and 22% in 46 patients who did not undergo liver transplantation in the studied period (1995–2010). For patients with colorectal liver metastases, efforts have been spearheaded by the Norwegian group through the SECA-I and subsequent SECA-II trials where liver transplantation resulted in a 5-year overall survival of 83% at a median follow-up of 36 months was achieved [45,46]. Though the disease-free survival was relatively low, at 35%, 73% of patients in the SECA-II trial were alive 4 years following relapse. These trials have not only identified prognostic factors that will form the basis for future trials and organ allocation policies for patient selection but also provided an option to maximize survival in patients who would otherwise be candidates for nothing more than palliative chemotherapy.

Elucidating the role of downstaging, immunosuppression, biomarkers and innovative surgical approaches (including RAPID) [47] will be critical for refinement and expansion of current criteria. Nonetheless, the expansion of cancer indications should be explored with caution to ensure a careful balance between maximizing the equity and utility of available organs and oncologic outcomes.

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Goldaracena – writing.
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Varvara A. Kirchner: Writing - original draft. **Nicolas Goldaracena:** Writing - original draft. **Gonzalo Sapisochin:** Writing - original draft. **Roberto Hernandez Alejandro:** Writing - original draft. **Shimul A. Shah:** Writing - original draft.

Declaration of competing interest

None.

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