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A Collection of Research in Transplantation Surgery: The Importance of Assessing Outcomes in a Field Dependent on the Availability of Limited Resources

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A COLLECTION OF RESEARCH IN TRANSPLANTATION SURGERY: THE IMPORTANCE OF ASSESSING OUTCOMES IN A FIELD DEPENDENT ON THE AVAILABILTY OF LIMITED RESOURCES

by

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Research, whether one likes it or not, is an integral part of being a physician. This stems from not only the need for advances in the understanding of medicine at its most basic form – the physiology, pathology, pharmacology, or technology that we utilize – the foundations for which the field was created and continues to grow, but also from the more direct need of continuous critical evaluation of our practice to ensure appropriate clinical decision making produces optimal outcomes. It is the latter that I personally find to be most conducive to my goals and interests. My background is such that I found myself in the middle of my surgical residency with little to no experience in research in the manner we see it as physicians. The typical surgical resident, if he or she so chooses to step out of the clinical training period to conduct research at such programs where this is an option, most likely enters a bench laboratory under the guidance of a faculty member conducting research in the realm of the basic sciences. With my non-traditional background in healthcare administration and experience in compliance measures and quality improvement, stepping out for two years to conduct bench research without a strong need for the experience based upon my career goals was not a fitting option. I am grateful for my general surgery residency program director, Dr. Tiffany Tanner, and my surgery department chairman, Dr. David W. Mercer, for acknowledging my unique needs and allowing for funding in my two years of research for this novel opportunity to focus on transplant outcomes while completing the Medical Sciences Interdepartmental Area graduate degree program. Without their support this would not have been possible.

Similarly, I must give thanks to my research committee chairman, Dr. Shaheed Merani, for additionally advocating for this opportunity and guiding me along the way. With a passion for transplant, yet a minimal amount of surgical training, I could not have brought these projects to life without his expertise in the field and guidance over these two years. His abilities are

limitless and span the areas of not only clinical and surgical transplantation, but areas truly indicative of an academic surgeon scientist – critical appraisal, study design, statistical analysis, mentorship, and teaching in the classroom, the lab, and in the operating room – to name but a few. His accomplishments are inspiring and, honestly, intimidating – to many more than just myself – but they are the foundation for which he builds his expectations and provides encouragement for growth within his trainees. As challenging as this experience has been, without his expectations and encouragement it would not have been possible.

Additionally, I owe thanks to the remaining members of my committee, Dr. Alan Langnas and Dr. Kurt Fisher. Their guidance along the way in building these projects was necessary to make it to the end with tangible results. It truly requires a team to look at a question from multiple viewpoints and come up with a reasonable plan to find an answer. Their suggestions along the way allowed me to reach conclusions that I would not have found without them.

Finally, I will always have gratitude towards every transplant surgeon, transplant physician, trainee, staff member, patient, and family member that I have encountered since my father's transplant two decades ago – an experience which served as the spark to my passion. Collectively, these people have been responsible for allowing me to *keep a fire* – a familiar Cherokee phrase used in passing throughout my childhood. These words of encouragement are reminders to maintain that vital sources of being, to keep doing whatever it is that you need to do, and to maintain your passion which is required for forward progress. Transplant is a remarkable field, but it is one which is challenging both physically and emotionally for all involved. So, thank you to everyone who makes this challenge possible to bear by contributing to my transplant passion in a meaningful way, allowing me to keep a fire without losing sight of why we are all here.

A COLLECTION OF RESEARCH IN TRANSPLANTATION SURGERY: THE IMPORTANCE OF ASSESSING OUTCOMES IN A FIELD DEPENDENT ON THE AVAILABILTY OF LIMITED RESOURCES

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University of Nebraska, 2021

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This thesis is a collection of three independent projects related to transplantation surgery. In summary, project I involves an assessment of long-term quality of life outcomes of intestinal transplantation in pediatric patients who are now in adulthood, with comparison to other solid organ transplant patients. Health related quality of life surveys were completed in 14 adult patients who underwent intestine, liver, or kidney transplants as children. Project II evaluates pre-surgical characteristics of patients undergoing liver transplant to assess predictive factors for the need of venovenous bypass utilization intraoperatively by assessing trends at the University of Nebraska Medical Center in 95 patients from 2001 to 20019. Project III is an appraisal of hepatocellular carcinoma characteristics in patients who undergo locoregional therapy prior to liver transplant and assessment of the concordance of response as determined by both radiologic and pathologic evaluations involving 30 liver transplants from the period of 2016 to 2019 occurring at the University of Nebraska Medical Center for an indication including hepatocellular carcinoma. Detailed individual abstracts for each of the three projects are included in the following pages of this thesis.

Abstract Project I: Long-Term Quality of Life Outcomes in Intestinal Transplantation

Intestinal transplantation (ITx) is indicated in patients with complications from dependency on parenteral nutrition due to intestinal failure (IF). ITx has seen improved outcomes since established, though, health related quality of life (HRQOL) remains lacking in ITx, especially in long-term survivors. Prior studies show relatively preserved HRQOL compared to healthy controls in patient reporting, however, caregivers consistently report lower HRQOL scores than healthy controls. This study aims to evaluate HRQOL of adults who underwent ITx at pediatric ages utilizing validated tools and compare such data to other solid organ transplant recipients of similar age. Of 74 ITx patients meeting criteria and matched to liver and renal transplant patients, completed HRQOL surveys were obtained in 14 patients (ITx N=3, Liver N=3, Kidney N=8). There were no significant differences of demographics in survey participants. Liver patients had higher scores than both ITx and kidney patients overall and within domains of physical functioning, physical limitations, general health, social functioning and energy-fatigue ($p < 0.05$). Assessments among age at transplant (< 6 vs. > 6) showed higher scores in those transplanted younger in all domains, though without statistical significance. Of those with high medical demand, significant differences were seen in physical health components of physical limitations and pain ($P < 0.05$) but demonstrated preserved scores in mental health components without statistical differences compared to those with low medical demand. This study is limited by the small number of participants but depicts promising HRQOL measures among long-term survivors of ITx not previously assessed.

Abstract Project II: Venovenous Bypass in Liver Transplantation

Utilization of venovenous bypass (VVB) in liver transplantation (LT) varies widely among institutions and lacks defined consensus for usage criteria, however, remains an acceptable practice to assist with physiologic intraoperative challenges related to venous occlusion during LT. This study aims to assess trends of VVB use in this institution as well as evaluate for the presence of pre-operative factors predict VVB use. Utilization at this institution depicts a dramatic decrease in the number of LT cases utilizing VVB beginning in 2003 and continuing through 2019. Assessment of 95 LT recipients with VVB utilization and 95 LT recipient controls from 2001 to 2019 established pre-operative differences among model end-stage liver disease scores (23.9±1.07 vs. 19.6±0.90, P=0.002), retransplantation status (31, 32.6% vs. 8, 8.4%, P=<0.001), fulminant liver disease status (5, 17.2% vs 0, P=0.019), and known portal vein thrombosis (6, 20.7% vs. 1, 3.4%, P=0.044) between the two groups respectively. Regression analysis indicated known portal vein thrombosis to be the only predictive factor of need for VVB utilization during LT (P=0.047). When compared to controls, LT recipients with VVB utilization had significantly higher usage blood products of all types intraoperatively (PRBCs P<0.001, FFP P<0.001, Platelets P=0.033, Cryoprecipitate P=0.022) and higher mean days in ICU following transplantation (P=0.014). No difference in overall survival was seen among the two groups. These intraoperative and postoperative differences are most likely related to the degree of illness as represented by the higher MELD seen in LT recipients with VVB utilization rather than being directly related to the use of VVB itself.

Abstract Project III: Locoregional Therapy and Liver Transplantation for Hepatocellular Carcinoma

Transplantation is the only current curative treatment for Hepatocellular Carcinoma (HCC) and cirrhosis. Locoregional therapies (LRT) are used in non-surgical candidates or as bridge to transplantation. This single center retrospective study included 30 liver transplants for HCC from 2016 – 2019 at the University of Nebraska Medical Center (UNMC), 21 which had LRT. A total 67 tumors were identified, 35 of which had LRT prior to LT. Radiologic complete response (CR) was seen in 21 of the tumors (60.0%) versus non-CR in 13 (37.1%) and 1 tumor (<1%) without post-procedure imaging before the time of transplant to assess treatment response. Pathologic CR was seen in 17 of the tumors (48.6%) versus non-CR in 13 (37.1%), 1 (<1%) was not noted on the final pathology report, and 4 (11.4%) were cholangiocarcinoma, not HCC. Discordance of radiologic and pathologic assessment was seen in 7 of 30 (23.3%) patients. Survival was not different among Pathologic CR vs. non-CR, Radiologic CR vs. non-CR, nor concordant vs. discordant assessments. Of those with discordant assessments, survival was favored in Pathologic CR versus Radiologic CR (P = 0.025). Radiologic evaluation after LRT for HCC remains a standard post-procedural tool for determining tumor response and dictating further treatment, however, is known to be imperfect in determining true tumor response as seen on pathologic evaluation, as demonstrated in this retrospective study with discordance amongst radiologic versus pathologic assessment of treatment response at a rate of 23.3%.

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CHQ	Child Health Questionnaire
CR	complete response
EMR	electronic medical record
FFP	fresh frozen plasma
HCC	hepatocellular carcinoma
HRQOL	health related quality of life
ICU	intensive care unit
IF	intestinal failure
IRP	intestinal rehabilitation program
ITx	intestinal transplant
LT	liver transplant
MELD	model for end-stage liver disease
MELD-Na	model for end-stage liver disease - sodium
OPTN	Organ Procurement and Transplantation Network
Peds-QL4.0	Pediatric Quality of Life Inventory Version 4.0
PR	partial response
PRBCs	packed red blood cells
SD	stable disease
SF-36	36-Item Short Form Survey Instrument
SRTR	Scientific Registry of Transplant Recipients
UNMC	University of Nebraska Medical Center
VVB	venovenous bypass

CHAPTER 1: INTRODUCTION

The field of transplantation in today's modern era of medicine is now a well-established specialty providing a treatment modality for patients with end-organ dysfunction. It evolved from experimental techniques which were initially so dismal such that a future in the field seemed nearly impossible. This evolution to what we know as transplantation today, which occurred relatively rapidly within the realm of medicine, was possible only through dedicated research into such areas as immunology, pharmacology, or the technical aspects of the procedures themselves. These experimental surgical procedures, beginning recently enough to be measured only in decades, were fraught with complications leading to disappointment, frustration, and immense hurdles to overcome in order to make progress in the field. Kidney transplantation, beginning in the 1950s, saw its first success in the winter of 1954 with donation from an identical twin to a sibling in need.[1] However, it went through a phase known as "the black period" due to exceedingly high rates of graft failure and patient mortality before becoming what we know of it today. After its first success in 1963, liver transplantation (LT) progress was stifled by such poor outcomes early on that the procedure was temporarily halted during a self-imposed moratorium from 1963 to 1967.[2] In intestinal transplantation (ITx), a variety of early attempts were complicated by the typical challenges: rejection, sepsis, or technical complications; additionally, the desired outcome of nutritional autonomy after ITx, independence from supplemental parental or intravenous nutrition, was only first achieved in 1988 for a 41 year-old woman with short gut syndrome.[3,4] Taking only a brief look through the history of transplantation, we see that the challenges and complications traversed in just the last 60 years mimic those of the early surgeries performed centuries ago. Before the development of surgery as an art and its refinement as a science, the practice was described as – "always frightening, often fatal, and frequently infected."[5(p2)] While transplant surgeons, even the pioneers, are far from the uneducated barber-

surgeons of centuries past, the prior description remains fitting for stories told of the early years of transplantation, only decades ago.

In addition to the technical advances made since the 1950s which improved patient mortality, advances in immunosuppression through the development of novel drugs, such as 6-mercaptopurine in 1959, azathioprine in 1962, and cyclosporine in the 1980s dramatically improved graft survival and decreased mortality rates – advances made possible only through continued research.[1] The most recent data from the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) reports of 2018 indicate just how significant transplantation surgery has become. LT numbers have continued to increase both in regards to waitlist registrants and transplants performed, with 8,250 being performed in the United States in 2018, more than any year previously.[6] In 2018, data for kidney transplantation projected that in the United States alone, there are now more than 250,000 kidney transplant recipients alive with functioning grafts and there have been continued increasing trends each year for the total number of kidney transplants, well over 22,000 in 2018.[7] While numbers for ITx have decreased recently, largely due to advances in medical management, it still remains an important therapeutic option for patients with intestinal failure and complications of medical therapies, occurring 104 times in 2018 with about half of these being in a pediatric population.[3,8] These numbers demonstrate the dramatic increase seen in transplantation in just decades.

With persistence and dedication to the science and the art of the field, transplantation has become a widely accepted treatment modality for those with end organ failure. The challenges faced today are much different than those from the early years. While the procedures remain to be technically difficult and the complications of immunosuppression arise, clinical management has become well established to meet these challenges. Efforts in advancement have shifted in focus towards long-term survival, improved quality of life, and refined criteria for candidate selection and expanding the donor pool – all efforts to ensure the best use of limited resources, the largest challenge facing transplantation today. Research in the field of transplantation

continues to be an integral part of advancement, one that plays an important role in ensuring that the use of such a finite resource is not only utilized in a technically successful manner, but also allocated in a manner that maximizes the potential of such a limited supply.

While much of the surgical techniques and medical management for transplantation have been well established, the limited number of available organs and relative mismatch of availability versus need means that efforts must be made to continue research in areas that contribute to increased understanding of what factors drive outcomes. It becomes important to consider and find ways to improve outcomes other than morbidity, mortality and survival – but also quality of life. This thesis aims to depict the areas in transplant where outcomes research, while dramatically different from the bench research which spurred the field, can contribute to an increased understanding of the overall picture of transplantation in all stages. The three independent projects detailed here depict each of these stages – post transplant outcomes, intraoperative transplant techniques, and pre-transplant factors that may affect selection and survival. The first project focuses on assessment of health-related quality of life (HRQOL) in pediatric ITx patients who have reached long term survival and adulthood to assess what life looks like after such a long period of time living as a transplant recipient and undergoing that process during the formative years of childhood. While there is no lack of data on HRQOL in pediatric ITx patients, there is a relative lack of data for those that have surpassed survival marks greater than five years. The second project focuses on the intraoperative use of venovenous bypass (VVB) utilization in LT to gather an understanding of what baseline patient variables are most useful in predicting the need to utilize such a technique, which has highly variable usage from program to program and no clearly depicted guidelines. The final project looks at LT for patients with hepatocellular carcinoma (HCC) who have undergone pretransplant locoregional therapies to determine if variations in these techniques contribute to differences in outcomes.

CHAPTER 2: LONG TERM QUALITY OF LIFE OUTCOMES IN INTESTINAL TRANSPLANTATION

Literature Review: Pediatric Intestinal Transplantation Outcomes

Intestinal transplantation (ITx) is a well-established therapy for individuals who remain dependent on parenteral nutrition due to intestinal failure (IF) of a variety of causes and encounter complications of such medical therapy. In the pediatric population, the leading causes of IF requiring ITx remains short bowel syndrome, most commonly occurring secondary to necrotizing enterocolitis followed by gastroschisis, atresia, and volvulus.[1] Other leading indications include motility disorders, malabsorption, and retransplantation.[2] Current trends over the past decade show a decrease in ITx, largely due to advances in medical management in the form of intestinal rehabilitation programs (IRP).[3] Data for IF patients therapeutically managed through IRP have shown long-term survival rates ranging from 75-94% with one single-center study recently reporting a 20-year survival rate at 85%.[3–7]

Relatively poor long-term outcomes of ITx, due largely to infection and rejection, have remained largely unchanged. The leading causes of death for pediatric ITx are sepsis, graft failure, and posttransplant lymphoproliferative disorder. Established rates of overall 1-year and 5-year patient and graft survival have been reported as 74%/58% and 68%/50% respectively.[8] This, in addition to the advancement of intestinal rehabilitation programs, is a major driving force for declining trends in ITx. Though less frequent, reports of long-term outcomes to the ten year mark have shown patient survival to range from 47-53%.[9] While ITx outcomes have not been shown to match those of IRP, ITx does remain beneficial in some patients and has continued as an accepted treatment modality for IF. Though, this is largely due to complications that arise with long-term use of intravenous nutrition such as loss of adequate venous access or the development of intestinal failure associated liver disease (IFALD), which leaves IF patients without other options for therapy outside of transplantation. This also provides justification to

pursue ITx in addition to a simultaneous liver transplantation, which is the most common of all ITx graft sub-types accounting for 52%.[1,2,8] Given this significant difference between patients of IRP versus ITx groups, an inherent selection bias exists with healthier patients without complications remaining in the IRP group and those struggling with medical therapies transitioning to ITx when required.

Long-term outcomes of ITx have been investigated, however, there is even less data related to long-term outcomes with regards to HRQOL. As survival itself has improved over time for ITx, this has led to a shift of focus on not only measuring clinical outcomes, but also measuring quality of life outcomes, which have become increasingly popular in recent years with HRQOL becoming a focus in all areas of medicine. This then opens the discussion of comparing not only survival among IRP and ITx, but quality of life among IRP and ITx, as the impact of long-term parenteral nutrition is not insignificant. Though the challenge faced in gathering this data is the relatively small number of patients undergoing ITx, about half of which are pediatric age at the time of transplant, followed by the even smaller group of those ITx patients that survive to long-term timelines post-transplant.

Within transplantation, ITx recipients make up a very small group relative to other solid organ transplant recipients. Worldwide, ITx numbers from the most recent report of the Intestinal Transplant Registry remained less than three thousand from initiation of the registry in 1985 to 2013; this includes both pediatric and adult patients which have remained to be distributed equally throughout this time period, each representing roughly half of all ITx annually.[2] The small number of this particular patient population additionally contributes to the lack of significant data regarding HRQOL in long-term survivors after ITx as there are a small number of institutions performing the procedure with small patient volumes, leading to small cohorts of patients for evaluation which are then subdivided among smaller age groups that typically each

have their own validated tool for obtaining HRQOL measures, rather than one standardized tool, used for example in a cohort of all adult aged patients.

Of the data this is available, most ITx HRQOL literature captures purely pediatric or adult populations at timelines relatively near the time of transplant, not assessing patients after periods considered long-term, with more data available in purely adult populations. A recent systematic review by Ceulemans et all in 2016, summarized data available in purely adult ITx populations quite well, however these studies utilizing only adult patients means that there is exclusion of up to half of the typical patient population undergoing ITx. This review describes a total of 9 studies gathering HRQOL measures in adult patients utilizing various validated tools, with a mean time post-transplant ranging from twenty-two months to six years. Many of these studies focused comparison of scores either pre- and post-ITx or between groups of patients undergoing ITx or remaining in IRP programs. Broad conclusions generated showed improvement in HRQOL after transplant compared to pre-transplant scores, higher HRQOL scores seen after longer follow up periods – though this suggests a selection bias related to the clinical status of those reaching survival at longer periods of time rather than time being a causative variable in HRQOL scores, and improved HRQOL scores in subdomains related to energy, social functioning, and travel ability compared to IRP patients. Though, the most significant conclusion of this review was the difficulty in obtaining such data in small groups allowing for overarching analysis and the wide variability in methodology utilized in HRQOL studies.[10]

While there are studies that have reported on long-term HRQOL measures following ITx, none have included periods greater than twenty years. There are institutions performing ITx which do have survivors well into this period, UNMC being one of those institutions. This timeline involves patients receiving ITx at pediatric ages with significant survival periods such that they are now well into adulthood. Most publications available that asses the HRQOL of ITx

patients categorize a long-term survival at > 5 years. While this captures relevant data, improved survival past the 5-year mark means that there is a large cohort of patients who can provide insight into HRQOL measures at even longer timelines that have not been considered before.

Some of the earliest data attempting to evaluate HRQOL in ITx occurred at our own institution. At the University of Nebraska Medical Center (UNMC), a 2004 study of 29 patients of pediatric age who underwent ITx with a minimum survival of one year reported quality of life post-transplant from both the patient and the parent's perspective.[11] This was a follow up from a prior first attempt at examining quality of life data at this institution.[12] The initial study reported on 31 of the 32 living ITx recipients who reached a minimum of 1-year graft survival, the majority of which were pediatric at the time of transplant (27 of 31 participants); in this population, quality of life was assessed by reporting data on hospital readmission, ileostomy closure, and stools/day. The mean number of admissions following initial discharge was 2.3 and occurred in half of the patients studied. Ostomy closure occurred 90% of participants with a median time of closure at 10 months post-transplant. And average daily stools were reported to be three. While not as detailed as later HRQOL studies this initial assessment marked the beginning of assessing the impact ITx has on daily life functions.

The follow up study published in 2004 examined HRQOL in 22 UNMC pediatric patients, ages 5 through 18 years, who reached minimum graft survival of 1-year survival with an average length of follow up after transplant of 4.5 years. HRQOL data was obtained through child and parent forms of the Child Health Questionnaire (CHQ); this marked one of the first studies utilizing assessment of the individual pediatric patient utilizing validated tools rather than assessment of HRQOL measures by the parent. While parents noted decreased function in domains related to their child's general health, physical functioning, and the impact of the illness on parental time, emotions and family activities, scores obtained from the pediatric patients were similar to normal school children without statistically significant differences in any of the

domains among the two groups, suggesting that once out of the perioperative phase, these children perceive their physical, social, and psychological wellbeing to be similar to the general population.[11]

The 2011 Ngo et al examined HRQOL in 24 pediatric patients, aged 2 to 18 years old, from the University of California, Los Angeles who were at a median age of 6.0 years and median time from transplant of 2.8 years utilizing the same CHQ tool previously used by Sudan et al, as well as a newer validated tool, the Pediatric Quality of Life Inventory Version 4.0 (Peds-QL4.0) – a tool that has been validated for younger aged children who make up a typical ITx population. Again, patient responses had similar scores to normal children, while parents noted decreased function in several domains.[11,13] Specifically there were no statistically significant difference in ITx patients evaluated and healthy norms on the CHQ, however, domains unique to the PEDs-QL4.0 which did show significant lower scores in the ITx group included domains of school functioning and psychosocial health. Subcategories receiving lower scores as reported by parents of ITx patients in his group included Physical Health, Social Functioning, School Functioning and Psychosocial Health Summary.

One of the largest studies came out of the University of Pittsburgh in 2012. Abu-Elmagd et al assessed 367 adult and pediatric ITx recipients over a 16 year period and reported on HRQOL measures as well as survival and nutritional autonomy data within the group.[14] Of those, 227 had survival over 5 years, a little over half being of pediatric age at the time of transplant. The study demonstrated through use of the Quality-of-Life Inventory for adults, obtained pre- and post-transplant, that domains of HRQOL related to psychological, emotional, and social measures were largely improved following ITx, however, interestingly they were not significantly different from a comparison group of non-transplanted home parenteral nutrition patients. Areas related to depression and financial obligations were significantly worse after transplant in this group. There were however areas in which ITx patients did score better than the non-transplanted group, which

included 12 domains of anxiety, appearance, coping, sexuality, digestive symptoms, sleep, energy, optimism, impulsiveness/control, social support, and leisure activities. While this study captured data over a large group, by the end of the study only 26 participants represented the group of pediatric recipients who have since become adults. Additionally, the HRQOL scores presented were among all adults without detailing the age at which the ITx occurred, lacking the ability to fully assess the impact of pediatric transplantation on HRQOL measures once patients reach adulthood.

A more recent study conducted by Andres et al in 2014 examined HRQOL in 31 Spanish adult and pediatric patients (age 1 – 29) at median time after transplant of 4.4 years utilizing a variety of assessment tools appropriate for age.[15] Due to the broad range of ages within this group, a total of five validated HRQOL tools were utilized for each dedicated age range; however, this presents difficulties in analysis of data due to such small subgroups available for analysis within in separate scoring method, leaving much of the further analysis of variables affecting HRQOL scores dedicated only to those obtained by caregivers of patients. Similar to prior studies discussed, HRQOL scores were lower than the general population in caregivers, and while some domains were statistically different among patients compared to healthy controls, overall scores were not dramatically or significantly different; in some subgroups were even reported as higher than healthy controls. Of note, scores from this study seemed to improve with longer periods of time from transplant, however, the main limiting factor in this study was the use of multiple HRQOL assessment tools making it difficult to conduct a more powered analysis utilizing the whole group of participating patients.

Given the relatively small amount of data on this topic and the historical volume of ITx patients at UNMC available for participation this project was conducted with the go to obtain long-term measures of HRQOL in ITx patients who experienced transplant at a pediatric age, who are not into adulthood. This allows the use of one validated tool for adult HRQOL for ease

of evaluation among participants rather than multiple age-appropriate tools which may not be easily compared. Additionally, it will allow for data to be captured that depicts how these patients function in daily life after not only getting past the perioperative period, but rather progressing and developing throughout childhood and into adulthood. As UNMC is one of the top contributors of data to the Intestinal Transplant Registry, the cohort fitting this population parameter is not an insignificant amount. This provides the ability to gather HRQOL information in ITx patients with regard to timelines that have not been significantly captured in studies to date.

Research Hypothesis and Specific Aims

The research hypothesis is that pediatric ITx patients who are now in adulthood have a measurable quality of life that is lower than other solid organ transplant patients, such as liver and kidney. Additionally, measurable quality of life is expected to differ when sub-groups are compared dependent on factors such as age at transplant (early vs. late childhood), level of nutritional autonomy following transplant, and current burden of medical care.

Specific Aims:

1) Research Aim One: Evaluate health related quality of life in adults who underwent ITx during childhood and have survived a minimum of $\geq$ 5 years from transplant, as well as control groups of liver and kidney recipients of similar ages.
2) Assess relationship between health related quality of life as determined by SF-36 questionnaire and current clinical status as determined by supplemental questionnaire (nutritional autonomy, burden of care related visits, social support structure) with relation to aggregate SF-36 score and within each of the individual domains (physical functioning,

bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions).

3) Compare health related quality of life between subgroups of participants based upon:
    a. Early childhood Age at Transplant vs. Late childhood Age at Transplant
    b. Low Medical Care Burden vs. High Medical Care Burden

Materials and Methods

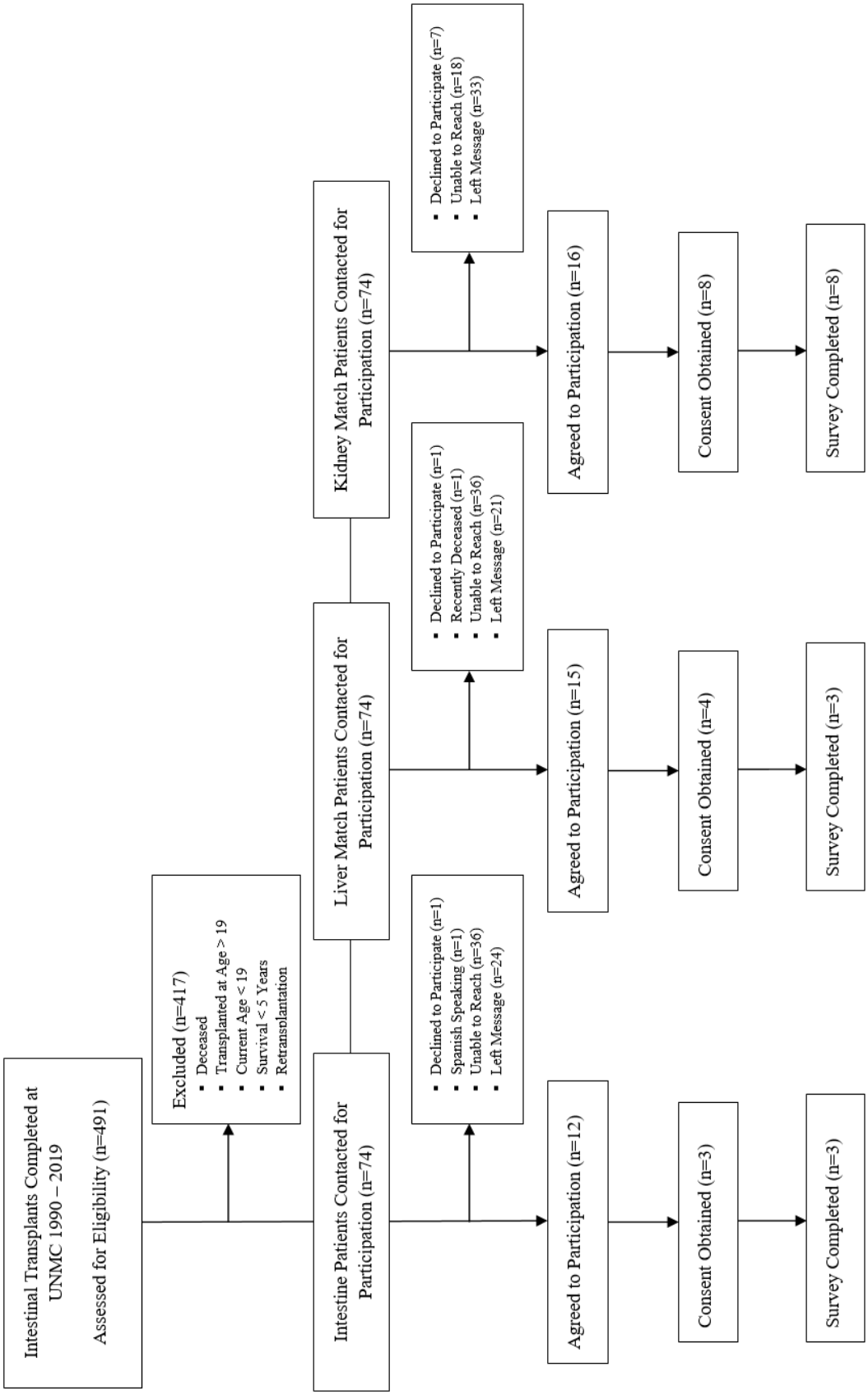
Study Participants

A single center cross sectional study was performed, including currently living adult patients (current age > 19 years old) who previously received ITx, isolated or multivisceral, during childhood (age at transplant < 19 years old) who had reached a minimum survival of 5 years. A review of ITx data at the University of Nebraska including these criteria identified a total of 74 unique patients upon initial screening who received an initial ITx during a twenty-year period from 1993 to 2013 at the University of Nebraska Medical Center. This twenty-year time frame was chosen as it captured the highest number of patients who were still living and had reached adult age, which is defined in Nebraska state law to be 19 years of age. Patients were excluded if the index operation during the screening period was a re-transplantation. Additionally, after the initial query for this study period, one patient had a native language other than English. Considering this very small number (n=1) this patient was excluded as statistically this would not provide good representation of this patient population as a subcategory and furthermore would limit confidentiality efforts if collected data in this study were easily identifiable to the one non-English speaking subject. Therefore, study participation included only English-speaking patients.

Study Groups

Control groups utilized for comparison included current adult patients who previously received an isolated kidney or isolated liver transplant in childhood during the period from 1993 to 2013. Similarly, control patients were excluded from the study if the index operation during the screening period was a re-transplantation or was part of a multi-organ transplant involving more than isolate kidney or liver. A total of 158 and 111 patients met criteria for the liver and kidney control groups respectively. These patients were then selected for inclusion in the study based on a 1:1 match to the ITx group considering the variables of age at transplant, gender, and current age. Priority was given in the manual match process first to age at transplant (+/- 2 years) and gender, with extended criteria allowed for the variable of current age (+/- 5 years). An exact match of liver patients meeting the set criteria was made for 65 of the 74 intestine patients, the remaining match was done such that criteria was as similar as possible. An attempt was made to manually match kidney patients, however due to the typical difference in age of transplant seen for pediatric kidney recipients, ideal matches were not possible based on the set criteria. Trends in pediatric kidney transplantation are such that they represent a very small proportion of total kidney transplants and kidney transplants occur in older children compared to ITx provided that dialysis prolongs the need for transplant such that the need is less life threatening in comparison to ITx.[16] This was addressed by utilizing the kidney patients with the lowest age at transplant values and foregoing the manual match. In total, an additional 74 liver and 74 kidney patients were included in the study. Figure 1 below depicts the flow chart for patient selection and participation in this study.

Figure 1: Patient Selection and Participation Flow Chart



Ethical Review

The study was approved by the University of Nebraska Medical Center Institutional Review Board and informed consent was obtained from all study participants prior to participation (IRB 628-20-EP). A copy of this approved IRB and consent form for patient participation can be found in Appendix A and Appendix B, respectively.

HRQOL Measures

Quality of life assessments were conducted via phone utilizing the RAND 36-Item Short Form Health Survey (SF-36) which has been validated and widely used to collect HRQOL scores in both healthy and ill populations of a wide range of medical disciplines.[17] The SF-36 obtains an individual's composite quality of life score of 1-100, with higher scores indicating a higher quality of life, and additionally describes multiple domains which subcategorize the composite quality of life score into two separate areas of physical and mental health. The domains are also scored from 1-100 in each of the following areas: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

Participants were asked to complete an additional questionnaire during the phone interview to gather demographic and lifestyle data not contained in the medical record (employment, education, housing, independence, relationship status, caregiver responsibly, and transportation use) as well as questions specific to ITx related to domains of nutritional autonomy and level of medical demand. The questions related to level of medical demand were utilized in grouping patients into either high or low demand. Criteria utilized delineate high from low medical demand where hospitalization days in last 12 months (low = 0, 1-3, or 3-5; high = 5-10, >10) and degree of medical follow up (low = annual; high = monthly or higher). A copy of these questionnaires may be found in Appendix B and Appendix C, respectively.

Statistical Analysis

Analysis of patient demographics and questionnaire results was performed utilizing Jamovi 1.0.7.0. statistical software. Continuous variables were expressed as mean ± standard error and categorical variables were presented as proportions. SF-36 scores were calculated utilizing the standardized SF-36 scoring criteria to determine each participant's total and domain scores and expressed as mean ± standard error. Correlations between demographic and clinical data of patients and HRQOL were assessed by either one-way ANOVA Kruskal-Wallis tests for nonparametric data assessing the three independent groups, independent-samples t test utilizing Nonparametric Mann-Whitney U test for two group comparison, or Pearson's Chi-Square test for nonnormally distributed categorical data. A value of $P < .05$ was considered significant.

Results

Patient characteristics of the three independent groups is depicted below in Table 1. The study group of pediatric ITx patients included 74 patients after exclusion, with a mean current age of 25.3 (±0.56) years, a mean age at time of transplant of 4.4 (±0.52) years, and a gender distribution favoring males at 58.1%. Most of these transplants involved simultaneous bowel and liver (55.4%), followed by isolated bowel (37.8%), and only a small number were that of bowel, liver, pancreas (6.8%). The pediatric liver transplant patients used as a control group were equally matched with no significant differences in mean current age of 26.7 (±0.55) years, mean age at time of transplant of 4.3 (±0.54) years, and male representation at 60.8%. The pediatric kidney transplant patients used as a control group were different in age, as expected and addressed in the selection methodology, with a mean current age of 28.5 (±0.69) years ($P < .001$), mean age at time of transplant of 10.0 (±0.48) years ($P <.001$), but with no difference in male representation at 56.8%.

Table 1: Demographics of Matched Groups

	Intestine	Liver	Kidney
N	74	74	74
Current Age	25.3 (0.56)	26.7 (0.55)	28.5 (0.69)*
Age at Transplant	4.4 (0.52)	4.3 (0.54)	10.0 (0.48)*
Gender			
Male	43 (58.1%)	45 (60.8%)	42 (56.8%)
Female	31 (41.9%)	29 (39.2%)	32 (43.2%)
Type of Transplant			
Isolated Bowel	28 (37.8%)		
Liver Bowel	41 (55.4%)		
Liver Bowel Pancreas	5 (6.8%)		

Baseline difference in demographic data utilized for control matching. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages. * denotes statistically significant difference ($P < .001$) in kidney control group to intestine case group.

Of those that did participate in the study to date, there were no significant differences in baseline demographics, shown in Table 2 below. Mean current age for the intestine, liver, and kidney groups were 33.7 (±3.53), 30.0 (±0.58), and 27.4 (±1.65) respectively. Age at time of transplant among the groups were 11.3 (±3.42), 8.1 (±1.86), and 9.1 (±1.53). Of the respondents in the intestine group, two were isolated bowel transplants and one was bowel and liver. Respondents were primarily Caucasian, following typical racial demographics seen at this institution, and included two African American participants, one in each of the intestine and kidney groups.

Table 2: Demographics of Survey Participants

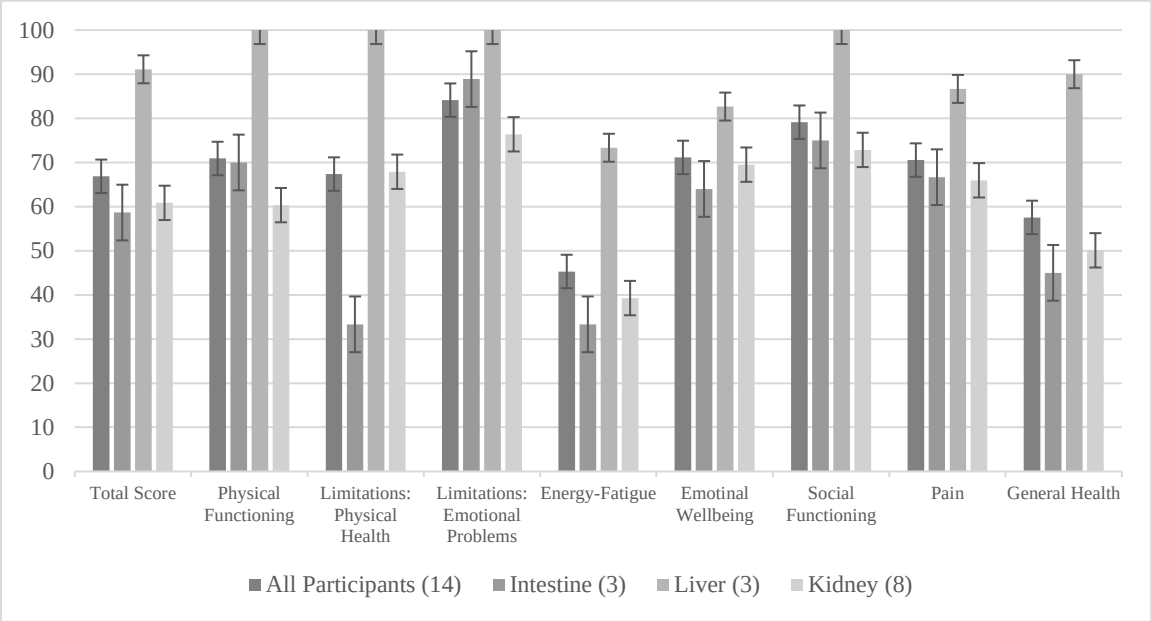
	Intestine	Liver	Kidney
N	3	3	8
Current Age	33.7 (3.53)	30.0 (0.58)	27.4 (1.65)
Age at Transplant	11.3 (3.42)	8.1 (1.86)	9.1 (1.53)
Gender			
Male	3 (100%)	3 (100%)	4 (50.0%)
Female	0 (0%)	0 (0%)	4 (50.0%)
Race			
Caucasian	2 (66.7%)	3 (100%)	7 (87.5%)
African American	1 (33.3%)	0 (0%)	1 (12.5%)
Type of Transplant			
Isolated Bowel	2 (66.6%)		
Liver Bowel	1 (33.3%)		
Liver Bowel Pancreas	0 (0%)		

Baseline difference in demographic of study participants, no significant differences were found. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages.

Results of the SF-36 assessment are depicted in Table 3 and Figure 2 below. There are no statistically significant differences when assessing the three groups individually given the small sample size today date, however, overall scores and domain scores are higher among liver transplant recipients compared to those of intestine or kidney patients, which remain similar to one another across all domains; mean total scores for liver recipients (92 ± 0.9) was significantly higher than total scores for intestine recipients (59 ± 11.9) and kidney recipients (61 ± 7.1).

When analyzed among the two groups, liver vs. other solid organ recipients (grouped intestine and kidney participants) scores are found to be significantly higher among liver patients. Statistically significant differences were found in the total score (P = 0.012), and for the domains of physical functioning (P = 0.011), role limitations due to physical health (P = 0.047), energy/fatigue (P = 0.014), social functioning (0.048), and general health (P = 0.006).

Figure 2: Mean SF-36 Scores by Transplant Group



Summary mean scores for the SF-36 questionnaire among all participants and divided per transplant groups for total and eight individual domains.

Table 3: SF-36 Survey Results

	Intestine	Liver	Kidney
N	3	3	8
Total Score	59 (11.9)	92 (0.9)*	61 (7.1)
Physical Domains			
Physical Functioning	70 (22.5)	100 (0)*	58 (8.0)
Limitations Physical	33 (33.3)	100 (0)*	66 (13.4)
Pain	67 (19.3)	87 (8.8)	66 (8.1)
General Health	45 (14.4)	90 (5.8)*	50 (9.1)
Mental Domains			
Limitations Emotional	89 (11.0)	100 (0)	81 (8.6)
Emotional Well Being	64 (8.3)	83 (3.5)	74 (7.2)
Social Functioning	75 (7.2)	100 (0)*	77 (11.7)
Energy-Fatigue	33 (12.0)	73 (6.7)*	37 (10.5)

Summary scores for the SF-36 questionnaire between groups. Data is displayed as mean (± SE) with higher scores indicating a better quality of life for both total scores and for individual domain scores which are grouped into physical components and mental components. Scores were not significantly different between intestine and kidney patients. * denotes statistically significant difference ($P < 0.05$) among the liver group compared to remaining groups.

Data collected from the additional questionnaire is summarized in Table 4. All intestine and liver patients were functioning outside of the home full time either in college or full-time employment, while half of kidney respondents were reported either disability or unemployment. All intestine and liver patients reported some level of college completion, with the majority earning bachelor's degrees (66.7% both groups). Half of kidney respondents have earned a high school diploma with the remaining reporting varying levels of college completion.

Regarding nutritional autonomy among intestine respondents, pre-transplant limitations to oral intake existed in two respondents. One was limited to only solid intake prior to transplant and now has full nutritional autonomy. The other reported no oral intake prior to transplant, unable to consume both solids and liquids, and was the only respondent who also reported continued need for supplemental nutrition following transplant. Oral aversion following transplant was not reported in any respondents.

The degree of medical need was assess based upon self-reported hospital days in the last 12 months and frequency of required routine follow up. Among intestine patients, two were considered high demand reporting greater than 5 hospital days in the last 12 months and monthly appointments (33%) or in-home care (33%) follow up requirements; the remaining intestine respondent had no hospitalizations and requires only annual visits. All liver respondents were considered low demand. Among kidney respondents, three were considered low medical demand (37.5%) and five were considered high medical demand (62.5%). Among all respondents, only four reported issues related to immunosuppression therapy, two related to significant side effects, one with financial constraints to maintain therapy, and one reporting infectious complications related to immunocompromised status.

Table 4: Additional Questionnaire Survey Results

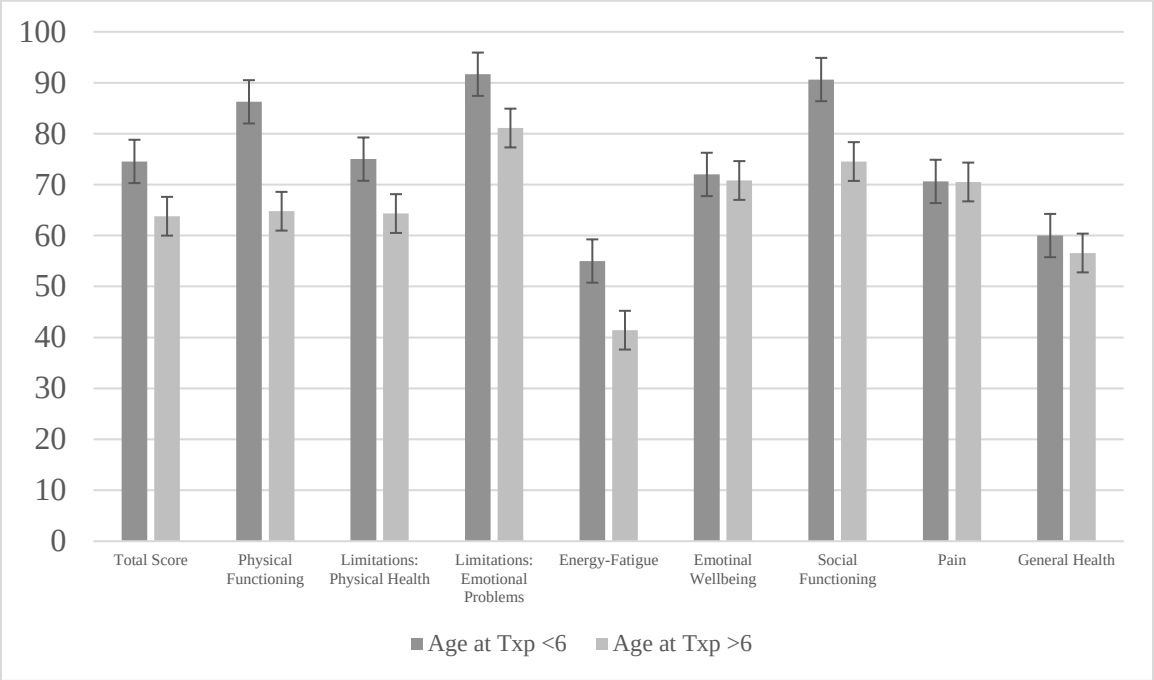
	Intestine	Liver	Kidney
N	3	3	8
Work Status			
Student	1 (33.3%)		1 (12.5%)
Part Time			1 (12.5%)
Full Time	2 (66.7%)	3 (100%)	2 (25.0%)
Disabled			3 (37.5%)
Unemployed			1 (12.5%)
Education Status			
High School Diploma			4 (50.0%)
Some College	1 (33.3%)	1 (33.3%)	1 (12.5%)
Associate Degree			1 (12.5%)
Bachelor's Degree	2 (66.7%)	2 (66.7%)	2 (25.0%)
Living Status			
Lives Alone			3 (37.5%)
Lives With Others	3 (100%)	3 (100%)	5 (62.5%)
Needs ADL Assistance	0 (0%)	0 (0%)	3 (37.5%)
Is a Caretaker to Child	1 (33.3%)	1 (33.3%)	1 (12.5%)
Is a Caretaker to Adult	0 (0%)	0 (0%)	0 (0%)
Has Driver's License	2 (66.7%)	3 (100%)	5 (62.5%)
Uses Own Vehicle	3 (100%)	3 (100%)	6 (75.0%)
Uses Rideshare			1 (12.5%)
Uses Public Transport			1 (12.5%)
Marital Status			
Single	1 (33.3%)		6 (75.0%)
Long-Term Relationship		1 (33.3%)	
Married	2 (66.7%)	2 (66.7%)	1 (12.5%)
Divorced			1 (12.5%)
Nutritional Autonomy			
Solids Only Pre Tx	1 (33.3%)		
No PO Pre Tx	1 (33.3%)		
IV Nutrition Now	1 (33.3%)		
Oral Aversion Now	0 (0%)		
Medical Needs			
Hospital Days Last Year			
0	1 (33.3%)	3 (100%)	3 (37.5%)
1-3			
3-5			2 (25.0%)
5-10	1 (33.3%)		
> 10	1 (33.3%)		3 (37.5%)
Immunosuppression			
Financial Issues			1 (12.5%)
ID Complications	1 (33.3%)		
Side Effects			2 (25.0%)
Degree of Follow-up Care			
Annual or Less	1 (33.3%)	3 (100%)	4 (50.0%)
Monthly	1 (33.3%)		4 (50.0%)
In-Home Care	1 (33.3%)		

Categorical counts are given with group percentages.

Further analysis of quality of life scores were performed based upon subgroups determined by age at transplant and level of medical demand. Age at transplant was separated into either before or after the age of 6 years old to divide the recipients into two categories that roughly depict those that received transplant before or after the onset of school age. Mean scores were higher as a total and within each domain for those that were transplanted at ages < 6 years old (N = 4) compared to those that were transplant at ages > 6 years old (N = 10. This data is depicted in Figure 3 below.

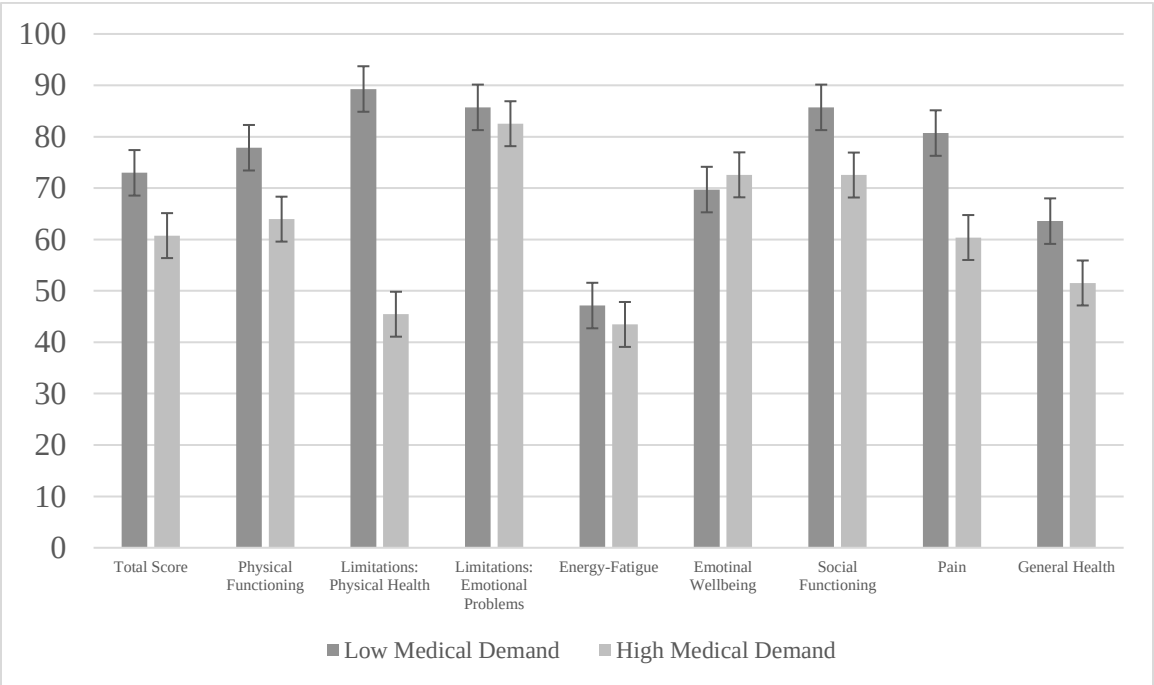
Among those surveyed, low medical demand and high medical demand were equally distributed (N = 14) based on criteria described previously in methods related to hospital days in the last 12 months and frequency of required follow up visits. Mean scores were generally higher across all domains for those with a low medical demand as expected, with the exception of emotional wellbeing, but with a more profound difference among those domains related to the physical health components rather than the emotional health components. This data is depicted in Figure 4 below. Significant differences were found among these groups for two physical health components. Those with low medical demand had statistically significant lower quality of life scores in the domains of role limitations due to physical health (P = 0.010) and pain (P = 0.047).

Figure 3: Mean SF-36 Scores by Age at Transplant



Summary mean scores for the SF-36 questionnaire among those with age at transplant less than and greater than 6 years of age.

Figure 4: Mean SF-36 Scores by Medical Demand



Summary mean scores for the SF-36 questionnaire among those with low medical demand and high medical demand.

Discussion

Review of the quality of life scores obtained in adulthood for patients who received ITx in childhood, over twenty years ago, shows that for this group of patients scores are not significantly different from those of other solid organ transplant recipients at similar timelines, specifically kidney transplant patients. As expected, scores were generally lower in the ITx cohort compared to liver patients at similar timelines, but rather unexpectedly scores in kidney patients matched that more closely of ITx patients rather than liver. While the small size of respondents to date makes drawing conclusions to these differences in scores difficult, the additional demographic data suggests slight differences that may attribute to the quality of life scores. Within the group of kidney patients there were far more patients reporting disability and unemployment, lack of college experience, and need for assistance with ADLs, compared to none reporting these variables in both the intestine and liver groups. This suggests that perhaps the more favorable outcomes of kidney transplantation and less severe complications compared to liver and intestine transplant which would presumably lead to higher HRQOL, is masked in this particular cohort by the differences in their current living situations that accounts for the unexpected results of their HRQOL scores.

The scores between those transplanted at younger ages did show trends of being higher than those transplanted during school ages. This warrants further assessment as more data is collected as this may have an impact in decision making of when to approach transplantation. Generally, ITx remains a therapeutic option for IF only when medical management has failed or created other complications requiring transplantation such as IFALD. This means that when clinically possible, IF patients reach older ages before approaching transplantation. A more powered study may be able to show that experiencing transplantation during more formative years has an impact on future quality of life compared to experiencing transplantation at a younger age.

An interesting finding among the surveys completed was the trend found when assessing the differences in quality of life scores among those with differing levels of medical demand for current follow up of their former transplantation. While there were significant differences among domains related to physical health components, there was a relative preservation of quality of life scoring within emotional health domains. This suggests that though differences exist between those that still struggle with health related issues from transplantation even in such long term timelines seen here such that their physical health is impacted, and significantly different from those with low medical demand, they are able to cope in such a manner that their quality of life within the emotional health domain is not impacted such that it is significantly different from those who are doing relatively well from a physical health standpoint.

Limitations of this study most significantly involves the low number of respondents with only 14 participants completing surveys to date, making statistical analysis difficult for this low powered study. Initial designs for the study focused solely on pediatric ITx recipients, however, as pediatric liver and kidney patients of similar ages and timeframes at this institution these groups were added with the idea to be used as controls with a similar level of health related impacts contributing to their HRQOL. While we were able to gather HRQOL data among each group (Aim 1) and compare subgroup findings (Aim 3), the relatively low response rate made further analysis based upon variables of the supplemental questionnaire difficult to obtain (Aim 2). Unexpectedly, an overwhelming response was received from the pediatric kidney transplant recipients rather than the targeted study group. While this has provided insightful information, it has shifted the focus slightly. While the sample sizes to date are not enough to appropriate differentiate response differences between the transplant groups (intestine, liver, kidney), the analysis of the group as a whole remains beneficial in depicting the HRQOL measures for patients at this institution and among subgroups identified related to age at transplant and level of current medical demand. Our supplemental questionnaire, while developed to capture more

specific details of lifestyle demographics, also includes a section on nutritional autonomy, which is relevant to the pediatric ITx recipients only. Additional questions related to other organ specific areas – such as dialysis requirements for the pediatric kidney recipient group – would capture data likely contributing to HRQOL for specific groups. Due to the timing of this study during the worldwide pandemic of the novel COVID-19 virus, it is reasonable to postulate that this could be a contributing factor to some domains of the SF-36 survey, largely those in the mental domains. Results in these areas may have had indirect impacts from pandemic experiences which vary among respondents dependent on the timing of the completion of the survey.

In conclusion, HRQOL scores obtained in adults who underwent solid organ transplant during childhood were most similar between intestine and kidney patients, with significantly higher scores among multiple domains and overall, in liver patients. Those transplanted younger tended to have higher HRQOL scores as well as those with current low medical demands; however, for those with high medical demands, lower HRQOL scores were specific to physical health domains with relatively preserved HRQOL scores in emotional health domains.

Future directions of this study involve continued completion of survey data for the remaining patients who initially agreed to participate but have not yet completed consent or survey at this time. We are hopeful that over the next year the response rate will reach a number to allow for more robust statistical analysis which can depict statistically significant differences among the groups which we see trends of now in the data, but lack power to fully analyze. Additionally, increased participation in the ITx group is anticipated to allow for comparison of another sub-group, those with and without nutritional autonomy.

CHAPTER 3: VENOVENOUS BYPASS IN LIVER TRANSPLANTATION

Literature Review: Utilization of Venovenous Bypass in Transplantation

The utilization of venovenous bypass (VVB) for liver transplantation (LT) began in the 1980s as a technique to overcome the physiologic challenges of complete venous occlusion during the anhepatic phase of LT, specifically for the surgical technique referred to as classical liver transplantation.[1] This technique is one in which the supra- and infra-hepatic vena cava is intentionally cross clamped, obliterating the flow of venous return to the right heart during which time anastomoses are completed by the transplant surgeon. This came at a time when liver transplantation outcomes had improved since their very dismal beginnings in the 1960s largely in part to the development of new immunosuppression pharmaceuticals, however, there remained technical challenges to the surgery itself.

During classical transplantation in the anhepatic phase occlusion of the inferior vena cava and the portal vein (PV) must occur for hemostatic control to allow for anastomosis of the donor allograft. This poses numerous physiologic challenges in the transplant patient, most notably hemodynamic instability, as there is a decrease in venous return to the right heart and thus reduction of preload. In addition to the cardiac instability which occurs, cessation of portal flow for a prolonged time can lead to mesenteric congestion.[2] These difficult physiologic conditions led to the development of venous bypass techniques during the anhepatic phase of the operation, however, bleeding became the consequential challenge when VVB was utilized with systemic heparinization until methodology was developed to perform bypass without systemic anticoagulation. Early assessment of VVB utilization without systemic heparinization demonstrated less renal damage postoperatively and lower blood product use intraoperatively in those patients where VVB was utilized.[3]

In the beginning of LT, VVB was utilized routinely as it was thought to be necessary to provide intraoperative stability similar to early canine experimentation models, this however has

dramatically changed. In the 1980s up to 91% of transplant centers routinely used VVB. Presently, transplant centers fall within one of three categories: routine use, selective use, or no use of VVB during LT. A survey of major transplant centers in North America demonstrated that utilization of VVB was routine in less than half of centers and had recently changed to selective use in 30% of the centers surveyed. This survey of VVB utilization, however, was completed in 1998 and the number of routine use centers is likely even less today.[4,5]

One of the large driving factors for the decline in use was the emergence of a different anastomotic technique which preserves the inferior vena cava rather than replaces it in the classical technique utilized since the beginning of LT. This piggyback technique allows for only partial clamping of the inferior vena cava and thus preserves partial blood flow throughout the case, allowing for maintenance of preload and cardiac output in comparison to the classical technique. While the piggyback technique was introduced in the late 1960s it became more utilized in the 1990s and allowed for a shift to selective use of VVB during LT.[2] Technical changes to the methods of VVB access additionally have occurred since its introduction. While cutdown methods for vascular access were initially used, today when initiated access is obtained with percutaneous techniques using Seldinger methodology.[6,7] This methodology has proven to be both easier to perform and safer than prior cutdown methods.[8]

The venovenous bypass technique, while providing means to improve hemodynamic stability in necessary cases is not without risk. Complication rates have been reported to occur 10-30% among centers who utilize the technique routinely.[4] The increased association of morbidity and mortality as well as the development of newer non-classical techniques without such profound physiologic changes during the anhepatic stage has shifted the once routine use of venovenous bypass to a more selective approach. Numerous known complications exist with a varying degree of significance, including but not limited to hypothermia, air embolism, thromboembolism, lymphoceles, hematoma formation, vascular injury, nerve injury, vascular thrombosis, hemothorax and pneumothorax.[6,9] Thrombotic complications are known to be

influenced by the use of VVB and reports of massive pulmonary embolism exist and often cause fatality either in the operation or shortly after.[1,10,11] Technical improvements to the venovenous bypass approach have decreased the incidence of some complications, yet the procedure does not remain without risk. The previously discussed change from earlier cutdown techniques of the saphenofemoral junction and axillary vein to a percutaneous cannulation technique has improved rates lymphorrhea, infection, and nerve damage; though vascular injury appears to occur more often with percutaneous technique.[8]

With a focus on the potential complications encountered with VVB utilization, questions arise for the continued need of the technique, though there is varying evidence for the benefit that VVB provides and the indications for use as these have largely been adopted on a center-by-center basis rather than through evidence-based global guidelines for the utilization of VVB in LT. The most common inciting factor for the initiation of VVB is failure to maintain adequate perfusion or cardiac index during a trial test clamp prior to the anhepatic phase of the operation. While there remains no consensus, reported indications for consideration of VVB have included preexisting cardiac disease, pulmonary hypertension, pulmonary edema, severe renal insufficiency, fulminant liver failure and increased intracranial pressures, severe portal hypertension, or age > 55.[4] At our own institution aside from patients with fulminant liver failure the decision to utilize VVB is rarely made preoperatively based upon any guidelines or known risk factors for the need of VVB, but rather is an intraoperative decision made at the time of cross clamp. Within the literature there remains a lack of consensus on the use of VVB in LT with acknowledgement that trends in utilization depend largely on the choice of practice within each institution. Additionally, there is evidence that regardless of technique used, outcomes do not vary significantly even without utilization of VVB, further providing question to the benefit of its utilization, the necessity of its utilization, and the need to risk the numerous complications which may occur.[5]

Research Hypothesis and Specific Aims

The research hypothesis is that there are baseline preoperative differences between patients undergoing liver transplant dependent on whether VVB was necessary to complete the case. These factors if established may be helpful to the transplant surgeon in anticipation of VVB usage prior to the start of the operative case.

Specific Aims:

1) Evaluate preoperative characteristics of cases and controls to determine if there are any predictive factors related to the need for intraoperative VVB utilization that may guide the transplant surgeon to anticipate and prepare for this need prior to the time of operation.
2) Compare intraoperative variables between those patients who had intraoperative VVB utilization and those without utilization to evaluate for any differences occurring during the case.
3) Compare outcomes between those patients who had intraoperative VVB utilization and those without utilization to evaluate for any benefit in postoperative variables.

Materials and Methods

Study Participants

This single center retrospective study looked at LT patients in which VVB was initiated intraoperatively during the period from July 2001 to June 2019 at UNMC. During this time, venovenous bypass was utilized in 100 hepatic procedures performed by the transplant surgeons at our facility. Of these, 94 were adult patients who underwent liver transplantation and were included in this review. The remaining six cases included three pediatric procedures, two hepatic resections, and one adult liver transplant recipient in which venovenous bypass was aborted

before fully initiated due to vascular depletion contributing to technical issues with flow rates, thus, these cases were excluded from this study. Control data was obtained utilizing a 1:1 match of adult liver transplant recipients which were chosen by utilizing the next LT patient who followed immediately after each VVB case, excluding those which were living donor LT recipients or multivisceral transplant recipients. The study was approved by the University of Nebraska Medical Center (UNMC) Institutional Review Board and was deemed minimal risk with an approved waiver of informed consent (IRB 0372-19-EP).

Data Collection

Patient demographic information as well as limited clinical data related to transplantation was obtained through electronic medical record (EMR) reporting for all patients within the period from 2001 to 2019. Manual chart review was further completed for the period from 2010 through 2019; prior to this time, operating room and intensive care unit (ICU) data was contained only in scanned hand-written documentation which was not easily obtained. Additional preoperative clinical data collected included primary diagnosis, fulminant liver failure status, preoperative imaging evidence of PV thrombosis, creatinine and dialysis status, preoperative cardiac disease and ejection fraction from echocardiogram performed for listing evaluation. Operative records were reviewed to obtain use of drip or push pressors, amount of blood product use, and any significant intraoperative events noted by the surgeon and/or anesthesiologist. Postoperative progress notes were reviewed to determine total ICU admission days, total days intubated, creatinine trends and need for dialysis, and any recorded complications arising from VVB use.

Statistical Analysis

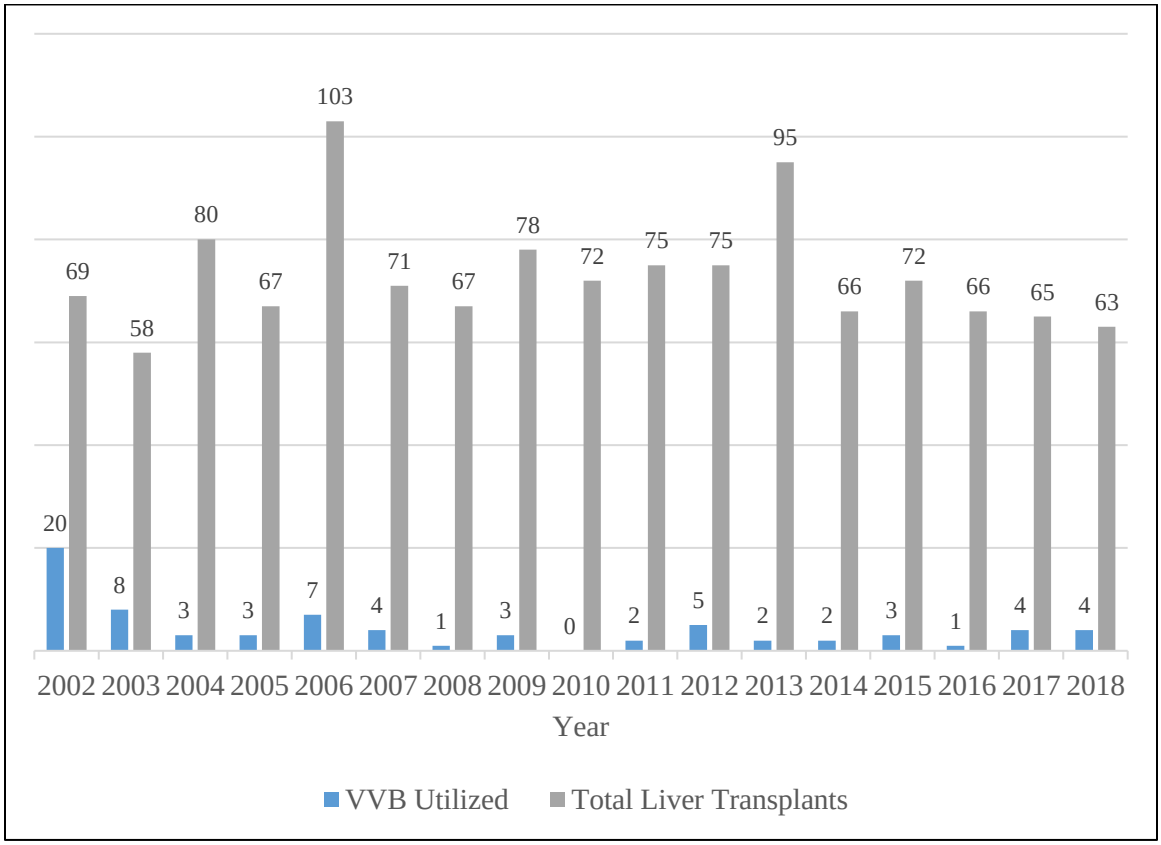
Analysis of patient demographics and clinical variables was performed utilizing Jamovi 1.0.7.0. statistical software. Continuous variables were expressed as mean ± standard error and categorical variables were presented as proportions. Correlations between demographic and clinical data of patients were assessed by independent-samples student's t test for normally distributed continuous data, or Pearson's Chi-Square test for normally distributed categorical

data. Kaplan-Meier survival analysis was performed to compare case and control groups. A value of $P < .05$ was considered significant.

Results

VVB utilization trends from 2002 to 2018 among adult liver transplant cases at UNMC is depicted in Figure 5 below, shown in comparison to total liver transplants per year. Prior to 2002 VVB had been utilized more frequently at this institution, however, decreased significantly beginning in 2003. The average number of times VVB was utilized in LT cases at UNMC has been less than 4 cases per year from 2003 to date. Annual data for 2001 and 2019 were excluded for this figure as the utilization report at the time of this study included only portions of those years rather than the full 12-month period, however, in the latter 6 months of 2001 alone 18 LT cases utilized VVB, which further depicts the previous trend and the dramatic decrease in utilization which occurred beginning in 2003.

Figure 5: VVB Utilization Trend in UNMC Adult Liver Transplants 2002 - 2018



17-year trend of total liver transplant cases performed at UNMC and proportion of those annually which utilized VVB intraoperatively, depicting downtrend in VVB utilization occurring since 2003.

Patient characteristics of the two groups, VVB Utilized cases and VVB Not Utilized controls is depicted below in Table 5 and Table 6. Table 5 details demographic characteristics of those patients (N = 58) included in the most recent 10-year period for which detailed chart review was conducted, 2010 – 2019. The groups did not differ significantly among baseline demographics. Mean age among cases and controls was 50.5 (±2.79) and 50.9 (±2.67) respectively; males represented 58.6% of cases and 44.8% of controls; demographics were similar among both groups and represented typical populations seen at this institution with majority representation of Caucasian patients, 82.8% and 93.1% respectively, with the remaining patients identifying as African American, Hispanic or Latino, and American Indian. Model end-stage liver disease (MELD) scores and Retransplantation status among these patients were higher in the VVB group at 26.7 (±1.83) compared to 22.2 (±1.75) and in 9 (31.0%) compared to 4 (13.8%), however these were not statistically significant differences. There was no difference found in preoperative serum creatinine, preoperative need for hemodialysis, or impaired preoperative ejection fractions (defined as < 55%). The groups did differ significantly with regards to presence of fulminant liver failure and known preoperative PV thrombosis. The VVB group included 5 (17.2%) cases of fulminant liver failure compared to zero in the control group (P = 0.019). PV thrombosis was identified preoperatively in 6 (20.7%) of the VVB group compared to only 1 (3.4%) in the control group (P = 0.044).

When looking at the group as a whole, from 2001 to 2019, baseline data of all patients (N = 190) was limited to those variables available in automatically generated EMR reports available in the electronic medical record. This data is depicted in Table 6. There remained no significant differences in age and gender, however the larger sample size was able to show statistically significant differences in MELD and Retransplantation status between these two groups. Among all patients who required VVB intraoperatively (N = 95) the mean MELD was significantly higher at 23.9 (±1.07) compared to 19.6 (±0.90) in those that did not require VVB

intraoperatively (P = 0.002). Additionally, Retransplantation status was present in 31 (32.6%) patients who required VVB intraoperatively compared to only 8 (8.4%) in the group that did not require VVB intraoperatively (P = < 0.001).

The pre-operative clinical factors which were significantly different among the VVB group and controls were further assessed utilizing binomial logistic regression. These pre-operative factors included presence of fulminant liver failure, known PV thrombosis, MELD, and retransplantation. Known PV thrombosis was the only statistically significant predictive factor for the need of VVB utilization in LT among these patients (P=0.047).

Table 5: Ten-Year Focused Preoperative Demographics 2010 – 2019

	VVB Utilized	VVB Not Utilized	
N	29	29	
Age	50.5 (2.79)	50.9 (2.67)	
Gender			
Male	17 (58.6%)	13 (44.8%)	
Female	12 (41.4%)	16 (55.2%)	
Race			
Caucasian	24 (82.8%)	27 (93.1%)	
African American	3 (10.3%)	0 (0.0%)	
Hispanic or Latino	2 (6.9%)	1 (3.45%)	
American Indian	0 (0.0%)	1 (3.45%)	
MELD	26.7 (1.83)	22.2 (1.75)	
MELD-Na	27.8 (1.70)	23.4 (1.69)	
Retransplantation	9 (31.0%)	4 (13.8%)	
Fulminant	5 (17.2%)	0 (0.0%)	* P =0.019
Preoperative Cr	2.40 (0.33)	1.97 (0.28)	
Preoperative HD	7 (24.1%)	7 (24.1%)	
Known PV Thrombosis	6 (20.7%)	1 (3.4%)	* P = 0.044
PV Thrombosis in OR	8 (27.6%)	3 (10.3%)	
Baseline EF			
Normal ($\geq$ 55)	26	28	
Decreased (< 55)	2	1	

Baseline difference in demographic data utilized for control matching. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages. * denotes statistically significant difference ($P < 0.05$).

Table 6: All Patient Preoperative Demographics 2001 – 2019

	VVB Utilized	VVB Not Utilized	
N	95	95	
Age	51.6 (1.17)	50.9 (1.20)	
Gender			
Male	60 (63.2%)	53 (55.8%)	
Female	35 (15.8%)	42 (44.2%)	
MELD	23.9 (1.07)	19.6 (0.90)	* P = 0.002
MELD-Na	23.4 (1.08)	20.5 (0.99)	
Retransplantation	31 (32.6%)	8 (8.4%)	* P < 0.001

Baseline difference in demographic data utilized for control matching. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages. * denotes statistically significant difference ($P < 0.05$).

The intraoperative characteristics surveyed included use of blood products during the LT case, this was significantly higher among VVB cases and controls, as shown in Table seven below. The mean number of units of packed red blood cells (PRBCs) in VVB cases was 23.3 (±3.59) compared to 8.7 (±1.32) in controls (P<0.001). The mean number of units of fresh frozen plasma (FFP) in VVB cases was 34.3 (±4.88) compared to 15.0 (±1.93) in controls (P<0.001). The mean number of units of platelets in VVB cases was 5.34 (±0.86) compared to 3.0 (±0.47) in controls (P=0.033). The mean number of units of cryoprecipitate in VVB cases was 16.5 (±6.40) compared to 1.31 (±0.47) in controls (P=0.022). While use of pressors as a drip was higher in VVB cases compared to push, this was not statistically significant among the two groups.

Table 7: Intraoperative Characteristics

	VVB Utilized	**VVB Not Utilized**	
Blood Products			
PRBCs	23.3 (3.59)	8.7 (1.32)	* P < 0.001
FFP	34.3 (4.88)	15.0 (1.93)	* P < 0.001
Platelets	5.34 (0.86)	3.0 (0.47)	* P = 0.033
Cryoprecipitate	16.5 (6.40)	1.31 (0.47)	* P = 0.022
Pressor Use	29 (100%)	26 (89.7%)	
Push	6 (20.7%)	8 (30.8%)	
Drip	23 (79.3%)	18 (69.2%)	

Differences intraoperative characteristics between case and control groups. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages. * denotes statistically significant difference (P < 0.05).

There was no significant difference in postoperative renal function between the VVB cases and controls. Postoperative AKI, determined by either notation in postoperative progress notes or based upon assessment of laboratory values meeting current definitions within Kidney Disease Improving Global Guidelines, was present in 11 (37.9%) of VVB cases and in 16 (55.2%) of controls.[12] Mean post-operative 24-hour/72-hour serum creatinine was not found to be different in VVB cases versus controls, at 2.05 (±0.28)/1.93 (±0.21) and 1.86 (±0.21)/2.03 (±0.24), respectively. The number of days to reach baseline pre-operative serum creatinine was no different at 4.00 (±0.92) and 3.57 (±0.58) for VVB cases and controls. The need for postoperative dialysis was equal in both groups at 8 (27.6%) patients. While there was no difference in the number of post-operative days of ventilator requirement, the number of ICU days was higher in VVB cases at 9.22 (±2.25) days compared to 3.55 (±0.49) days in control patients (P = 0.014).

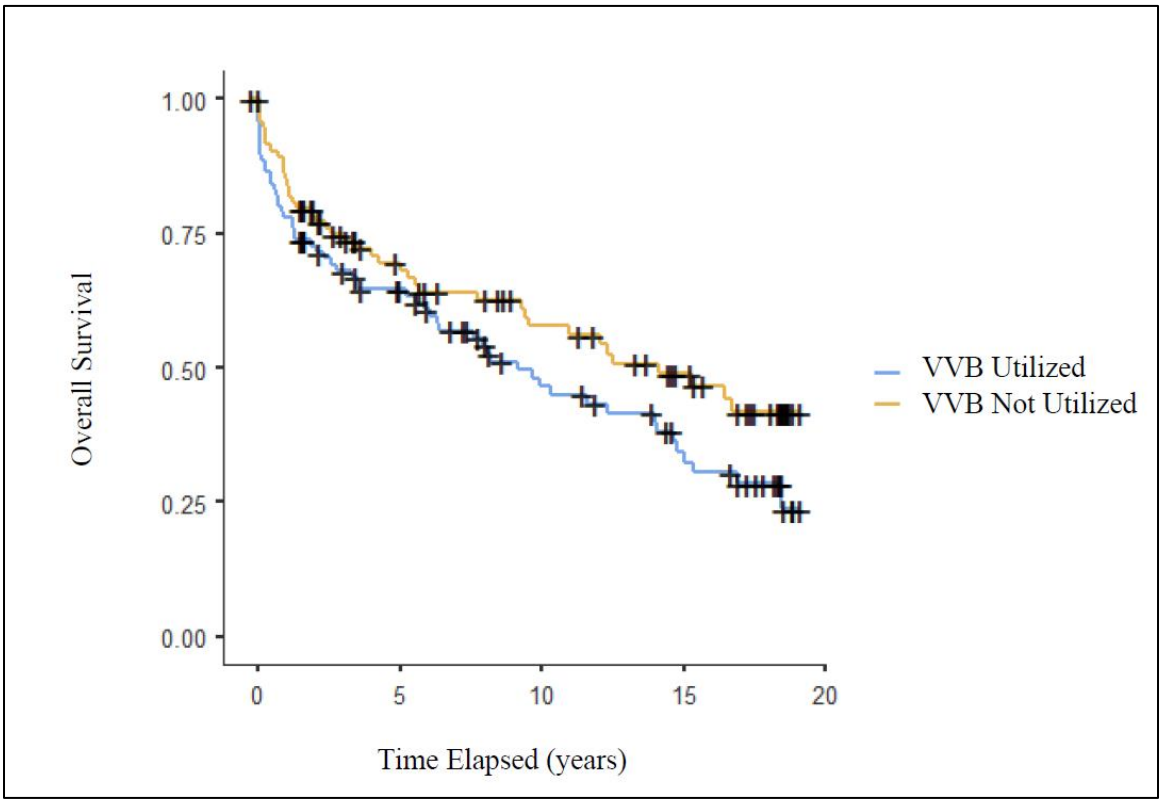
Table 8: Postoperative Characteristics

	VVB Utilized	**VVB Not Utilized**	
Renal Function			
Postoperative AKI	11 (37.9%)	16 (55.2%)	
24 hr Cr	2.05 (0.28)	1.86 (0.21)	
72 hr Cr	1.93 (0.21)	2.03 (0.24)	
Days to Baseline Cr	4.00 (0.92)	3.57 (0.58)	
Postoperative HD	8 (27.6%)	8 (27.6%)	
Days in ICU	9.22 (2.25)	3.55 (0.49)	* P = 0.014
Days on Ventilator	4.30 (1.74)	1.28 (0.17)	

Differences postoperative characteristics between case and control groups. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages. * denotes statistically significant difference (P < 0.05).

Overall survival for both groups is shown below in Figures 6. There was no statistically significant difference in survival among those that required VVB utilization during LT compared to controls which did not utilize VVB intraoperatively for LT.

Figure 6: Overall Survival After Liver Transplantation



Overall survival following liver transplantation among the two groups of those utilizing VVB intraoperatively and those not utilizing VVB intraoperatively, with no clear difference depicted in overall survival between the two groups.

Discussion

In this group of patients assessed at UNMC during the current period of selective use of VVB during LT, the clear differences in baseline clinical data, fulminant liver failure status, higher meld, re-transplantation status, and presence of PV thrombosis, clearly depict a trend that patient's requiring VVB intraoperatively are those that are presenting to LT with overall more critical condition than those not requiring VVB. While these factors may not necessarily be independently predictive of the need for VVB, they characterize those patients that at the time of cross clamp, do not have the hemodynamic stability to proceed without VVB support. Interestingly, the presence of cardiac or hemodynamic instability at the time of cross clamp as the driving factor in the majority of these cases for usage of VVB did not correlate to any specific cutoff for EF when assessed. This is mostly likely representative of the fact that candidates that reach listing and eventually transplant are those that have preserved cardiac function as evaluated prior to listing. With regards to the significantly higher number of fulminant liver failure patients being in the VVB case group (N = 5 vs. N = 0), this reflects the preoperative decision making for utilizing VVB to for cerebral protection rather than an intraoperative need for VVB related to instability at the time of cross clamp.

There were profound differences in the utilization of blood products intraoperatively between the VVB cases and controls, with the latter using far less of all subtypes of products than the cases. This is contradictory of prior studies showing decreased blood product requirements during surgery in VVB patients.[3] Again, this likely is not directly related to VVB usage itself, but more a representation of the more critical clinical status of those patients requiring VVB utilization also requiring more product support during the cases. The significantly higher number of retransplantation patients in the VVB case group likely also plays a role as these dissections during the hepatectomy portion are often more difficult given the prior surgery with a propensity for longer dissection times and greater bleeding. Similarly, the difference in ICU days with regards to postoperative characteristics of the two groups is likely more dependent on the overall

more critical clinical status of those patients requiring VVB utilization rather than a direct result of the use of VVB itself.

While prior evaluations of VVB usage have demonstrated improved renal function in comparison to those without VVB usage during LT, comparison of the VVB case group and controls showed not significant differences in any indicators of renal function assessed here.[3] While this does not provide justification for the use of VVB in providing better postoperative outcomes with regard to renal function, this does demonstrate that there was no missed opportunity for improving renal function in the group without VVB utilization. In this aspect there is no indication that the shift away from more routine use of VVB versus selective use has left any detrimental outcomes on renal function when VVB is not utilized in LT as there were no significant differences among the two groups with regard to rates of postoperative AKI, postoperative need for hemodialysis, or number of days to return to baseline serum creatinine.

Of the 29 patients who received LT with utilization of VVB, there were 6 documented complications either directly or potentially related to VVB utilization. Of these, two were related to vascular injury during cannulation and required further operative repair by a consulting vascular surgery team. One resulted in a pseudoaneurysm of the left superficial femoral artery following failed percutaneous attempt at cannulation that was successful after moving to the right groin. Following successful transplantation, hematoma was noted in the ICU and further imaging confirmed the suspected pseudoaneurysm. An ultrasound guided thrombin injection and obliteration of the pseudoaneurysm was completed by a vascular surgery team after returning to the operating room. The other resulted in injury to the right common femoral artery during percutaneous access requiring a bovine patch repair which was completed during an intraoperative consult to the vascular surgery team, not requiring a later return to the operating room. One case resulted in a retroperitoneal hematoma presumed to be related to vascular access for cannulation which did not require further operative interventions. As discussed previously, the transition from open to percutaneous access has decreased some complications known to be

related to VVB utilization such as wound complications and lymphatic leakage, however, as we see in this series, vascular injury is not an uncommon complication related to percutaneous vascular access.

Two cases involved intraoperative death. The first of these resulted in a re-transplantation patient after failed attempts at cardio-pulmonary resuscitation for pulseless electrical activity which occurred following anastomosis and disconnecting the bypass circuit in the setting of profound acidosis and coagulopathy. The clinical picture during this case was that of suspected transfusion-related acute lung injury given the large volume of blood product required, rather than a complication related to VVB. The other resulted after intraoperative pulmonary embolism. The second death was related to pulmonary embolism occurring in the operating room, verified on intraoperative transesophageal echocardiography with clots visualized in the right atria. The other complication noted in this series was technical in nature with failure to maintain adequate flows in the VVB circuit despite resuscitation. VVB was aborted in this case and the patient was later able to withstand cross clamp after an additional attempt and the LT case was successfully completed.

While the adaptation to the piggyback technique has been attributed to the declining use of VVB during LT, this has not been the trend seen at UNMC. At this institution, the classical technique continues to be routinely used, though a decline in the use of VVB has also occurred at this institution with a transition to selective use of VVB during LT rather than routine use. VVB during LT was much more utilized in 2001 and 2002. Approximately 40% of the cases in the 19-year period of review were from those two years alone with dramatic decline following in the years after, with a steady trend in 2010 to current of approximately 4 cases per year, the period utilized for detailed chart review and analysis. While this changing trend was not due to a change in technique, it is not clear what drove this change. A likely cause for fewer cases requiring VVB during LT is the utilization of dedicated transplant anesthesia team members and expertise specific to transplant in the management and support of these patients such that they are

hemodynamically stable during the anhepatic phase of the procedure. UNMC remains a high-volume transplant center with dedicated transplant surgical teams as well as anesthesia teams and maintains one of the few fellowship training programs dedicated to transplant anesthesiology in the United States.

As with any study involving an event of rare occurrence, the limitation most pronounced is that of lack of power related to a small cohort. While the number of VVB cases done at UNMC is not insignificant, the slowing trend is such that in in the ten-year period of 2010 through 2019 where chart review is accessible in the EMR there were only 29 LT cases in which VVB was utilized, making statistical analysis challenging.

In conclusion, the pre-operative variables that were most predictive of the utilization of VVB during LT in this cohort were presence of fulminant status as this is a means for cerebral protection, known portal vein thrombosis, higher MELD, and retransplantation status. Those patients undergoing VVB during LT utilized significantly more blood product intraoperatively than those that did not undergo VVB. There were no differences in post-operative renal function markers among the two groups, but those in the VVB group did have longer ICU stays postoperatively. The most interesting of these findings is the presence of retransplantation status being largely predictive of VVB use, however, not being fully predictive as there were still 4 retransplantation patients that did not require VVB use during LT. Future directions of this study include an in-depth analysis of this smaller cohort to determine any significant differences among those who had retransplantation status to determine if any differences among this group can be found to describe the discrepancy of VVB use.

CHAPTER 4: LOCOREGIONAL THERAPY AND LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Literature Review: Transplantation for Hepatocellular Carcinoma

Resection and/or transplantation remain the only potentially curative treatment modalities for Hepatocellular Carcinoma (HCC), however, not all patients with HCC are eligible candidates for these surgical treatments. Lack of donor organs further restricts the use of transplantation as treatment for those patients that do meet listing criteria and evaluation. Thus, alternative locoregional therapies (LRT) performed by interventional radiology are commonly used exclusively in non-transplant candidates, or as bridge therapies for those candidates awaiting transplantation.

HCC has had an increasing incidence and mortality in the United States such that it is among the top indications for liver transplantation. HCC remains the most common primary tumor of the liver, is among the top five most common cancers worldwide and has been the fastest-rising cause of cancer-related deaths in the United States. This is largely related to prevalence of hepatitis C and hepatitis B virus among the population, especially in the group of males aged 55-64 years, and the risk of HCC development in the setting of these chronic infections. In addition to HCC development seen in the setting of these chronic viral infections, liver disease as a result of heavy alcohol use and nonalcoholic fatty liver disease, a newer leading cause of liver disease worldwide and within the United states, also contribute to the development of HCC.[1]

While transplantation remains the optimal curative treatment, this is a resource limited therapy option not readily available to all patients with HCC. The utilization of non-surgical treatment options in those patients who do not meet criteria for transplantation or as bridge therapies while awaiting transplantation has emerged. The Milan Criteria developed in 1996 remains the dominant means of evaluation of candidacy for transplantation, dependent on tumor

burden characteristics defined as a solitary lesion no larger than 5 cm or multiple lesions no more than 3 and no larger than 3 cm to maintain low risk for recurrence and ideal post-transplantation survival. Additional expanded criteria have been developed such as the San Francisco criteria, a single lesion of no more than 6.5 cm, or multiple lesions no more than 3 and no larger than 4.5 cm individually or total of 8 cm, given the acceptable rates of 5-year survival seen in centers which choose to transplant patients who exceed the Milan Criteria.[2] For patients outside of these criteria, LRT can aid in the means of definitive treatment in unresectable candidates, down-staging to allow for transplant candidacy, or bridging to transplantation by maintain diseases status within criteria for the prevention of waitlist dropout.[3] The utilization of LRT for downstaging in patients who exceed Milan Criteria has demonstrated posttransplant survival and recurrence characteristics that are similar for those that were transplanted within Milan Criteria.[4]

The method of LRT utilized varies based upon tumor characteristic, anatomy, and practices, but the most commonly used therapies include transarterial chemoembolization, being the most commonly used, either conventional or with utilization of drug eluding beads providing higher concentrations of local chemotherapy effects, transarterial radioembolization, and radiofrequency ablation for both treatment while waiting for transplantation and downstaging efforts.[1,5] While Kulik et al reported in a review on LRT utilization prior to LT that nonsignificant trends exist for improved waitlist and posttransplant outcomes with the low quality evidence available, this remains a standard practice for patients awaiting transplant among transplant centers including our own at the University of Nebraska Medical Center (UNMC).[6] A single center review from the University of Pennsylvania showed that in the group of patients most often treated with LRT, those with expected waitlist times of greater than 6 months, the use of LRT improved survival in those that received transplant, if largest tumor was greater than 30 mm) and was significantly longer in those that did not reach transplant.[7] A multicenter study assessing bridging LRT specifically in patients within Milan Criteria, did not find a significant

difference in survival rates when assessed for comparison alone of LRT utilization or not, but rather demonstrated improved survival if those treated with LRT showed CR.[8]

While awaiting transplantation MRI imaging is the modality of follow up between LRT therapies for assessment of tumor response. As biopsy is not necessary for diagnosis of HCC or utilized regularly, pathologic response to treatments is unknown until assessed on the explanted specimen during transplantation. This allows for comparison of radiologically assessed tumor response to LRT and pathologically assessed response to LRT only in the setting of transplantation, or if resection is utilized. For patients never undergoing surgical treatments, a pathologic confirmed response is not obtained, and it is the response assessed on imaging that drives further treatment decisions. Data on the correlation of imaging-based response to LRT and pathology-based response to LRT exist but is known to not correlate accurately. Current studies have shown that poor tumor responses to these locoregional therapies indicates an increased risk for recurrence after transplant.[9] A single center review from Cleveland Clinic demonstrated concordance of imaging and pathology tumor responses in only 57% of the cases. Of those patients with discordant results, 43% of the cases, the majority of the imaging assessments underestimated tumor state (49, 89%) compared to overestimate (6, 11%).[10] While obtaining a pathologically complete response to LRT provides more favorable overall survival and recurrence free survival, Habibollahi et al demonstrated that determining CR on imaging compared to histology differ widely; in their stud of 108 patients, response was determined to be CR in 65 patients (60%) based on imaging, but was noted as pathologic CR in only 36 patients (33%).[11] The assessment of concordance in these studies alone demonstrates the notion that pretransplant imaging studies following the use of LRT for HCC tumors do not accurately represent the tumor response that is seen on final pathology after transplantation. While transplanted patients have pathology characteristics which can be predictive of survival and recurrence trends, those that do not progress to transplantation may have inaccurate representations of tumor response on imaging that do not fully correlate to their unassed tumor histology. This is similar to trends of

concordance seen in assessing pre- and post-transplant status of Milan Criteria comparing imaging and pathology, not specific to the utilization of LRT.[12,13]

Research Hypothesis and Specific Aims

In most patients, there is concordance between preoperative radiographic assessment of HCC tumor response to LRT and postoperative pathologic assessment of tumor response to LRT as evaluated on explant pathology following liver transplantation. However, there remains a group of patients with poor correlation of preoperative radiographic assessment and postoperative pathologic assessment in which there is discordance of response between the two. The research hypothesis is that concordance rates at this institution fall in line with published known rates. When analyzed separately more recent data will show higher rates of concordance than historical data. Concordance will be higher in those patients with lower time intervals from final IR treatment to transplantation. Those with discordant radiographic and pathologic responses will have higher numbers of tumors, size of tumors, and numbers of treatments. While concordance status alone may not impact survival, as pathologic response is known to have an association with poorer survival and recurrence outcomes, it would be expected that those with discordance of radiologic and pathologic responses would have poorer outcomes, specifically when a patient with radiologic complete response is found to have incomplete response on pathology.

Specific Aims:

1) To evaluate concordance rates at this single institution of HCC tumor response to locoregional therapies utilized as bridge to liver transplantation as seen on radiographic evaluation prior to transplantation versus pathologic evaluation of the explanted native liver.

2) To evaluate characteristics between concordant and non-concordant groups, as well as between radiographic and pathologic response determinations to analyze what individual characteristics and tumor characteristics may drive concordance.
3) To evaluate overall and disease-free survival with respect to concordance rates as predictors of outcomes.

Materials and Methods

Study Participants

This single center retrospective study was performed, reviewing records of patients with HCC diagnosis who received a liver transplant Aug 2016 – Feb 2019 at the University of Nebraska Medical Center (UNMC). A total of 35 patients were identified upon initial screening. All adult patients were included if liver transplantation was indicated for a diagnosis of HCC and if LRT was administered prior to transplantation during the indicated time period. Patients were excluded if LRT was not at UNMC or if the surgery during the indicated time period was a re-transplantation without current HCC tumor burden. The study was approved by the University of Nebraska Medical Center (UNMC) Institutional Review Board and was deemed minimal risk with an approved waiver of informed consent (IRB 0372-19-EP).

Data Collection

Patient demographic information as well as limited clinical data related transplantation was obtained through electronic medical record (EMR) reporting for all patients within the targeted period who had a diagnosis of HCC. Manual chart review was further completed for these patients to obtain details of pre-transplant targeted therapies and imaging obtained for post-treatment assessment. Subjective imaging reports were reviewed and assessed to determine response to LRT and were graded as either incomplete or complete response. If the imaging

report was equivocal or depicted any uncertainty of response rate it was deemed incomplete. Final pathology reports were reviewed and deemed incomplete or complete based on the presence of tumor cells as reported in the histology section. Other data obtained from chart review included meld scores at time of transplant, alpha-fetoprotein levels at the time of diagnosis and transplant, initial MRI dates, tumor characteristics at initial diagnosis/during treatment/on pathology (number, size, Milan criteria status, changes in size), LRT characteristics (number of interventions, number of tumors treated, dates of treatments, type of treatments), and details of the pathology report.

Statistical Analysis

Analysis of patient characteristics, pre-operative tumor characteristics, LRT and surgical pathology was performed utilizing Jamovi 1.0.7.0. statistical software. Continuous variables were expressed as mean ± standard error and categorical variables were presented as proportions. Correlations between demographic and clinical data of patients were assessed by independent-samples student's t test for normally distributed continuous data, or Pearson's Chi-Square test for normally distributed categorical data. Kaplan-Meier survival analysis was performed to compare between groups based on concordance status. A value of $P < .05$ was considered significant.

Results

Analysis on 30 patients, 21 of which had LRT, was conducted. Table 9 depicts patient demographics with mean age at transplant of 61.6 (±1.13), male gender in 21 of 30 patients (70.0%), demographics consistent with institutional norms with 90.0% Caucasian patients and 3.3% each representing Hispanic or Latino, Asian, or other races as indicated in the medical record. Mean MELD and MELD-Na were 15.2 (±1.13) and 16.7 (±1.49), with special exception scores being more indicative of listing status given the HCC diagnosis at a mean of 27.3 (±1.03).

Tumor characteristics per patient are indicated in Table 10 below. Patients at the time of diagnosis had an average of 1.56 (±0.172) tumors, with the largest one at a size of 25.2 mm (±2.65), and an alpha-fetoprotein level of 20.0 (±6.34). Of those with imaging available for chart review in the UNMC system at the indicated times of diagnosis and prior transplant, the majority fell within Milan criteria both at diagnosis and at time of transplant (25/27 (92.6%) and 19/21 (90.5%), respectively). At time of transplant, the mean size of the largest tumor had decreased to 20.1 mm (±3.45) and the mean alpha-fetoprotein level increased to 59.5 (±39.7) yet had a wider range of variability at time of transplant compared to time of diagnosis.

A total 67 individual tumors were identified and followed with serial imaging prior to transplant, 35 of which had LRT treatments. Of the 56 LRT treatments occurring, the majority were TACE/DEB-TACE (43, 76.8%), followed by cryoablation (6, 10.7%), ethanol injection (2, 3.6%), and yittrium-90 (1, 1.8%). Radiologic complete response (CR) was seen in 21 of the tumors (60.0%) versus non-CR in 13 (37.1%) and 1 tumor (<1%) without post-procedure imaging before the time of transplant to assess treatment response. Pathologic CR was seen in 17 of the tumors (48.6%) versus non-CR in 13 (37.1%), 1 (<1%) was not noted on the final pathology report, and 4 (11.4%) were not HCC, but were consistent with Cholangiocarcinoma. Discordant responses were seen in 7 of 30 (23.3%) patients, 3 showing Pathologic CR/Radiologic non-CR and 4 showing Radiologic CR/Pathologic non-CR, Table 11. Survival analysis was performed with no significant differences in those patients with Pathologic CR vs. non-CR (Figure 7, $P = 0.234$), Radiologic CR vs. non-CR (Figure 8, $P = 0.806$), or concordant vs. discordant CR findings (Figure 9, $P = 0.114$). Of those with discordant response, survival was favored in Pathologic CR versus Radiologic CR (Figure 10, $P = 0.025$).

Table 9: Demographics of HCC Patients Receiving LRT and LT 2016-2019

N	30
Age at Transplant	61.6 (1.13)
Gender	
Male	21 (70.0%)
Female	9 (30.0%)
Race	
Caucasian	27 (90.0%)
Other	1 (3.3%)
Hispanic or Latino	1 (3.3%)
Asian	1 (3.3%)
MELD	15.2 (1.13)
MELD-Na	16.7 (1.49)
Special Exception Score	27.3 (1.03)

Baseline demographic data of HCC patients receiving LRT and LT at UNMC from 2016 to 2019. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages

Table 10: Tumor Characteristics

Total Number of Tumors at Diagnosis	1.56 (0.172)
Largest Tumor at Diagnosis (mm)	25.2 (2.65)
Largest Tumor at Transplant (mm)	20.1 (3.45)
AFP at Diagnosis	20.0 (6.34)
AFT at Transplant	59.5 (39.7)
Beyond Milan Criteria at Diagnosis	
No	25 (92.6%)
Yes	2 (7.4%)
Beyond Milan Criteria at Transplant	
No	19 (90.5%)
Yes	2 (9.5%)

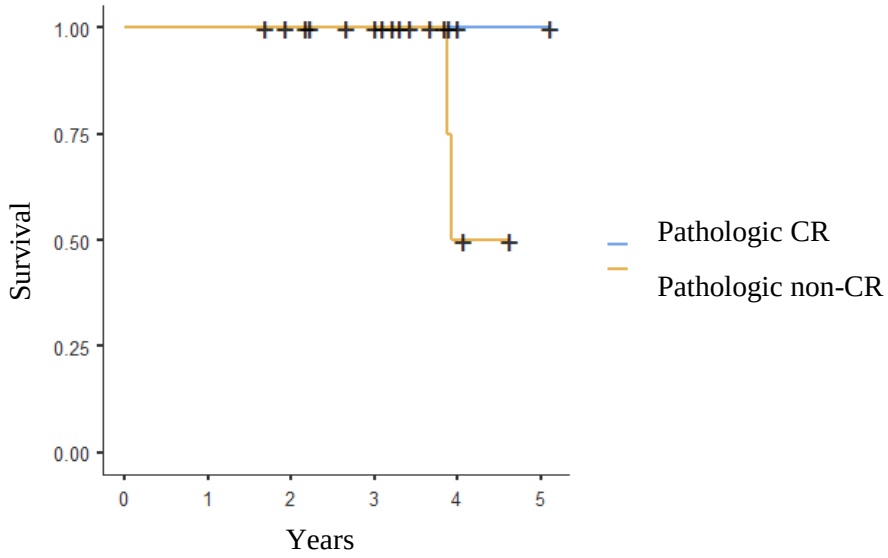
Characteristics of tumor data obtained for each patient with HCC receiving LRT and LT at UNMC from 2016 to 2019. Continuous data is reported as mean (±SE). Categorical counts are given with group percentages

Table 11: Tumor Response to Pre-Transplant LRT

	Pathologic Response		
Radiologic Response	**Complete**	**Incomplete**	**Total**
Incomplete	3	9	12
Complete	14	4	18
Total	17	13	30

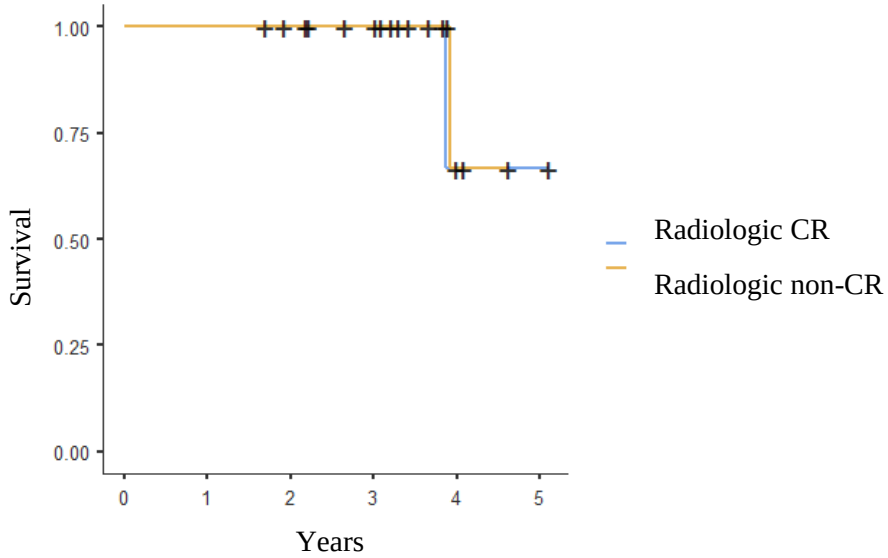
Chi Square analysis of radiologic interpretation of tumor response to LRT on pre-transplant imaging compared to pathologic interpretation of tumor response to LRT on post-transplant explanted liver specimen. $P = 0.004$

Figure 7: Survival Among Pathologic Response to LRT



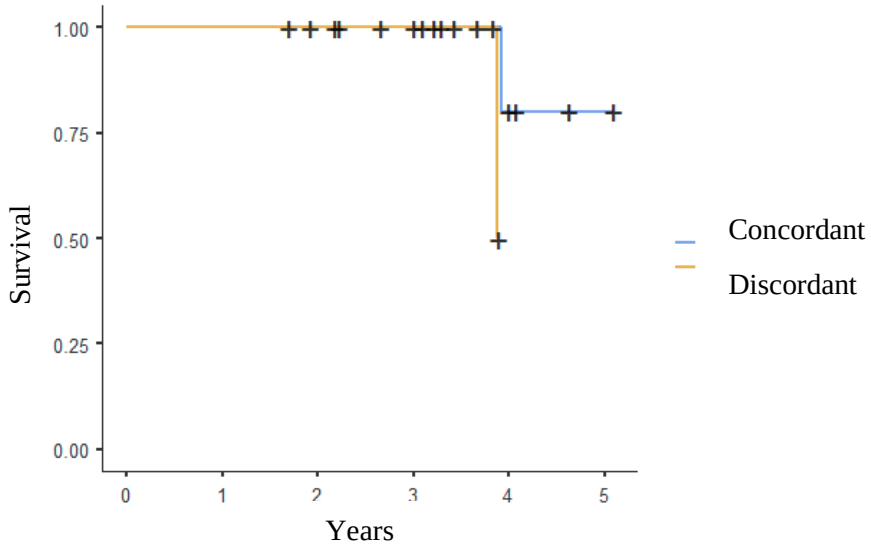
Overall survival curves among those with difference in pathologic interpretation of response to LRT prior to LT, complete response (CR) versus non-complete Response (non-CR). P = 0.234

Figure 8: Survival Among Radiologic Response to LRT



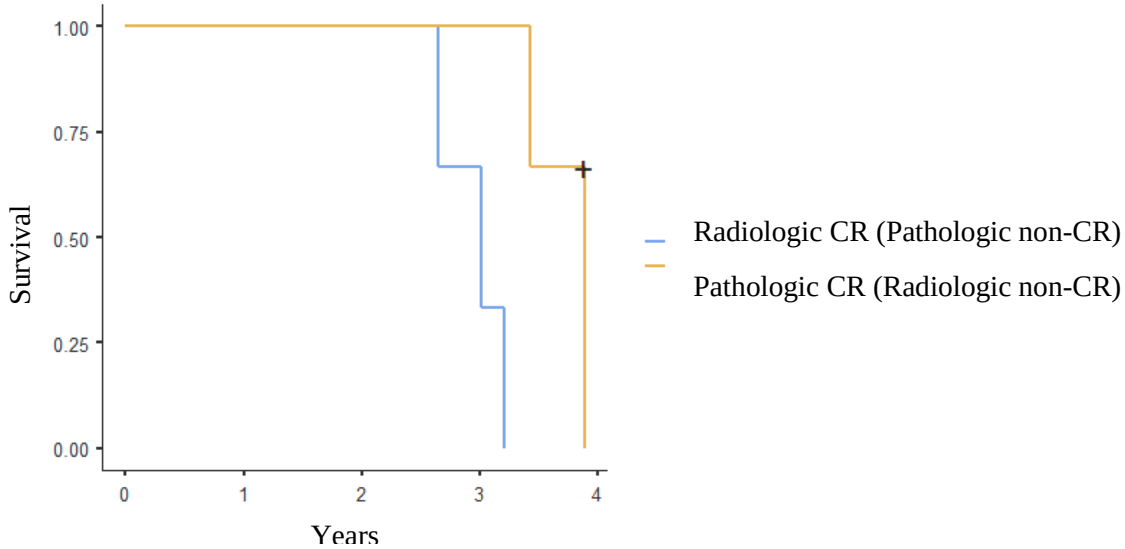
Overall survival curves among those with difference in radiologic interpretation of response to LRT prior to LT, complete response (CR) versus non-complete Response (non-CR). P = 0.806

Figure 9: Survival Among Concordance of Radiologic vs. Pathologic Response to LRT



Overall survival curves among those with difference in interpretation of tumor response to LRT prior to LT based on interpretation of pre-transplant radiologic assessment versus post-transplant pathologic assessment. P = 0.114

Figure 10: Survival of Discordant Assessments Among Radiologic Complete Response (Pathologic Non-CR) vs. Pathologic Complete Response (Radiologic non-CR)



Overall survival curves among those with discordant assessments based upon complete responses reported either by pathologic assessment or radiologic assessment. P = 0.025

Discussion

Radiologic evaluation after LRT for HCC remains a standard post-procedural tool for determining tumor response and dictating further treatment plans, however, is known to be imperfect in determining true tumor response as seen on pathologic evaluation, as demonstrated in this retrospective study with discordance amongst radiologic versus pathologic treatment response at a rate of 23.3%. Our concordance rate in this small sample of only 3 years appears higher than other single institution studies reporting concordance in the range of 50-60%.

Future aims for this ongoing project include further addition of data retrospectively prior to 2016 and detailed analysis to differentiate concordance rates based upon characteristics of tumor size and number, alpha-fetoprotein levels, LRT intervention types, frequency, and time variations from diagnosis to LRT to transplant. Additional expansion of a larger data set can allow for more robust analysis of survival with regards to groups differing with regards to each of these characteristics.

A more important analysis would include determining withing this group a subset of those patients who have recurrence to analyze for factors that contribute to recurrence in those individuals. While there is no clear associate of differences in outcomes based upon discordant interpretation of response to LRT either by preoperative imaging or postoperative pathology, clearly a benefit exists in those individuals who exhibit complete response on pathologic analysis of explanted liver specimen.

CHAPTER 5: CONCLUSION

In conclusion, while transplantation surgery has evolved greatly over recent decades, through advanced made possible through dedicated research and persistence, it is still a relatively new field of surgery with potential for continued improvements. Much of what is managed in the field within the realm of the technical procedures themselves, the immunosuppression management, and the medical co-management of the multitude of complications which can arise given the complex disease processes and immunosuppression risk is well established. However, there remains much to be understood about influencing factors not only prior to transplant but based upon decision making intraoperatively and how those factors impact outcomes from both a clinical standpoint regarding survival but also quality of life.

These three projects showcase how outcomes research, while different from the early research which began the field in that it does not necessarily influence groundbreaking clinical management changes, can provide a means for furthering our understanding of just how much each small factor plays into the overall picture of transplantation. It is a field that has grown tremendously in a relatively small amount of time creating a significant volume of patients who are either living post-transplant or awaiting transplant and remain in the medical community cared for by not only providers within the field but of all areas. This alone drives the need for continued consideration of how these patients are managed in order to continue to improve outcomes going forward, either preoperatively to ensure judicious selection and use of limited resources or intraoperatively to drive survival outcomes higher. It also drives the need, due to the improvement of patient and graft survival in recent decades, to consider all measurable areas of outcomes after transplantation such as function or quality of life in order to really understand the impact of transplantation and its true benefit in the long-term for the patient.

For me personally, these projects highlight the consideration required in approaching a career in transplantation surgery. As a trainee, the focus remains for many years in the simple

pursuit of the knowledge and technical skills required to complete the surgical tasks at hand, however, the larger picture requires thoughtful evaluation of each decision along the way prior to the operating room to really ensure that the best choices are being made for the patient in all aspects of their care. Each of these decisions plays a role in not only the outcome of the patient with regards to graft survival, patient survival, disease-free survival, but also their quality of life. These projects have provided me with a larger understanding of the overall process of transplant and evaluation of outcomes, much more than can be gathered among surgical training alone.

BIBLIOGRAPHY

CHAPTER 1: INTRODUCTION

1. Sayegh MH, Carpenter CB. Transplantation 50 Years Later — Progress, Challenges, and Promises. *N Engl J Med*. 2004;351(26):2761-2766. doi:10.1056/nejmon043418

2. Song ATW, Avelino-Silva VI, Pecora RAA, Pugliese V, D'Albuquerque LAC, Abdala E. Liver transplantation: Fifty years of experience. *World J Gastroenterol*. 2014;20(18):5363-5374. doi:10.3748/wjg.v20.i18.5363

3. Russell N. Intestinal and multivisceral transplantation. *Surg (United Kingdom)*. 2020;38(7):411-417. doi:10.1016/j.mpsur.2020.05.003

4. Grant D, Wall W, Mimeault R, et al. Successful small-bowel/liver transplantation. *Lancet*. 1990;335(8683):181-184. doi:10.1016/0140-6736(90)90275-A

5. Rutkow I. The Rise of Modern Surgery: An Overview. In: Townsend Jr. CM, Beauchamp DR, Evers MB, Mattox KL, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 20th ed. Elsevier; 2017:1-19.

6. Kwong A, Kim WR, Lake JR, et al. OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant*. 2020;20(s1):193-299. doi:10.1111/ajt.15674

7. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Kidney. *Am J Transplant*. 2020;20(s1):20-130. doi:10.1111/ajt.15672

8. Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant*. 2020;20(s1):300-339. doi:10.1111/ajt.15675

CHAPTER 2: LONG TERM QUALITY OF LIFE OUTCOMES IN INTESTINAL TRANSPLANTATION

1. Mezoff EA, Minneci PC, Dienhart MC. Intestinal Failure: A Description of the Problem and Recent Therapeutic Advances. Clin Perinatol. 2020;47(2):323-340. doi:10.1016/j.clp.2020.02.008

2. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal transplant registry report: Global activity and trends. Am J Transplant. 2015;15(1):210-219. doi:10.1111/ajt.12979

3. Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. Am J Transplant. 2020;20(s1):300-339. doi:10.1111/ajt.15675

4. Jo SYC, McCallum Z, Shalley H, et al. Outcomes of Children with Chronic Intestinal Failure: Experience over 2 Decades at a Tertiary Paediatric Hospital. J Pediatr Gastroenterol Nutr. 2019;69(3):e79-e87. doi:10.1097/MPG.0000000000002384

5. Diamanti A, Basso MS, Castro M, et al. Irreversible intestinal failure: Prevalence and prognostic factors. J Pediatr Gastroenterol Nutr. 2008;47(4):450-457. doi:10.1097/mpg.0b013e31817af979

6. Fullerton BS, Sparks EA, Hall AM, Duggan C, Jaksic T, Modi BP. Enteral autonomy, cirrhosis, and long term transplant-free survival in pediatric intestinal failure patients. J Pediatr Surg. 2016;51(1):96-100. doi:10.1016/j.jpedsurg.2015.10.027

7. Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: Initial report from the pediatric intestinal failure consortium. J Pediatr. 2012;161(4):723-728.e2. doi:10.1016/j.jpeds.2012.03.062

8. Venick RS, Duggan E, Whatley J. Current status of pediatric intestinal transplantation in the United States. Curr Opin Organ Transplant. 2020;25(2):201-207. doi:10.1097/MOT.0000000000000744

9. Courbage S, Canioni D, Talbotec C, et al. Beyond 10 years, with or without an intestinal graft: Present and future? Am J Transplant. 2020;20(10):2802-2812. doi:10.1111/ajt.15899

10. Ceulemans LJ, Lomme C, Pirenne J, De Geest S. Systematic literature review on self-reported quality of life in adult intestinal transplantation. Transplant Rev. 2016;30(2):109-118. doi:10.1016/j.trre.2016.02.004

11. Sudan D, Horslen S, Botha J, et al. Quality of Life after Pediatric Intestinal Transplantation: The Perception of Pediatric Recipients and Their Parents. Am J Transplant. 2004;4(3):407-413. doi:10.1111/j.1600-6143.2004.00330.x

12. D.L. Sudan, A. Iverson, R.A. Weseman, S. Kaufman, S. Horslen, I.J. Fox, B.W. Shaw Jr and ANL. Assessment of Function, Growth and Development, and Long-Term Quality of Life After Small Bowel Transplantation. Transplant Proc. 2000;32(6):1211-1212. doi:10.1016/s0041-1345(00)01190-8

13. Ngo KD, Farmer DG, McDiarmid S V., et al. Pediatric health-related quality of life after intestinal transplantation. Pediatr Transplant. 2011;15(8):849-854. doi:10.1111/j.1399-3046.2011.01590.x

14. Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012;256(3):494-508. doi:10.1097/SLA.0b013e318265f310

15. Andres AM, Alameda A, Mayoral O, et al. Health-related quality of life in pediatric intestinal transplantation. Pediatr Transplant. 2014;18(7):746-756. doi:10.1111/petr.12348

16. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Kidney. Am J Transplant. 2020;20(s1):20-130. doi:10.1111/ajt.15672

17. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I.

Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. doi:10.1097/00005650-199206000-00002

CHAPTER 3: VENOVENOUS BYPASS IN LIVER TRANSPLANTATION

1. Shaw BW, Martin DJ, Marquez JM, et al. Advantages of venous bypass during orthotopic transplantation of the liver. *Semin Liver Dis*. 1985;5(4):344-348. doi:10.1055/s-2008-1040631

2. Fonouni H, Mehrabi A, Soleimani M, Muller SA, Büchler MW, Schmidt J. The need for venovenous bypass in liver transplantation. *Hpb*. 2008;10(3):196-203. doi:10.1080/13651820801953031

3. Shaw BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. *Ann Surg*. 1984;200(4):524-534. doi:10.1097/00000658-198410000-00013

4. Chari RS, Gan TJ, Robertson KM, et al. Venovenous bypass in adult orthotopic liver transplantation: Routine or selective use? *J Am Coll Surg*. 1998;186(6):683-690. doi:10.1016/S1072-7515(98)00101-X

5. Barbas AS, Levy J, Mulvihill MS, et al. Liver transplantation without venovenous bypass: Does surgical approach matter? *Transplant Direct*. 2018;4(5):1-6. doi:10.1097/TXD.0000000000000776

6. Reddy K, Mallett S, Peachey T. Venovenous bypass in orthotopic liver transplantation: Time for a rethink? *Liver Transplant*. 2005;11(7):741-749. doi:10.1002/lt.20482

7. Sakai T, Gligor S, Diulus J, McAffee R, Wallis Marsh J, Planinsic RM. Insertion and management of percutaneous veno-venous bypass cannula for liver transplantation: A reference for transplant anesthesiologists. *Clin Transplant*. 2010;24(5):585-591. doi:10.1111/j.1399-0012.2009.01145.x

8. Lapisatepun W, Lapisatepun W, Agopian V, Xia VW. Venovenous Bypass During Liver Transplantation: A New Look at an Old Technique. *Transplant Proc*. 2020;52(3):905-909. doi:10.1016/j.transproceed.2020.01.048

9. Sakai T, Planinsic RM, Hilmi IA, Marsh JW. Complications Associated With Percutaneous Placement of Venous Return Cannula for Venovenous Bypass in Adult Orthotopic Liver Transplantation. *Liver Transplant*. 2007;13(5):961-965. doi:10.1002/lt.21072

10. Feltracco P, Barbieri S, Cillo U, Zanus G, Senzolo M, Ori C. Perioperative thrombotic complications in liver transplantation. *World J Gastroenterol*. 2015;21(26):8004-8013. doi:10.3748/wjg.v21.i26.8004

11. Markin NW, Ringenberg KJ, Kassel CA, Walcutt CR, Chacon MM. 2018 Clinical Update in Liver Transplantation. *J Cardiothorac Vasc Anesth*. 2019;33(12):3239-3248. doi:10.1053/j.jvca.2019.02.004

12. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron - Clin Pract*. 2012;120(4):179-184. doi:10.1159/000339789

CHAPTER 4: LOCOREGIONAL THERAPY AND LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

1. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology*. 2019;156(2):477-491.e1. doi:10.1053/j.gastro.2018.08.065

2. Yao FY. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. *Hepatol Res*. 2007;37(s2 Fourth JSH S):S267-S274. doi:10.1111/j.1872-034X.2007.00195.x

3. Mazzaferro V, Regalia E, Doci R, et al. Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. *N Engl J Med*. 1996;334(11):693-700. doi:10.1056/NEJM199603143341104

4. Affonso BB, Galastri FL, Filho JM da ML, et al. Long-term outcomes of hepatocellular carcinoma that underwent chemoembolization for bridging or downstaging. *World J Gastroenterol*. 2019;25(37):5687-5701. doi:10.3748/wjg.v25.i37.5687

5. Song JE, Kim DY. Conventional vs drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma. *World J Hepatol*. 2017;9(18):808-814. doi:10.4254/wjh.v9.i18.808

6. Kulik L, Heimbach JK, Zaiem F, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology*. 2018;67(1):381-400. doi:10.1002/hep.29485

7. Habibollahi P, Hunt S, Gade T, et al. The Impact of Bridging LRT on Survival in Patients Listed for Liver Transplantation. *Cardiovasc Intervent Radiol*. 2018;41(1):112-119. doi:10.1007/s00270-017-1759-1

8. Agopian VG, Harlander-Locke MP, Ruiz RM, et al. Impact of Pretransplant Bridging

Locoregional Therapy for Patients with Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients from the US Multicenter HCC Transplant Consortium. *Ann Surg*. 2017;266(3):525-535. doi:10.1097/SLA.0000000000002381

9. Sandow T, Pavlus J, Field D, et al. Bridging Hepatocellular Carcinoma to Transplant: Transarterial Chemoembolization Response, Tumor Biology, and Recurrence after Transplantation in a 12-Year Transplant Cohort. *J Vasc Interv Radiol*. 2019;30(7):995-1003. doi:10.1016/j.jvir.2018.12.736

10. El-Gazzaz G, Sourianarayanane A, Menon KN, et al. Radiologic-histological correlation of hepatocellular carcinoma treated via pre-liver transplant locoregional therapies. *Hepatobiliary Pancreat Dis Int*. 2013;12(1):34-41. doi:10.1016/S1499-3872(13)60003-X

11. Habibollahi P, Shamchi SP, Choi JM, et al. Association of Complete Radiologic and Pathologic Response following Locoregional Therapy before Liver Transplantation with Long-Term Outcomes of Hepatocellular Carcinoma: A Retrospective Study. *J Vasc Interv Radiol*. 2019;30(3):323-329. doi:10.1016/j.jvir.2018.11.037

12. Ecker BL, Hoteit MA, Forde KA, et al. Patterns of discordance between pretransplant imaging stage of hepatocellular carcinoma and posttransplant pathologic stage: A contemporary appraisal of the milan criteria. *Transplantation*. 2018;102(4):648-655. doi:10.1097/TP.0000000000002056

13. Grąt K, Grąt M, Rowiński O, Patkowski W, Zieniewicz K, Pacho R. Accuracy of Computed Tomography in the Assessment of Milan Criteria in Liver Transplantation for Hepatocellular Carcinoma. *Transplant Proc*. 2018;50(7):2002-2005. doi:10.1016/j.transproceed.2018.02.145

APPENDIX A: IRB # 628-20-EP LONG-TERM QUALITY OF LIFE OUTCOMES IN PATIENTS UNDERGOING INTESTINAL REHABILITATION AND/OR TRANSPLANT

Social/Behavioral
SECTION I

Therapeutic/Non-Therapeutic
Does your research involve a drug, medical device, technique or other intervention or strategy (including means like diet, cognitive therapy, behavioral therapy, exercise) to diagnose, treat or prevent a particular condition or disease: "THERAPEUTIC RESEARCH"?
No

1. Title of Protocol:
Long Term Quality of Life Outcomes in Patients Undergoing Intestinal Rehabilitation and/or Transplant

2. Responsible Personnel:
A. Principal Investigator (PI):
Merani, Shaheed - Surgery-Transplant - 402-559-6771 - shaheed.merani@unmc.edu - alt #: 402-559-8501 - degree: MD - address: MSB 4507 UNMC Midtown (Zip 3285) - phone: 9-6771

B. Secondary Investigator (SI):
Bilyeu, Camden Vanderhoof - Surgery-Transplant - 402-559-6771 - camden.bilyeu@unmc.edu - alt #: 402-559-6955 - degree: BS - address: MSB 4515 UNMC Midtown (Zip 3285) - phone: 9-6771

Brown, Cindy Ross - Dept Of Sur Tx Home - 402-559-6776 - cbrown@nebraskamed.com - alt #: 402-559-6776 - degree: APRN - address: Medical Sciences Bui (Zip 68105) - phone: 402-559-6776

Glas, Jessica Ashley - Student - Medicine - 630-806-5409 - jessica.glas@unmc.edu - alt #: 630-806-5409 - degree: BS - address: - phone:

Hargrove, Amy J - Surgery-House Officers - 402-559-5510 - amy.hargrove@unmc.edu - alt #: 402-559-8501 - degree: MD - address: MSB 4538 UNMC Midtown (Zip 3280) - phone: 9-5510

Kaiser, Melanie Anne - Surgery-Transplant - 402-559-6170 - melanie.kaiser@unmc.edu - alt #: 402-559-8501 - degree: N/A - address: MSB 4507 (Zip 3285) - phone: 402-559-6170

C. Participating Personnel:

D. Lead Coordinator:

E. Coordinator(s):

F. Data/Administrative Personnel:
Povondra, Jill M - Surgery-Transplant - 402-559-2556 - jill.povondra@unmc.edu - alt #: 402-559-2556 - degree: N/A - address: MSB 4510 UNMC Midtown (Zip 3285) - phone: 9-2556

G. Are you a student or house officer?
No

3. Funding Source:
Check all that apply and provide the source of the funding.
Cooperative Group:
Center for Clinical and Translational Research (CCTR)
Federal (e.g., NIH) Grant - Provide source:
Other Grant:
Departmental funding
Commercial - Provide company name:
Department of Defense
♦ Other - Provide source (e.g. personal funding): No funding. Research performed under PI academic appointment.

4. Deadline for IRB Approval:
Yes - Explain and provide date:
♦ No

5. Contract:
Is there a contract associated with this study?
No

6. Agreements
Is there a Material Transfer Agreement (MTA) associated with this study?
No

Is there a Data Use Agreement (DUA) associated with this study?
No

Is there a Data Transfer Agreement (DTA) associated with this study?
No

7. Study Sites:
A. Provide the names and locations of all study sites where this research will be conducted under the oversight of the UNMC IRB or Joint Pediatric IRB.
UNMC

B. Will the research be conducted at external sites under the oversight of an external IRB?
No

C. Does UNMC, TNMC, CHMC or UNO serve as the lead site with responsibility for data and/or safety monitoring?
No

D. Does this study involve any international sites where the PI will either; 1) conduct 2) supervise or 3) receive / ship HBM or data to / from UNMC?
No

E. Does this study involve face to face contact with subjects?
No

8. Principal Investigator Assurance
The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study:
I certify that:

- **I have carefully reviewed this application and all supporting documents. I have determined that the application is accurate, complete and ready for submission to the IRB.**
- **I, and all listed research personnel, have the necessary qualifications, expertise, and hospital credentials to conduct this study in a manner which fully protects the rights and welfare of research subjects.**
- **There are, or will be, adequate resources and facilities to safely initiate, carry out and complete this research at the study sites specified in Section I.7. This includes sufficient staff, funding, space, record keeping capability, and**

resources necessary to address adverse events and any unanticipated problems involving risk to the subject or others. If the necessary resources become unavailable I will promptly notify the IRB.

- All listed research personnel, including external investigators, will be given a copy of the final IRB approved application and any other relevant study-related documents in accordance with their defined responsibilities.
- All listed research personnel, including external investigators, will be notified promptly of any changes in protocol, in accordance with their defined responsibilities.
- Research personnel, including data and administrative personnel who have access to protected health information (PHI) or subject identifiers will have adequate training in confidentiality and protection of PHI.
- The minimum amount of protected health information (PHI) or other identifiers necessary will be used and disclosed to conduct this research study (if applicable). I will implement reasonable safeguards to protect the PHI/identifiers at all times.
- I and all other personnel listed in Section I.3A-E of the IRB Application have disclosed all potential financial conflicts of interest as required and are in full compliance with the UNMC Conflict of Interest Policy #8010 and HRPP Policy. I further certify that all potential financial conflicts of interest are appropriately managed in order to ensure protection of the rights and welfare of subjects.

I recognize that:

- As the PI it is my responsibility to ensure that this research and the actions of all research personnel involved in conducting the study will comply fully with the IRB-approved protocol (including all amendments), all applicable federal regulations, state laws, and HRPP policies.
- It is my responsibility to ensure that valid informed consent/assent will be obtained, as appropriate, from all research subjects or their legally authorized representative(LARs).

I will:

- Ensure that all research personnel involved in the process of consent/assent are properly trained and are fully aware of their responsibilities relative to the obtainment of informed consent/assent according to federal regulations, state laws, and HRPP policies.
- Promptly inform the IRB of internal adverse events, as well as any unanticipated problems involving risk to the subjects or to others, as required within the time frame defined by HRPP policies. I will analyze each internal adverse event/reported problem to determine if it impacts the risk-benefit relationship of the study, the safety of the subjects, or informed consent.
- Analyze each MedWatch/safety report to determine if it impacts the risk/benefit

relationship of the study, the safety of the subjects, or informed consent.
- Promptly submit external adverse event reports in accordance with HRPP policies.
- Promptly inform the IRB if I become aware of 1) any complaints from research subjects, LARs, or others about research participation, 2) violations of federal regulations or state law, 3) violations of the HIPAA Rule, or 4) violations of HRPP policies.
- Promptly inform the IRB of the results of external audits performed by sponsors, Contract Review Organizations (CROs), cooperative groups, FDA, or other external groups.
- Not initiate any change in protocol without IRB approval except when it is necessary to reduce or eliminate a risk to the subject, in which case the IRB will be notified as soon as possible.
- Promptly inform the IRB of any significant negative change in the risk/benefit relationship of the research as originally presented in the protocol and approved by the IRB.
- Maintain all required research records on file and I recognize that representatives from the IRB, OHRP, HHS, FDA, and other Federal Departments or Agencies may inspect these records in accordance with granted authority.

I understand that:
- Continuing review by the IRB is required at least annually, or as per Federal Regulations and HRPP Policy, in order to maintain approval status. I will maintain IRB approval as long as this study is active.
- I am responsible for appropriate research billing in accordance with UNMC Clinical Trial Professional and Technical Fee Billing Policy #8008 or applicable Children's Hospital & Medical Center policy.

Failure to comply with the Common Rule, applicable Subparts B, C, and D of HHS regulations at 45 CFR 46, applicable FDA regulations, the HIPAA Rule, applicable state law, HRPP policies, and the provisions of the IRB-approved protocol may result in suspension or termination of IRB Approval of my research project and/or other administrative or legal actions.

Merani, Shaheed - 2021-04-08 11:43:15.230

9. Principal Investigator Financial Interest Disclosure

A. As the PI, I declare:

♦ I have no financial interest in this research.

I have a financial interest in this research.

B. As the PI, I understand

♦ I must disclose any change in my financial interest during the course of this research

within five (5) business days from the time the change becomes known.

C. As the PI, I certify that:
♦ No Responsible Personnel have a financial interest in this research.
The Responsible Personnel listed below have informed me that they have a financial interest in this research.

D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed within five (5) business days from the time the change becomes known.
Merani, Shaheed - 2021-04-08 11:43:15.230

11. Scientific/Scholarly Merit and Resource Review Certification
Scientific Reviewer:
Mercer, David Wayne - Surgery - 402-559-8272 - dwmercer@unmc.edu - alt #: 402-559-4000 - degree: MD - address: MSB 4529B UNMC Midtown (Zip 3280) - phone: 9-8272

As the Scientific Reviewer,
♦ I do not have a financial conflict of interest associated with this study.
I do have a financial conflict of interest associated with this study.

My signature certifies that:

- **this application has been reviewed for scientific/scholarly merit and available resources. It has been determined that the application merits consideration by the IRB based upon the following:**
- **The proposal has an acceptable level of scientific/scholarly merit which justifies the involvement of human subjects.**
- **The proposal has a sound research design in consideration of the stated objectives,**
- **The PI has the necessary qualifications, experience and credentials to conduct this research.**
- **The PI has or will have the necessary funding to support this research**
- **There is or will be adequate physical space required for the research interventions at all study sites specified in Section I.7. In addition, there is or will be adequate laboratory and administrative support, data storage capability, and any other resources necessary to complete this research.**
- **At all study sites specified in Section I.7, there is or will be emergency**

equipment, personnel, or services necessary to respond promptly to adverse events or unanticipated problems involving risk to the subject or others.
- I will promptly notify the IRB if the necessary resources to support this research become unavailable.

Mercer, David Wayne - 2020-08-17 13:03:00.000

SECTION II

PROTOCOL ABSTRACT

1. Provide a brief (less than 2500 characters) abstract of the research protocol. (2500 characters)
This summary should include: 1)) a brief description of the purpose of the study, 2) eligibility criteria, 3) interventions and evaluations and 4) follow-up.
Intestinal transplantation is a well established therapy for individuals who remain dependent on parenteral nutrition due to intestinal failure, however, there is little data related to long term outcomes especially with regards to quality of life. Through a retrospective review of intestinal transplant and/or rehabilitation patients over the last 30 years who are now adults (age 19 years and over), we propose to capture outcomes data including quality of life. This one time survey will be conducted via phone interview, primarily utilizing the Rand 36-Item Health Survey (SF-36) with the addition of transplant and rehabilitation specific questions. Additionally a medical records review will be conducted to capture clinical data pertaining to each patient. For this study we will also obtain the same quality of life survey data for similar aged adults who were transplanted at UNMC with other solid organs (kidney, liver) as children; this group will be utilized as a control group to compare to intestinal transplant/rehabilitation patients.

PURPOSE OF THE STUDY AND BACKGROUND

2. Purpose of the Study
What are the specific scientific objectives of the research?
Aim 1: Collect long term outcomes data for intestinal transplant patients at UNMC, who are now adults, including quality of life measures.

Aim 2: Collect and compare long term outcomes data for adult intestinal rehabilitation patients at UNMC who have not undergone transplantation to evaluate for differences in these two cohorts.

Aim 3: Collect and compare long term outcomes data for adult kidney and liver transplant patients at UNMC to utilize as a control group to compare to intestinal patients.

3. Background and Rationale
Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill.
Intestinal transplantation is a well established therapy for individuals who remain dependent on parenteral nutrition due to intestinal failure, however, there is little data related to long

term outcomes especially with regards to quality of life. Much of the published data on quality of life outcomes for these patients is relatively short term, usually within 5 years. Through a retrospective review of intestinal transplant and/or rehabilitation patients over the last 30 years who are now adults (age 19 years and over), we propose to capture long term outcomes data including quality of life. This one time survey will be conducted via phone interview, primarily utilizing the Rand 36-Item Health Survey (SF-36) with the addition of transplant and rehabilitation specific questions. Additionally a medical records review will be conducted to capture clinical data pertaining to each patient, to gain further knowledge of trends in these patients in the long term following their transplantation or continued need for rehabilitation program if they do not receive or are not eligible for transplantation.

CHARACTERISTICS OF THE SUBJECT POPULATION

4. Accrual
A. Is this study conducted solely at sites under the oversight of the UNMC IRB (e.g. UNMC, Nebraska Medicine, CHMC, UNO)?
Yes

1. How many subjects will need to be consented (per group, as applicable) in order to achieve the scientific objectives of the research?
A preliminary review of historical intestinal transplant data utilizing the OTTR transplant database at UNMC indicated that there were 54 individuals who received intestinal transplants who are currently adults who would be eligible to be included in the study to assess their long term outcomes and quality of life following transplantation.

A preliminary review of similar aged kidney and liver transplant patients to be utilized as a control group indicates potentially an additional 44 and 140 patients, respectively.

Following IRB approval of these groups, reports generated in the Epic medical records system with these inclusion criteria were able to capture more patients than initially anticipated. These reports indicate the final numbers in these groups meeting eligibility who will be invited to participate in the study are 69 patients in the intestine transplant group, 158 isolated liver transplant patients and 111 isolated kidney transplant patients for the two control groups.

2. What is the statistical or other justification for the total number of subjects described above?
The inclusion of subjects in this quality of life study is based upon the number of subjects who were patients at UNMC beginning in 1990 who received and have survived intestinal transplantation during childhood and who are now of adult age. Additionally, those who

survived kidney and liver transplants during the same time period as children who are now of adult age will also be included as control group subjects. The liver and kidney groups will be utilized as a control population for the study population of intestinal transplant patients. Statistical analysis plans ideally include a 1:1 match conducted based on age at transplant, sex, and current age. The larger number within the control groups is needed to ensure the best possible match after initial chart review for quality of study purposes. Not all of these control group patients may be contacted for inclusion into the study once matching has concluded.

5. Gender of the Subjects
A. Are there any enrollment restrictions based on gender?
No

6. Age Range of Subjects
A. Will adults be enrolled ?
Yes

1. What is the age range of the adult subjects?
Age 19 or greater

2. What is the rationale for selecting this age range?
Adult Patients Only

B. Will children (18 years of age or younger) be included in this research?
No

1. What is the justification for excluding children from participating in this research?
Research is irrelevant to children (e.g. disease or condition rarely encountered in children).
Knowledge being sought in the research is already available for children or will be obtained from another ongoing study.
♦ A separate study in children is warranted and preferable.
Insufficient data are available in adults to judge the potential risk in children.
♦ Other. Explain. As this study will evaluate long term outcomes, the majority of patients meeting inclusion criteria will be of adult age.

7. Race and Ethnicity
Are there any subject enrollment restrictions based upon race or ethnic origin?
No

8. Vulnerable Subjects
A. Will prisoners be included in the research?
No

B. Select from the list all of the vulnerable populations that will specifically be recruited to participate in this research.
Decisionally-impaired persons
Critically ill patients
Students of the investigator
Employees of the investigator
Educationally disadvantaged individuals
Socially or economically disadvantaged individuals
Individuals with a stigmatizing illness or condition
Individuals from a marginalized social or ethnic group
Other.
♦ No vulnerable subjects will be specifically recruited

9. Inclusion Criteria
What are the specific inclusion criteria?
Surviving adult patients who formerly underwent intestinal transplant or intestinal rehabilitation, kidney transplant, or liver transplant at University of Nebraska Medical Center within the last 30 years.

10. Exclusion Criteria
What are the specific exclusion criteria?
Patients will be excluded from study if without capacity for 1. providing consent to participate and 2. participating in telephone survey.

11. Pregnancy and Contraception Requirements
A. Are women of child bearing potential (WOCBP) included in this research?
Yes

a. Are there any specific contraception requirements for subjects?
No

1. Provide justification for absence of contraception requirements
♦ There are no interventions that are likely to be of risk to a fetus
Investigational drug(s) is (are) not systemically absorbed
Investigational drug(s) is (are) systemically absorbed, but there is no evidence from human

studies, or from clinical experience, that there is risk to a fetus
Other

B. Are pregnant women included in this research?
Yes

C. Are breast feeding women included in this research?
Yes

Provide justification
There are no interventions that are likely to be of risk to a fetus or child of breast feeding women, intervention includes quality of life survey only via telephone.

METHODS AND PROCEDURES (NON-THERAPEUTIC)

12. Methods and Procedures Applied to Human Subjects
A. Describe the research plan, including all procedures, interventions, evaluations and tests. If subjects will be randomized to a specific intervention, the randomization plan should be explained.
Study participants will be screened based on criteria of all current adult patients who received intestinal transplantation as children at UNMC beginning in 1990 in order to obtain quality of life data for these long term survivors of intestinal transplantation. Additionally adult patients in the intestinal rehabilitation program at UNMC, who may not have yet received or may not be eligible for intestinal transplant will be included to obtain similar quality of life data for these rehabilitation patients not undergoing transplantation. Other control groups will include adult patients who underwent liver and kidney transplantation as children at UNMC beginning in 1990. These patients will be initially contacted to gauge interest in participating in the study which would include a brief telephone interview assessing quality of life measures by utilizing the RAND 36-item health survey and additional intestinal specific questions formulated by our team. The approximate time for conducting the survey of 36 RAND questions in addition to 16 intestine specific questions including instructions is 20 minutes. After obtaining consent the subjects may schedule to complete the telephone interview at their convenience with research personnel involved in this study. Additionally a medical records review will be conducted utilizing UNMC electronic medical records systems to obtain clinical data on those participating patients, including laboratory values, immunosuppression regimens, occurrences of rejection, hospitalizations or treatments related to surgical or immunosuppression complications.

B. Are all of the procedures, interventions, evaluations and tests being performed solely for research purposes?

Yes

C. Describe briefly the statistical methods used to analyze the data (or reference the appropriate section of the detailed protocol or grant).
Statistical analysis of the quality of life survey results as well as data obtained from medical record review will utilize descriptive statistics including mean/standard deviation, and proportions for categorical variables. Between the different transplant groups and between intestinal transplant and rehabilitation groups, comparison will be assessed utilizing independent t- or chi square testing.

D. Does this study involve the collection of blood, urine, saliva or other human biological material (HBM)?
No

DRUGS, BIOLOGIC DRUGS AND DEVICES

13. Drugs and Biologic Drugs
1. Does this research involve the use of drugs or biologics?
No

14. Devices
1. Does this research involve a medical device(s)?
No

CONFIDENTIALITY AND PRIVACY

15. Confidentiality and Privacy
A. Describe where research data will be stored. Check all that apply.
On a secure server at UNMC, CHMC, Nebraska Medicine, and/or UNO (including REDCap)
♦ On a secure cloud server - Specify the secured cloud serve: UNMC Office 365
On a firewall protected database accessible through the internet - Specify who has administrative responsibility for maintenance of the server:
On an encrypted, password protected local hard drive
On an encrypted, password protected portable computer
On an encrypted, password protected flash drive
In hard copy
Other

B. Will any of the following subject identifiers be recorded (at any time) in association with the research data?
Yes

1) Indicate the subject identifiers that will be recorded. Check all that apply.
♦ Name
♦ All elements of dates (except year) related to an individual (e.g. birth, admission, discharge)
♦ Postal address information: street address, city, county, precinct, ZIP code
♦ Telephone numbers
Fax numbers
Electronic mail addresses
Social Security numbers
♦ Medical Record numbers
Health plan beneficiary numbers
Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web Universal Resource Locators (URLs) Internet Protocol (IP) address numbers
Biometric identifiers, including finger and voice print
Full face photographic images [and any comparable images]
No Identifier

2) Will a unique subject identifying number (e.g., S1, S2, S3), characteristic or code be used to link data to any of the identifiers listed above?
Yes

a. Where will the key (that links the unique subject identification code to the subject's name or other identifier) be stored?
The key that links unique subject identification code to the subject name and medical record number will be stored on a single computer at the University of Nebraska Medical Center in the Division of Transplantation on a secure UNMC owned computer in a locked office.

b. Does the code number include the subject's initials or other subject identifier as part of the code?
No

3) What is the justification for recording the specific subject identifiers listed above?

Check all that apply.
Schedule appointments
♦ Collect continuous clinical information from the medical records
♦ Follow-up with subjects
Link stored tissue with subject identification for it to be withdrawn in the future if requested
Compensation
Other. Explain.

4) How long will the subject identifiers be maintained in association with the research data?
To satisfy HRPP Policy 3.5, research records and data will be maintained for 10 years following the completion of the study.

5) How will all of the identifiable research data be destroyed (e.g., all identifiers stripped from the data and destroyed, hard copies shredded etc) when the identifiable data is no longer required?
Electronically destroyed when no longer required.

C. Will research data that contain subject identifiers be disclosed to:
Other investigators at UNMC, NM, UNO or CHMC who are not listed in Section I of this application?
No

2. Investigators outside of UNMC, NM, UNO or CHMC?
No

3. Will research data that contain subject identifiers be disclosed to any commercial sponsor or contract research organization (CRO), or to any other external organization or entity (e.g., NCI cooperative groups)?
No

D. What provisions will be in place to protect the subject's privacy? Check all that apply.
♦ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process.
Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research.
Ensuring that the research activities are performed in as private of a place as possible.
Other. Explain.

E. Does this research involve data banking at UNMC, NM, UNO or CHMC, or by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future research that is not related to this study?
No

RISK/BENEFIT ASSESSMENT

16. Potential Risks
What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility.
There is a possible risk to the subject of a loss of confidentiality if there is a breach of data on the secure UNMC server where non-anonymized data is being stored in the initial data collection phase. This will be minimized by using a UNMC owned computer which is encrypted and in a locked office in the Division of Transplantation.

17. Risk Classification
What is the overall risk classification of the research?
♦ Minimal risk
Greater than minimal risk

18. Minimization of Risk
A. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety.
Research procedure involves telephone survey only, involves minimal risk, no physical or pharmacological treatments will be conducted.

B. Describe how the data collected will be monitored to ensure the safety of subjects. Identify who will perform the ongoing data and safety analysis, and describe the frequency of data analysis. If there is an independent Data and Safety Monitoring Board (DSMB) provide the charter, or describe (1) the composition of the DSMB membership, (2) the frequency of DSMB meetings and reports.
Research procedure involves telephone survey only, involves minimal risk, no physical or pharmacological treatments will be conducted. Data collected will be stored securely using a UNMC owned computer which is encrypted and in a locked office in the Division of Transplantation.

C. Describe the auditing plan for research conducted. Identify who will conduct the audits and specify the audit frequency.

Auditing of the methods of survey completion, to include completeness and standardization, will be conducted by the investigator.

D. Describe the specific subject withdrawal criteria.
Criteria for subject withdrawal in the study are not expected as there is minimal risk to the study participants,Auditing o telephone survey only, and no physical intervention taking place.

E. Describe the stopping rules for the research (e.g., the specific criteria for halting or early termination of the study).
Criteria for halting or early termination of the study are not expected as there is minimal risk to the study participants, telephone survey only, and no physical intervention taking place.

F. Describe plans and resources available to promptly address any subject injury.
Research related injuries are not expected as there is minimal interaction with the study participants, telephone survey only.

19. Potential Benefits to the Subject
Is there the prospect for direct benefit (eg, research on diagnosis or treatment of disease)?
No

20. Potential Benefits to Society
Describe the potential benefits to society that may reasonably be expected to result from this research.
Potential benefits include expansion of knowledge of long term outcomes and quality of life measures in intestinal transplant and rehabilitation patients.

FINANCIAL OBLIGATIONS AND COMPENSATION

22. Financial Obligations of the Subject
A. Who will pay for research procedures, interventions, evaluations and tests? Check all that apply.
Sponsor
Grant
CRC, CCTR
Costs or fees waived by Nebraska Medicine, UNMC- P, CHMC or CSP
Department/Section funds
♦ Other. Explain No funding. Research performed under PI academic appointment.

B. Will any of these procedures, interventions, evaluations and tests will be charged to the Subject, the Subject's health insurance, or Medicare/Medicaid?
No

C. Are there any other financial obligations that the subject will incur as a result of participating in the study?
No

23. Compensation to the Subject for Participation
A. Will the subject receive any compensation for participation?
No

PRIOR REVIEW

24. Prior IRB Review
A. Has this study (or one substantially similar) been previously submitted to the UNMC IRB (or the Joint Pediatric IRB) and then withdrawn by the investigator for any reason?
No

B. To the best of your knowledge, has this study (or one substantially similar) been considered by another IRB and disapproved?
No

SUBJECT IDENTIFICATION & RECRUITMENT

25. Method of Subject Identification and Recruitment
A. Will prospective subjects be identified through initial contact by the investigator?
Yes

1. Identified through: Check all that apply.
Clinic
Hospital inpatient units
Previous research participants
♦ Investigator or clinic databases or registries
Hospital Opt-In Database (thru Nebraska Medicine, BMC or CHMC Conditions of Treatment)
School records
Support groups, or other Interest Groups
♦ Other. Explain. Eligible pateints will be identified through database search of piror

intestinal transplant and rehabiliatation patients at UNMC.

2. Describe how the research staff has ethical access to the potential subjects?
Research staff are employed within transplant surgery division for clinical and or research purposes. Potential subjects are those who have historical clinical encounters with surgeons who are in the division.

3. Who will initially screen potential subjects to determine eligibility?
♦ Investigator with an existing clinical relationship
Investigator with other legitimate access
Investigator whose professional responsibilities that require access to names of potential subjects
Honest broker (thru Nebraska Medicine or Bellevue Medical Center COT Opt-in database)
Research coordinator or other person without ethical access

B. Will prospective subjects make the initial contact with the research personnel to inquire about the study?
No

C. Will this study be listed in the clinical trial registry at www.clinicaltrials.gov?
No

OBTAINMENT OF INFORMED CONSENT

26. Waiver or Alteration of Informed Consent
A. Is a complete waiver or alteration of consent requested?
No

27. Waiver of Signed Consent
Is a waiver to obtain signed consent requested?
No

29. Process of Informed Consent
A. When will the prospective subject/parent(s)/guardian(s)/LAR be approached relative to their/the subject's actual participation in the study?
Initially subjects will be notified by phone of the study to seek their interest in participating in the survey. If they agree to participate, the informed consent form and a copy of "The Rights of Research Subjects" and "What Do I Need to Know?" will be provided prior to the remote consent process via their choice of mail, email, or fax.

B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration?
Informed consent will be obtained via phone at the subject's convenience after they have received the informed consent form and a copy of "The Rights of Research Subjects" and "What Do I Need to Know?" either by mail, email, or fax. This will be conducted via phone so that a discussion may occur at a time and location which is best for the subject, i.e. not while at work or school, and where privacy may be maintained. They will then be instructed to return their signed informed consent form via their choice of mail, fax, or a scanned copy via email. The form will be signed and dated by the investigator upon receipt of the document with a note added on the form which explains the lapse in time between signatures.

C. Who will be involved in the process of consent and what are their responsibilities?
Initial contact to inquire about willingness to participate in the study will be obtained by the clinical research personnel under direction of the PI, Dr. Shaheed Merani, a transplant surgeon who provides care for kidney, liver, pancreas, and intestinal transplant patients of both pediatric and adult ages. Those that will be conducting the consent and survey may include the PI or any co-PI as listed in this application. These personnel will be responsible for discussing the purpose and methods of the study with the subjects, obtaining consent, and conducting the phone interview survey utilizing the RAND 36-item health survey and the additional intestinal questionnaire. These personnel will also be conducting medical record review of each patient in the UNMC electronic medical record to obtain data regarding current clinical outcomes: TPN or tube feed dependence, complications of surgery, and/or complications of immunosuppression.

D. How much time will be allotted to the process of consent?
The allotted time for obtaining consent for this minimal risk research is estimated to take no more than one half hour time.

E. How will the process of consent be structured for subjects who are likely to be more vulnerable to coercion or undue influence?
If any vulnerable subjects are identified during the course of this study, involvement of appropriate family members or guardians will be utilized to ensure protection of subjects. Additionally as consent will be obtained via phone it will be read to all participants providing additional protection during the consent process.

F. Will non-English speaking subjects be enrolled in this research?
Yes

Describe the plan to conduct the process of informed consent in the language of the subject/parent(s)/guardian(s)/LAR
An initial query of all intestinal transplants done within the program at UNMC for this study period showed that there is only one patient who has a native language that is not English. In light of this very small number (n=1) we feel that statistically this would not provide good representation of this patient population as a subcategory and furthermore would limit confidentiality efforts if collected data in this study were easily identifiable to the one non-English speaking subject. Therefore, study participation will include only the remaining patients for which English is the native language and interpretive services and translation of documents will not be necessary.

G. How will it be determined that the subject/parent(s)/guardian(s)/LAR understood the information presented?
The personnel obtaining consent via phone will at conclusion of the informed discussion conversation ask that the subject provide a summary of their understanding of the study regarding the quality of life survey to ensure that the subject has obtained appropriate understanding of their role in the study.

30. Documentation of Informed Consent and Assent
Select who will obtain consent from the subject/parent(s)/LAR.
Bilyeu, Camden Vanderhoof

Brown, Cindy Ross

Hargrove, Amy J

Merani, Shaheed

31. Consent Forms and Study Information Sheets
Indicate the type of consent forms and study information sheets to be used in this research. Check all that apply.
♦ Adult consent form
Legally authorized representative (LAR) consent form
Parental/Guardian consent form
Youth study information sheet
Child study information sheet
Adult study information sheet (decisionally-impaired)
Screening consent form

Addendum consent form
Other. Explain.

32. Information Purposely Withheld
Will any information be purposely withheld from the subject during the research or after completion of the research?
No

RESOURCES

33. Describe the resources available to safely conduct this study at each study sites specified in Section I.7.
No additional resources are necessary as study is conducted solely over the phone for survey.

LITERATURE REVIEW

34. References
Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study.
Andres, AM, Alameda, A, Mayoral, O, Hernandez, F, Dominguez, E, Martinez Ojinaga, E, Ramos, E, Prieto, G, Lopez Santamaría, M, Tovar, JA. (2014) Health‐related quality of life in pediatric intestinal transplantation. *Pediatr Transplant*, 18: 746 756. DOI: 10.1111/petr.12348.

Annunziato, R. A., Parbhakar, M., Helcer, J., Kapoor, K., Henkel, K., & Arnon, R. (2014). Strategies for Measuring Quality of Life among Pediatric Solid-Organ Transplant Recipients. Progress in Transplantation, 24(3), 247256. https://doi.org/10.7182/pit2014171

Aureliane Chantal Stania Pierret, James Thomas Wilkinson, Matthias Zilbauer, Jake Peter Mann, Clinical outcomes in pediatric intestinal failure: a meta-analysis and meta-regression, *The American Journal of Clinical Nutrition*, Volume 110, Issue 2, August 2019, Pages 430436, https://doi.org/10.1093/ajcn/nqz110
Cousino MK, Rea KE, Schumacher KR, Magee JC, Fredericks EM. A systematic review of parent and family functioning in pediatric solid organ transplant populations. *Pediatr Transplant*. 2017;21(3):10.1111/petr.12900. doi:10.1111/petr.12900

Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. *Semin Pediatr Surg*. 2017;26(5):328-335. doi:10.1053/j.sempedsurg.2017.09.006Jo SC, McCallum Z, Shalley H, et al. Outcomes of Children With Chronic Intestinal Failure: Experience Over 2

Decades at a Tertiary Paediatric Hospital. *J Pediatr Gastroenterol Nutr*. 2019;69(3):e79-e87. doi:10.1097/MPG.0000000000002384
Rovera, Giuseppe M.1; DiMartini, Andrea2; Schoen, Robert E.1; Rakela, Jorge1; Abu-Elmagd, Kareem3; Graham, Toby O.1,4 QUALITY OF LIFE OF PATIENTS AFTER INTESTINAL TRANSPLANTATION, Transplantation: November 15th, 1998 - Volume 66 - Issue 9 - p 1141-1145

Sudan D. Long-term outcomes and quality of life after intestine transplantation. Current Opinion in Organ Transplantation. 2010 Jun;15(3):357-360. DOI: 10.1097/mot.0b013e3283398565.

SECTION III

SUBMISSION DEADLINE

A. Full Board Review:
The IRB meets twice monthly, on the first and third Thursday of the month, with the exception of January and July when the IRB meets only on the third Thursday of the month. No more than 15 applications (e.g., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a first-come first-served basis. The IRB meeting schedule and deadline dates can be found on the IRB website at www.unmc.edu/irb.

B. Expedited Review
Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review.

ADDITIONAL REVIEW REQUIREMENTS

Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes:
Conflict of Interest Committee (COIC): All responsible personnel listed in Section I of the IRB application (e.g., PI, Secondary Investigator, Participating Personnel, and Coordinator(s)) must disclose **any** financial interest in the research. Data and Administrative Personnel are exempt. The COIC will review any financial interest which is classified as significant.
Institutional Biosafety Committee (IBC): Review by the IBC is required for all protocols involving the use of gene transfer and vaccines.
Pharmacy and Therapeutics (P&T) Committee: Review by the P&T Committee is required for all protocols involving the use of investigational or marketed drugs.
Radioactive Drug Research Committee (RDRC): Review by the RDRC is required for all protocols involving the use of a radio-labeled drug for which the investigator or the institution holds the IND.
Sponsored Programs Administration (SPA)/Office of Regulatory Affairs: For commercial sponsored studies, the consent form and contract will be compared for consistency by the ORA. Final IRB approval and release is contingent upon completion of a signed contract, verified by SPA, for all commercially sponsored research.
UNMC Eppley Cancer Center Scientific Review Committee (SRC): Review by the SRC is required for all protocols involving cancer patients.
Other Review

♦ No Additional Reviews Required

ADDENDUM B
Research Involving Pregnant Women, Fetuses and Neonates of Uncertain Viability or Non-Viable

Title of Protocol
Long Term Quality of Life Outcomes in Patients Undergoing Intestinal Rehabilitation and/or Transplant

Principal Investigator
Merani, Shaheed - Surgery-Transplant - 402-559-6771 - shaheed.merani@unmc.edu

1. Preclinical Studies and Studies on Non-Pregnant Women [45 CFR 46.204(A)]

A. Will Pregnant women/fetuses be included in the research?
Yes

B. Have scientifically appropriate preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, been conducted?
No

C. Do these studies provide data for assessing potential risks to pregnant women and fetuses?
No

2. Risks and Benefits to the Pregnant Woman or Fetus which are Associated with the Research [45 CFR 46.204(B)]
A. Is there *any prospect* of direct benefit for the woman or the fetus?
No

1) Describe any risks to the fetus.
This study involves only quality of life survey questions conducted via phone, there is no clinical intervention that would pose risk to the fetus or to the pregnant woman.

2) Describe how the research could lead to the development of important biomedical knowledge.
In order to include all groups in participation of obtaining long term outcomes of intestinal transplantation we find it to be important to include subjects who meet criteria of inclusion

even if subjects are currently pregnant.

3) Could the research be conducted without involvement of pregnant women?
Yes

3. Minimization of Risks to the Pregnant Woman and Fetus [45 CFR 46.204(C)]
A. Describe how the risks to the pregnant woman and fetus are minimized to the greatest extent possible consistent with the objectives of the research.
This study involves only quality of life survey questions conducted via phone, there is no clinical intervention that would pose risk to the fetus or to the pregnant woman.

4. Pregnancy Termination and Determination of Viability [45 CFR 46.204(H-J)]
A. Will the research involve termination of a pregnancy?
No

5. Consent of the Pregnant Woman and Father [46.204(B), 205(B), 205(C)]
Information Only

	BENEFITS				
RISK TO FETUS		**NONE**	**TO MOTHER ONLY**	**TO MOTHER & FETUS**	**TO FETUS ONLY**
	MINIMAL	**Consent of mother**	**Consent of mother**	**Consent of mother**	**Consent of mother AND father***
	GREATER THAN MINIMAL	**Not allowable**	**Consent of mother**	**Consent of mother**	**Consent of mother AND father***

***Except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence or temporary incapacity or the pregnancy resulted from rape or incest.**

6. Research Involving Neonates of Uncertain Viability [45 CFR 46.205]
A. Will the research involve neonates of uncertain viability?

No

7. Research Involvng Nonviable Neonates [45 CFR 46.205(c)]
A. Will the research involve nonviable neonates?
No

APPENDIX B: IRB # 628-20-EP CONSENT FORM

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

PT NAME:
MR#:

CONSENT FORM

CONSENT FORM
Adult Consent Form

Title of this Research Study
Long Term Quality of Life Outcomes in Patients Undergoing Intestinal Rehabilitation and/or Transplant

Invitation and Summary

You are invited to be in this research study. Taking part in this research is voluntary. You do not have to take part. For the purposes of this document: "You" can refer to:

- Yourself
- The person for whom you are the Legally Authorized Representative (LAR)
- Your child under the age of 19.

"Organization" can refer to: University of Nebraska Medical Center (UNMC), Nebraska Medicine (NM), University of Nebraska at Omaha (UNO) or Children's Hospital & Medical Center (CH&MC).

Here is a summary of the purpose, methods, risks, benefits, and alternatives, to help you decide whether or not to take part in the research.

Description
You are being invited to join this study because you had a gut, kidney, or liver condition when you were a child. Being in this research study is voluntary. You can choose not to participate.

Purpose
Patients with gut, liver, or kidney conditions often need medical treatment. This can affect quality of life. The purpose of this study is to learn about long term quality of life.

Methods
This study involves reviewing records. We will look at your medical record. We will get information about your treatment and follow up. We will also do a phone survey. The survey takes about 20 minutes. The survey asks about your condition. We will ask about your treatment. We will ask about your activities. We will ask about your symptoms. And we will ask about your quality of life.

Risks and Discomforts
Sometimes talking about these topics can cause people to become upset. You do not

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Approved 02/09/2021

have to answer any questions that make you uncomfortable. Completing the survey might contribute to fatigue. Breaks will be provided as needed.

Confidentiality is about how private information that has been disclosed to others is used and stored. Complete confidentiality cannot be guaranteed. It is possible that others could learn you have been treated for a gut condition. It is possible others could learn your answers to the survey. The risk of this happening is very small but may grow in the future. Researchers have a duty to keep your information confidential.

Potential Benefits
You are not expected to get any benefit from being in this research study. However, your participation in this study may enhance understanding about quality of life in patients treated for a gut condition.

Alternatives to Participation
Instead of being in this research study, you can choose not to participate. You will still get treatment and/or follow up for your intestinal condition.

Why are you being asked to be in this research study?
You are being invited to participate in this research study because you were treated for a gut, liver, or kidney condition as a child.

What is the reason for doing this research study?
The purpose of this study is to learn about quality of life in patients with a gut, liver, or kidney condition over long periods of time.

What will be done during this research study?
This study involves a review of your medical record and a phone survey. The survey takes about 20 minutes. The survey asks about symptoms, activities and your quality of life. There are also questions about your gut condition. These questions are about diet changes, lifestyle changes, and complications.

We will review your medical record. We will gather information about your surgery and your follow up. This information includes tests you have on your gut condition, treatments, and visits for medical care.

What are the possible risks of being in this research study?
There is a possible risk of a loss of confidentiality if subject data is lost, however, this

is minimized with use of secure servers for all study data.

What are the possible benefits to you?
You are not expected to get any benefit from being in this research study.

What are the possible benefits to other people?
The study may help to increase our understanding of the long term effects of these treatments on functional status and quality of life in patients.

What are the alternatives to being in this research study?
Instead of being in this research study, you can choose not to take part.

What will being in this research study cost you?
There is no cost to you to be in this research study.

Will you be paid for being in this research study?
You will not be paid to be in this research study.

Who is paying for this research?
This research is being paid for by the Department of Surgery, Section of Transplantation of the University of Nebraska Medical Center.

What should you do if you are injured or have a medical problem during this research study?
Your health and safety is our main concern. If you are injured or have a medical problem or some other kind of problem because of the study call someone listed at the end of this consent form.

How will information about you be protected?
In the course of this research we may collect information about you. This can be things that could be used to find out who you are (like your name, phone number, birthdate, address). We call this "identifiable private information". We will keep this information as confidential as possible.

Who can see information about you?
We also will get medical information about you from your chart (like medical record number, medical history, or the results of physical exams, blood tests, x-rays or other medical or research procedures). We call this "protected health information" or PHI. PHI is protected by a law called the HIPAA Privacy Rule. We will collect the smallest amount of PHI that we can. We will keep your PHI as confidential as possible.

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

PT NAME:
MR#:

CONSENT FORM

IRB PROTOCOL # 628-20-EP **Page 4 of 6**

By signing this consent form, you are letting us (the researchers listed on this consent form and other people involved in this research at the Organization) have access to your PHI. Your PHI will be used only for the purposes described in the section "What is the reason for doing this research study?"

You can change your mind and tell us to stop collecting your PHI for use in this research at any time by writing to the principal investigator. We can still use the PHI we have already collected. If you tell us to stop collecting your PHI, you will have to stop being in this research.

We may share your PHI with other groups listed below:

- The UNMC Institutional Review Board (IRB)
- Institutional officials designated by the UNMC IRB
- The HHS Office for Human Research Protections (OHRP)

You are letting us use and share your research data for as long as the research is going on.

How will results of the research be made available to you during and after the study is finished?

In most cases, the results of the research can be made available to you when the study is completed, and all the results are analyzed by the investigator or the sponsor of the research. The information from this study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

If you want the results of the study, contact the Principal Investigator at the phone number given at the end of this form or by writing to the Principal Investigator at the following address:

983285 Nebraska Medical Center
Omaha, NE 68198-3285

What will happen if you decide not to be in this research study?

You can decide not to be in this research study. Deciding not to be in this research will not affect your medical care or your relationship with the investigator or the organization. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

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Approved 02/09/2021

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

PT NAME:
MR#:

CONSENT FORM

What will happen if you decide to stop participating once you start?
You can stop being in this research (withdraw) at any time. Just call the researcher or any research staff. If you stop being in the research study it will not affect your care or your relationship with the investigator or the organization. You will not lose any benefits to which you are entitled.

Will you be given any important information during the study?
We will tell you right away if we get any new information that might make you change your mind about being in the study.

What should you do if you have any questions about the study?
If you ever have any questions about this study, call the Principal Investigator or anyone else listed on this consent form.

What are your rights as a research participant?
You have rights as a research subject. These rights have been explained in this consent form and in The Rights of Research Subjects that you have been given. If you have any questions concerning your rights, or want to discuss problems, concerns, obtain information or offer input, or make a complaint about the research, you can contact any of the following:

- The investigator or other study personnel
- Institutional Review Board (IRB)
    - Telephone: (402) 559-6463
    - Email: IRBORA@unmc.edu
    - Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-7830
- Research Subject Advocate
    - Telephone: (402) 559-6941
    - Email: unmcrsa@unmc.edu

Documentation of informed consent
You are deciding whether to be in this research study. Signing means that:

- You have read and understood this consent form.
- You have had the consent form explained to you.
- You have been given a copy of The Rights of Research Subjects
- You have had your questions answered.
- You have decided to be in the research study.
- You have been told you can talk to one of the researchers listed below on this consent form if you have any questions during the study.

IRB
Approved 02/09/2021

Nebraska Medicine
SERIOUS MEDICINE. EXTRAORDINARY CARE.

PT NAME:
MR#:

CONSENT FORM

IRB PROTOCOL # 628-20-EP **Page 6 of 6**

- You will be given a signed and dated copy of this consent form to keep.

Signature of Subject_____ Date_____

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the subject possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate

Signature of Person Obtaining Consent_____
Date_____

Authorized Study Personnel
Principal
* Merani, Shaheed
phone: 402-559-6771
alt #: 402-559-8501
degree: MD

Secondary
* Bilyeu, Camden
phone: 402-559-6771
alt #: 402-559-6955
degree: BS

* Brown, Cindy
phone: 402-559-6776
alt #: 402-559-6776
degree: APRN

* Hargrove, Amy
phone: 402-559-5510
alt #: 402-559-8501
degree: MD

IRB
Approved 02/09/2021

Institutional Review Board (IRB)

What Do I Need To Know Before Being In A Research Study?

You have been invited to be in a **research study**. Research studies are also called "clinical trials" or "protocols." **Research** is an organized plan designed to get new knowledge about a disease or the normal function of the body. The people who are in the research are called **research subjects**. The **investigator** is the person who is running the research study. You will get information from the investigator and the research team, and then you will be asked to give your **consent** to be in the research.

This sheet will help you think of questions to ask the investigator or his/her staff. You should know all these answers before you decide about being in the research.

What is the **purpose** of the research? Why is the investigator doing the research?

What are the **risks** of the research? What bad things could happen?

What are the possible **benefits** of the research? How might this help me?

How is this research different than the care or treatment I would get if I wasn t in the research? Are there other treatments I could get?

Does **everyone** in this research study get the same treatment?

Will being in the research **cost** me anything extra?

Do I have to be in this research study? Will the doctor still take care of me if I say **no**?

Can I **stop** being in the research once I ve started? How?

Who will look at my **records**?

How do I reach the investigator if I have more **questions**?

Who do I call if I have questions about being a **research subject**?

Make sure all your questions are answered before you decide whether or not to be in this research.

Academic Research & Services Building 3000 / 987830 Nebraska Medical Center / Omaha NE 68198-7830
402-559-6463 / FAX 402-559-3300 / Email: irbora@unmc.edu / http://www.unmc.edu/irb

Institutional Review Board (IRB)

THE RIGHTS OF RESEARCH SUBJECTS
AS A RESEARCH SUBJECT YOU HAVE THE RIGHT

to be told everything you need to know about the research before you are asked to decide whether or not to take part in the research study. The research will be explained to you in a way that assures you understand enough to decide whether or not to take part.

to freely decide whether or not to take part in the research.

to decide not to be in the research, or to stop participating in the research at any time. This will not affect your medical care or your relationship with the investigator or the Nebraska Medical Center. Your doctor will still take care of you.

to ask questions about the research at any time. The investigator will answer your questions honestly and completely.

to know that your safety and welfare will always come first. The investigator will display the highest possible degree of skill and care throughout this research. Any risks or discomforts will be minimized as much as possible.

to privacy and confidentiality. The investigator will treat information about you carefully, and will respect your privacy.

... to keep all the legal rights you have now. You are not giving up any of your legal rights by taking part in this research study.

to be treated with dignity and respect at all times

The Institutional Review Board is responsible for assuring that your rights and welfare are protected. If you have any questions about your rights, contact the Institutional Review Board at (402) 559-6463.

Academic Research & Services Building 3000 / 987830 Nebraska Medical Center / Omaha NE 68198-7830
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APPENDIX C: 36-ITEM SHORT FORM SURVEY INSTRUMENT (SF-36)

RAND HEALTH

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

---

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

---

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

---

21. How much **bodily** pain have you had during the **past 4 weeks**?

- ○ 1 - None
- ○ 2 - Very mild
- ○ 3 - Mild
- ○ 4 - Moderate
- ○ 5 - Severe
- ○ 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- ○ 1 - Not at all
- ○ 2 - A little bit
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

APPENDIX D: ADDITIONAL QUESTIONNAIRE

ADDITIONAL QUESTIONNAIRE

Choose one option for each questionnaire item.

The following questions are about your current employment and education.

1. Are you currently employed (in the last 12 months)?
    a. Full Time
    b. Part Time
    c. Unemployed – seeking employment
    d. Unemployed – not seeing employment
    e. Student
    f. Retired
    g. Disabled
    h. Other (describe):
    _____

2. What is the highest grade or level of school that you have completed?
    a. 8th grade or less
    b. Some high school but did not graduate
    c. High School Diploma or Equivalent (GED)
    d. Trade School or Certificate
    e. Some College but no degree
    f. Associate degree
    g. Bachelor's degree (BA, BS)
    h. Master's degree (MA, MS, MBA)
    i. Professional School degree (MD, DDS, DVM, JD)
    j. Doctorate degree (PhD, EdD)

The next questions ask about your current living situation.

3. Which of the following best describes your current living situation?
    a. Live alone in own home (house, apartment, condo, trailer, etc.); may have a pet
    b. Live in a household with other people
    c. Live in a residential facility where meals and household help are routinely provided by paid staff (or could be if requested)
    d. Live in a facility such as a nursing home which provides meals and 24-hour nursing care
    e. Temporarily staying with a relative or friend
    f. Temporarily staying in a shelter or homeless
    g. Other (describe): -
    _____

4. Do you need help with any activities of daily living such as bathing, preparing meals, shopping, housekeeping, managing finances, etc.?
    a. Yes
    b. No

5. What is your current marital or relationship status?
    a. Married/domestic partner
    b. Living with a partner in a committed relationship
    c. In a serious or committed relationship, but not living together
    d. Single
    e. Separated
    f. Divorced
    g. Widowed

6. Are you a primary caregiver for a child under the age of 18 or for someone who is frail, chronically ill, or has a physical or mental disability?
    a. Yes, Children
    b. Yes, Someone who is frail, ill, or has a disability
    c. Yes, both children and someone who is frail, ill, or has a disability
    d. No

7. Do you have a driver's license?
    a. yes
    b. no

8. What kind of transportation do you use for daily activities including work, pleasure, or health related appointments?
    a. Your own vehicle, you are the driver
    b. Your own vehicle, family or friend is the driver
    c. Public transportation (bus, taxi, etc.)
    d. Personal Rideshare transportation (Uber, Lyft, etc.)

Now we will ask questions about your nutrition habits.

9. Do you require any supplemental Nutrition <u>not</u> taken by mouth?
    a. yes
    b. no

10. If yes, what kind?
    a. Not applicable, I do not require any supplemental nutrition not taken by mouth
    b. Parenteral Nutrition – (TPN, PPN, or IV fluids on a weekly basis)
    c. Enteral Nutrition – (NG, J-tube, G-tube feeds on a weekly basis)

11. If yes, how is it administered?
    a. Not applicable, I do not require any supplemental nutrition not taken by mouth
    b. Central Line
    c. PICC
    d. G-tube
    e. J-tube
    f. NG tube

12. Do you regularly take nutrition by mouth currently?
    a. Both
    b. Solids
    c. Liquids
    d. None

13. Did you regularly take nutrition by mouth prior to your transplant?
    a. Both
    b. Solids
    c. Liquids
    d. None

14. Do you have difficulty with nutrition by mouth for one of the following reasons?
    a. Limited due to a medical reason
    b. Limited due to oral aversion
    c. Other (describe):
       _____
    d. No

The final set of questions asks about your medical care.

15. How many days were you hospitalized in the last 12 months related to your intestinal condition?
    a. 0
    b. 1-3
    c. 3-5
    d. 5-10
    e. >10

16. If you are taking immunosuppression do you find difficulty with any of the following?
    a. Not applicable, I am not taking immunosuppression
    b. Having to take pills
    c. Side effects
    d. Complications – infections, etc.
    e. Financial constraints
    f. None

17. What degree of medical care is required for follow up of your transplant condition?
    a. Appointments 1/year or less
    b. Appointments 1/month
    c. Visits ER/Clinic every week
    d. Need to visit outpatient infusion x/week
    e. In home nursing care
    f. None