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Quality of life, Risk Assessment, and Safety Research in Liver Transplantation: New Frontiers in Health Services and Outcomes Research

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Abstract

Purpose of review—In this review, we briefly summarize three fruitful, emerging areas in liver transplantation research: quality of life; risk assessment; and patient safety. Our goal is to highlight recent findings in these areas, with a call for increased integration of social scientists and transplant clinicians to address how best to shape policy and improve outcomes.

Recent findings—After liver transplantation, recipients generally experience clinically significant, sustained improvement in their physical, social and emotional well-being. However, a sizeable minority of patients do experience excess morbidity that may benefit from ongoing surveillance and/or intervention. There is growing body of research that describes risks associated with liver transplantation, which can be useful aids to better inform decision making by patients, clinicians, payers, and policy makers. In contrast, there has been a relative lack of empirical data on transplant patient safety vulnerabilities, placing the field of surgery in stark contrast to other high risk industries, where such assessments inform continuous process improvement.

Summary—Health services and outcomes research has grown in importance in the liver transplantation literature, but several important questions remain unanswered that merit programmatic, interdisciplinary research.

Keywords

liver transplantation; recipients; quality of life; risk assessment; patient safety; outcomes

Over the past decade, as liver transplantation (LT) has become a more prevalent procedure in the United States, there has been growing interest in transplant health services and outcomes research related to the procedure. Health services and outcomes research is broad in scope, but provides clinicians and researchers vital information that can be used to

complement traditional clinical endpoints, such as graft and patient survival. Generally speaking, health services and outcomes research may include investigation of how patients access care, as well as the cost and the quality of that care. Identifying the most effective ways to organize, manage, finance, and deliver care would seem to be key elements to optimizing clinical outcomes. In this review, we briefly summarize three fruitful, emerging areas in liver transplantation research: recipient quality of life; risk assessment; and patient safety. Our goal is to highlight recent findings in these areas, with a call for increased integration of social scientists and transplant clinicians to address how best to shape policy and improve outcomes.

Recipient Quality of Life

Quality of life (QOL) is defined by the Centers for Disease Control as “an overall sense of well-being, including aspects of happiness and satisfaction with life as a whole.” It is a broad definition that includes more specific, measurable concepts such as mental well-being, physical functioning, and overall health status.[1] With improving survival rates following LT, patient QOL has become an increasingly important outcome. Arguably, many symptoms and most aspects of health-related quality of life are best assessed by asking the patient directly, using a standardized measure.

A variety of instruments have been used to assess QOL in the context of LT, and the selection of standardized scales should be made with the purpose of assessment in mind.[2] In general, QOL measures can be divided into two general categories, based on their level of specificity. Generic instruments, such as the Short Form-36 (SF-36),[3] have been designed to evaluate physical, social, and mental well-being across a variety of patient populations. In contrast, targeted instruments include items that assess symptoms specific to the population or procedure of interest, such as the Liver Disease Quality of Life Questionnaire (LDQOL) which was designed to assess quality of life in patients with end-stage liver disease (ESLD). [4] More recently, Saab *et al.* have developed and validated a post liver transplant QOL instrument, designed to assess domains of QOL specific to LT recipients.[5*] While this instrument has not yet been applied in subsequent publications, it holds promise as a targeted QOL assessment in LT recipients.

QOL in LT recipients has been described in a number of studies and there is evidence that many domains of QOL show improvements that are maintained after LT. However, recipient QOL scores generally remain lower than healthy comparison populations.[6] In studies that utilized standardized assessment instruments, QOL tends to improve from the expected worsening in the immediate post-operative period. There is a general improvement in QOL across many domains 18–24 months post-LT, reaching near normal levels in longer-term survivors.[7–9]

Patient-reported physical well-being is poorest within the first year post-LT, likely related to muscle weakness, fatigability, and difficulties with daily activities, with scores typically being significantly below the general population mean.[10, 11] This poor physical functioning has been associated with external factors, such as work status and ability to participate in recreation and past-times.[12, 13] Based on Organ Procurement and Transplantation Network (OPTN) data, unemployment after LT is highly prevalent, with one study reporting a 75.6% unemployment rate within 24 months.[14**]

Studies investigating the clinical and sociodemographic correlates of QOL in the context of ESLD and liver transplantation have not been consistent. Not surprisingly, those patients with Childs Class C cirrhosis have worse QOL when compared with patients with less severe ESLD.[15, 16] Other measures of liver disease severity, though, such as higher Model for End-stage Liver Disease (MELD) scores and need for intensive care unit during

hospitalization, have not been reliably associated with worse pre-LT QOL.[15, 17] Although further research in this area is needed, Volk *et al.* recently found no impact of the donor risk index (DRI) on recipient QOL.[18*]

Psychiatric comorbidity is not uncommon in the post-LT population.[19] Despite overall improvement in post-LT QOL compared with pre-LT, more than half of patients experience at least one episode of significant anxiety or depression within the first two years post-LT. [20] Symptoms of posttraumatic stress disorder (PTSD) are also prevalent in LT recipients, with 23% of post-LT patients displaying associated symptoms in one study.[21] Cognitive dysfunction, negative affect, and diminished social networks are common pre-LT psychosocial and psychiatric deficits that may be sustained after transplant.[22, 23] DiMartini and colleagues recently demonstrated that recipients with increasing or consistently high levels of depression were more than twice as likely to die (all cause) compared to a low depression group, even after controlling for relevant medical factors. [24**] One report suggested that LT recipients who experience no psychosocial benefit 6 months post-LT, have psychosocial decline over the subsequent 18 months.[8]

After LT, recipients generally experience clinically significant, sustained improvement in their physical, social and emotional well-being. However, a sizeable minority of patients do experience excess morbidity. Although additional longitudinal data are necessary to produce a robust predictive model, there appears to be QOL benefit conferred by male sex,[25] being married,[26] having higher levels of psychosocial support,[27] attaining more education,[28] and having private insurance coverage.[29] In addition to comprehensive, long-term observational trials of liver recipients, there is an increasing need to develop behavioral intervention trials to improve QOL for recipients at risk for poor QOL. In fact, data from two early randomized controlled trials in LT recipients suggest that this may be possible. For example, QOL improved in response to psycho-educational counseling in LT patients in one trial,[30] and in response to a post-LT exercise and diet program, in another.[31]

Risk Assessment

The Scientific Registry of Transplant Recipients (SRTR) provides reporting of risk-adjusted outcomes of all transplant recipients in the US.[32] Recently, the Centers for Medicare and Medicaid Services (CMS) issued Conditions of Participation requiring that center-specific survival meet or exceed expected risk-adjusted outcomes.[33] Increasing scrutiny of transplant center performance and the pivotal role of risk adjustment necessitates a broader understanding of the evolving donor and recipient risks in LT. In addition to regulatory oversight, the policy fosters transparency in risk communication to better inform decision making by patients, clinicians, payers, and policy makers.

The severe deceased donor organ shortage highlights the need for pre-transplant risk assessment to ensure optimal graft and patient survival rates.[34] The broader application of LT to recipients of advanced age is characterized by substantial risks of co-morbid conditions which can adversely impact outcome.[35] Moreover, adoption of MELD-based liver allocation has led to transplantation of the “sickest first,” rendering established recipient risk factors, such as ICU hospitalization and mechanical support more common. [36*, 37**]

Hepatocellular carcinoma (HCC) presents another illustrative example of the need for risk adjustment. Candidates with HCC are at increased risk of tumor progression and waitlist dropout. [38] Once transplanted tumor relapse becomes an important mechanism of post-transplant mortality. However, locoregional therapies that inhibit tumor progression [39] might advantage HCC patients under current liver allocation policy, particularly in non-competitive donor service areas.[40, 41] More granular data regarding pathologic tumor

stage and rate of tumor growth may be necessary to facilitate more accurate risk assessment. [42] Not surprisingly, donor factors may also improve prediction of recipient outcomes of LT. Donation after cardiac death (DCD), an important component of a liver-specific donor risk index (DRI), has garnered much attention recently as an option to safely expand the liver donor pool.[43] However, DCD recipients are at greater hazard of mortality,[36*] graft failure,[37**, 44] and biliary complications.[44, 45] The risks of a DCD liver must be tempered against the mortality risk awaiting a donation after brain death (DBD) liver. We have demonstrated that DCD livers provide a survival benefit to patients with a MELD score above 20.[46] In addition, HCC patients without MELD exception points also derived a survival benefit. Together, these data demonstrate conditions in which the mortality risks associated with liver disease or HCC progression exceed the risks of DCD LT.

Living donor liver transplantation (LDLT) is a safe and efficacious alternative to deceased donor LT.[47*] Ethical and logistical challenges including risks to both the donor and recipient have limited the wider application of LDLT. The findings of the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) cohort study, while consistent with the national experience, demonstrate opportunities for improvement in risk adjustment.[48**] A comparison of data collected in the A2ALL study to data submitted to OPTN/SRTR showed that of 50 data points reported on recipients, 28 (56%) were either missing from OPTN/SRTR or discrepant between the two sources for more than 10% (and up to 78%) patients. [49] Augmentation of risk adjustment by using sample data derived from multi-institution cohorts might be an attractive strategy to improve current models.

Patient Safety

Medical errors have received considerable attention since the release of the Institute of Medicine Report[50**] “To Err Is Human: Building a Safer Health System,” in which the authors estimated that each year 44,000 to 98,000 deaths were due to medical errors. This estimate is more than the annual number of deaths by motor vehicle accidents or breast cancer.[50, 51] Notably, these estimates fail to include the frequent “near misses,” that either do not reach the patient or, fortuitously, fail to cause harm. Event data suffer from significant underreporting.[52] Data suggest that the medical errors collected through a hospital incident reporting system capture only 10% of those collected by proactive reporting systems.[53*]

Furthermore, clinicians continue to underestimate safety vulnerabilities in medicine,[54, 55] although press coverage,[56] and lay publications of medical errors and preventable complications have raised public awareness. Clinicians, in particular, traditionally equate medical errors with human shortcomings and often fail to understand the importance of redesigning the systems and processes of care to anticipate and mitigate potential errors. Moreover, clinicians tend to dismiss medical errors and focus on advancements of modern medicine.[57, 58] However, with the implementation of the CMS denial of reimbursement for “never events,” the introduction of the National Surgery Quality Improvement Program and increased public reporting of center-specific quality parameters (e.g. surgical site infections),[59, 60*] clinicians have become considerably more aware of the issues related medical errors.[61]

Recipient surgical care in LT is usually highly complex given the severity of end-stage liver disease. DDLT surgery often involves extensive resources and complex coordination of care. Accordingly, DDLT is assigned one of the highest numbers of Relative Value Units (RVUs) in the Medicare Fee Schedule compared to other complex surgical procedures. Although liver transplantation has evolved over the past several decades, it still consists of a lengthy surgical procedure, significant blood product transfusions, varying periods of

hemodynamic instability, and is associated with a higher number of intra-operative deaths than almost any other surgical procedure. The surgery also includes surgical, anesthesia, and nursing teams, as well as perfusionists and other specialized teams (e.g., coagulation, blood bank). Consequently, liver transplantation surgery and post LT care routinely test the full capacities of the systems and processes of surgical care, exposing safety vulnerabilities that otherwise might remain masked until an adverse event occurs.[62–65*]

Costs for injuries related to medical errors in the United States were estimated at \$19.5 billion in 2008 with an average cost of \$13,000 per error.[66**] These costs are likely to be underestimated, as they do not include costs for medical errors that did not lead to patient injury (e.g. wrong medication prepared, but not given to the patient).[67] These conservative estimates nonetheless account for a significant portion of healthcare expenditures. In 2010, an actuarial report estimated that there were 5,147 medical errors for transplant patients costing \$55,654 per error and amounting to \$286 million per year. Hence, the costs for each error is significantly higher for transplantation than for care of lower complexity, for which the costs per error are ten times less.[66**]

Despite the occurrence of high profile safety events in transplantation, such as errors in ABO compatibility between donor and recipient,[68] transmission of communicable diseases,[69] an increasing incidence of primary non-function of organs resulting in the need for re-transplantation, and occasionally death,[70, 71] there are numerous accounts of unpublicized and unpublished near misses. However, there has been limited research examining the range of patient safety vulnerabilities that occur in transplantation. While safety events such as ABO-incompatible organ transplantation,[72] infection,[73] organ rejection, and complications after surgery[74] have been reported, a systematic review of the literature on patient safety in transplantation found that the majority of articles are based on expert opinions, not data.[75*] The relative lack of empirical patient safety data for the multidisciplinary and complex field of surgery stands in stark contrast to other high risk industries such as air and land transportation, where safety vulnerability assessments are routinely performed, analyzed, and lead to continuous process improvement.[76]

To improve patient safety in liver transplantation, vigorous and comprehensive studies are required to understand vulnerabilities in related systems and processes. Once these vulnerabilities are identified, improvements in systems and processes need to be implemented, which may require a significant culture shift at the clinical level. We believe that such streamlining holds promise to maximize patient safety, as well as realize cost-savings in transplantation.

Conclusions and Future Directions

In this brief review, we highlighted three areas in which the relatively new frontier of health services and outcomes research can influence the conduct and evaluation of LT. Recipient quality of life, risk adjustment, and patient safety are areas that have grown in importance in the published literature, but several important questions remain unanswered in these areas that merit programmatic, interdisciplinary research.

We believe that there will be significant growth in the health services and outcomes research in liver transplantation. To achieve this growth most effectively, the field will see the growth of cooperative research groups, including clinicians (who help formulate the particular need), health services and outcomes researchers (who frame the need for information in the context of the potential impact on outcomes), and investigators with specific knowledge and expertise in state-of-the-art research methodologies (who formulate the experimental design/approach necessary to assess/address the substance of the information/data). We have

formed just this type of collaborative at our institution (Northwestern University Transplant Outcomes Research Collaborative, www.NUTORC.org; see Figure 1), with the premise that the interdependence and collaboration of seemingly disparate disciplines will provide fertile ground for ongoing innovation in transplantation outcomes research.

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Key points

- Liver recipients generally experience sustained improvement in their physical, social and emotional well-being; however, a significant minority of patients do experience excess morbidity and should be targeted for additional supportive care and intervention.
- Initiatives aimed at quality improvement and increasing regulatory oversight in liver transplantation necessitate a comprehensive risk assessment capable of better informing decision-making by patients, clinicians, payers and policy makers.
- The relative lack of empirical patient safety data in liver transplantation stands in stark contrast to other high risk industries, where routine vulnerability assessments are performed, lead to continuous process improvement
- We believe that cooperative research groups, that incorporate clinicians, health services and outcomes researchers, and investigators with specific knowledge and expertise in state-of-the-art research methodologies, are necessary to optimize the full spectrum of liver transplantation outcomes.

Figure 1. Depiction of the multi-department, inter-school, transdisciplinary Northwestern University Transplant Outcomes Research Collaborative (NUTORC). [NMH = Northwestern Memorial Hospital]