Variability in General Health Status Post Liver Transplantation

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Abstract

Transplantation outcomes focus has shifted beyond increasing survival to decreasing the negative effects of liver disease, focusing on outcomes related to physical and social health. These measures have been studied as isolated variables, but they have not been examined as a cluster of recipient characteristics, representing their wellbeing. This paper aims to compare liver transplantation recipient's general health status pre- and 2-years post-liver transplant, and to examine whether age, gender, race, and comorbidities are associated with better health status post-transplant. We used data derived from electronic health records of recipients 18 years or older who underwent liver transplantation between 01/01/2008 and 3/31/2017. We excluded recipients who died within 2 years from transplant or did not have follow-up data. A Cox proportional hazard model was used to build severity scores for health status pre- and 2 years post-transplant. Age, gender, race, and comorbidities were also examined. A t-test and ANCOVA were used to examine differences pre- and post-LT. Results showed that better health status pre-transplant was not statistically significant associated with better health status post-transplant. However, health status posttransplant was less variable than pre-transplant. There was a statistically significant association between female gender and kidney severity with worse health status post-transplant; thus, gender and kidney disease may be associated with liver transplant recipients' wellbeing and play an important role in health status post-transplant.

1 Introduction

Liver transplantation (LT) is a life-prolonging treatment for a variety of acute and chronic liver conditions [Bachir *et al.*, 2012]. Rates of survival from LT have increased since its introduction, but other outcomes of LT that reflect overall recipient wellbeing have not improved significantly in recent years because rates of disease-related complications remain high [Pruinelli et al., 2018; Sullivan et al., 2014]. Neither LT research has not benefitted from computational methods, such as machine learning (ML) and artificial intelligence (AI), to uncover data-driven approaches to stablish better models predictive of better health. Each year, around 8,000 patients undergo LT in the United States (US) and the procedure is expensive [U.S. Department of Health and Human Services, 2019; van der Hilst et al., 2008]. Success of LT is often measured in terms of physiological outcomes, such as rates of recipient survival, rates of graft survival, and the presence of comorbidities. Very few studies investigate non-physiological outcomes, such as health-related quality of life, mental health, and psychosocial health [Bachir et al., 2012; Duffy et al., 2010; Pruinelli et al., 2016a; Stilley et al., 2011; Sullivan et al., 2014].

One of the major barriers to develop better models in LT is patient heterogeneity. The LT population is highly heterogeneous, or has high clinical variability, with different groups of recipients having different characteristics, and suggest having different outcomes according to these characteristics [Pruinelli et al., 2018]. Another factor is the fast deterioration of LT patient's health while they are waiting for a transplant. That is due to the number of comorbidities and complications from the end-stage liver disease, affecting musculoskeletal, respiratory, and other body systems. Some of these characteristics could be amenable to change, such as the functional status and physical capacity. Although many outcome measures aim to evaluate the effectiveness of LT, research surrounding LT outcomes lacks analysis of outcomes in clusters, and clustering recipient characteristics can identify new subcategories of disease and different trends associated with these subcategories [Pruinelli et al., 2016b]. A ML approach that analyzes outcomes in clusters plays an essential role in improving patient care because it identifies trends in outcomes that can potentially be addressed with interventions pre- and post-transplant [Pruinelli et al., 2019]. If this approach successfully the po-

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tential to predict and even change the progression of liver disease complications, LT field has a lot to gain from more advanced computational methods, such as AI, and then be able to improve overall LT patient's wellbeing. In this study, general health status (GHS) is one such cluster of recipient characteristics used to analyze outcomes and identify trends.

Overall, functional status and physical capacity are measured in a variety of ways pre- and post-transplantation to predict mortality, evaluate efficacy of LT, and determine whether LT recipients have ideal functional status and physical capacity after transplantation when compared to other patient populations. Many studies have examined functional status and physical capacity prior to transplantation and after transplantation in order to provide information about the efficacy of LT, and most demonstrate improved functional status and physical capacity [Casanovas et al., 2016; Eshelman et al., 2010]. Several studies have examined functional status and physical capacity using the 36-item Short Form Health Survey (SF-36), which is a widely used selfreport measure of health-related quality of life in the LT population [Goetzmann et al., 2006; Pieber et al., 2006]. The SF-36 contain eight subscales, and the physical functioning subscale reflects limitations in a patient's ability to participate in strenuous physical activities, such as running, to activities of daily living, such as bathing and dressing [Ware & Sherbourne, 1992]. One of the main drawbacks of using self-reported surveys, such as SF-36 and SF-12, is that it is found that a great number of patients pre-LT (~30%) are in intensive care unit just before LT. In addition, many other patients are unable to self-report at the time of LT; thus, resulting in many missing and biased data, specifically lacking data from who is critically ill. To suffix this barrier, a provider reported survey capturing these measures could more efficiently picture the overall health status of these patients; thus, informing care delivery.

GHS is a summative score that describes the health of an individual based on functional, physical, and social health and combines four measures, which are functional status, physical capacity, how the liver disease impacts work status, and employment description. In addition, these measures are nationally collected are part of the US transplant system and if successful in demonstrating LT GHS, could be generalized to entire US LT population as a measure of GHS. This combined approach shows that a single score can indeed predict LT outcomes; thus, facilitating clinicians' work by reducing the burden of analyzing multiple measures for decision-making. In a retrospective cohort study that examined GHS, it was found that recipients with better GHS prior to LT had statistically significant, better rates of survival after transplantation [Pruinelli et al., 2019]. Although these results suggest that GHS is a predictor of survival posttransplant, there is a lack of evidence surrounding whether there is a change in GHS after transplantation, both in the immediate post-transplant period and years after transplantation. Specifically, it is unknown if there is an improvement in GHS post-transplant if compared with pretransplant GHS considering patient's wellbeing as a whole.

The purpose of this study is to determine whether the GHS of the LT's recipient improves, stays the same, or worsens after transplantation. Our hypotheses for this study are that 1) among a sample of LT recipients, GHS will improve two years after transplantation when compared with recipients' pre-transplantation GHS; and 2) there will be associations between GHS and recipient characteristics, specifically age, gender, race, and comorbidities. Understanding the GHS of recipients before and after transplantation is important for nursing practice because it helps target specific nursing interventions to improve GHS prior to and after transplantation to decrease morbidity and mortality and improve overall quality of life of transplant recipients. Results from this study could provide support for implementation research to develop and test clinical decision models at the point of care targeting aspects of GHS that are amenable to change, such as functional status and physical capacity.

2 Methods

This study is a retrospective observational study using data derived from the electronic health records (EHR) of a Midwest institution. The Wellbeing Model by Kreitzer [Kreitzer, 2012] was used as the study framework, which focuses on factors that promote health and wellbeing rather than focusing on factors that cause illness or disease, and encompasses six dimensions: Health, Purpose, Relationships, Community, Security, and Environment. The dimensions of the Wellbeing Model and how they are related to this study are illustrated in Figure 1. In a systematic review of 26



Figure 1: The dimensions of the Wellbeing Model as they relate to General Health Status adapted from Kreitzer [2012].

large-scale studies that examined predictors for LT recipient survival, predictors were categorized according to the Wellbeing Model, and the majority (69.77%) of the predictors were found to reflect the Health dimension of wellbeing [Pruinelli et al., 2016a]. This review concluded that further research is needed to examine factors that represent the whole person that can be used not only to predict survival after transplant, This study seeks to examine the general health status of LT recipients pre- and post-transplantation by combining variables from the Health and Security dimensions of the Wellbeing Model.

2.1 Sample and Setting

All adults who received LT between January 1st, 2008 and December 31st, 2014, with follow-up data until March 31st, 2017 were included. The data were obtained through the Transplant Information Systems and collected using the United Network for Organ Sharing (UNOS) Adult Liver Transplant Recipient Registration (TRR) Worksheet linked to the electronic health record. The TRR is a standardized form used across all US Transplant centers and collect these data and report back to UNOS. The initial sample consisted of 372 adult recipients. Inclusion criteria for selection were being 18 years or older at the time of transplantation, undergoing transplantation with living or deceased organ donations, receiving a LT for the first time, and not having combined organ transplantation (e.g. liver and kidney). Recipients who died and recipients who did not have follow-up data within two years after transplantation were excluded. These data were used to build a severity score for general health status and a severity score for comorbidities by body system. The final sample consisted of 109 recipients. The University of Minnesota Institutional Review Board (IRB) approved this study (# 0000092).

2.2 Measures

For the purpose of this study, Health refers to physical health characterized by functional status and physical capacity, and Security refers to stable employment characterized by work status and employment description. Physical health includes functional status, defined as the LT recipient's ability to carry out normal activities and self-care. level of assistance required in completing these activities, and presence of signs and symptoms of disease. Physical health also includes physical capacity, defined as the LT recipient's limitations in mobility, ranging from no mobility limitations to major mobility limitations. Security includes work status, defined as whether or not the LT recipient is currently working. Lastly, Security also includes employment description, defined as the type of work of the LT recipient, as well as the health-related reasons the recipient works part-time or does not work.

The main measures of interest were questions about health status: functional status, physical capacity, work status, and employment description. The functional status, physical capacity, work status, and employment descriptions of recipients were measured with the same questions preand post-transplant. Functional status was measured using the Karnofsky Performance Status scale, a 10-point scale correlating to percentage values ranging from 100% to 10% [Péus et al., 2013]. Physical capacity was measured using a question about mobility limitations with three possible responses: major mobility limitations, some mobility limitations, or no mobility limitations. Work status was measured using a question about whether or not the recipient was currently working with three possible responses: yes, currently working; no, currently not working; and not applicable, patient hospitalized. Employment description was measured using a question about the reason for the work status identified in the previous question suggesting whether working was not possible due to the liver disease, with four possible responses for not currently working, and eight possible responses for currently working.

These measures have not been validated in the LT population; however, the reliability and validity of the Karnofsky Performance Status scale as a measure of functional status have been evaluated in cancer patients. The Karnofsky Performance Status scale has shown to have good inter-rater reliability and construct validity with cancer patients, suggesting that this measure is a useful indicator of the functional status of cancer patients [Schag *et al.*, 1984; Yates *et al.*, 1980]. Although the reliability and validity of the Karnofsky Performance Status scale has not been demonstrated among LT recipients, authors suggest that the Karnofsky Performance Status scale could be useful for evaluating the functional status of patients with other forms of chronic disease [Yates *et al.*, 1980].

The GHS Severity Score was built using a Cox proportional hazard approach using responses from questions about functional status, physical capacity, work status, and employment. GHS scores is a summative score and quantify the deterioration of health status with higher scores indicating a greater degree of impairment and the full modeling is published elsewhere [Pruinelli *et al.*, 2019]. For this study, two GHS severity scores were created for recipients, one within 48 hours pre-transplant and one two years posttransplant.

Covariates included age, gender, race, and comorbidities of recipient's pre-LT. Comorbidities were categorized by body system, including blood, circulatory, endocrine, gastrointestinal, kidney, biliary, respiratory, and musculoskeletal systems. Comorbidity scores modeling is published elsewhere [Pruinelli *et al.*, 2016b].

2.3 Data Analysis

Descriptive statistics are used to describe the included sample and mean and standard deviation for continuous variables, and counts and percentages for categorical data. A sensitive analysis was performed to compare recipients who were included in the sample and recipients who were excluded from the sample in order to test for independence between samples. A simple paired *t*-test was used to compare the GHS severity score of recipients prior to and after transplantation. Spearman's rho was used to determine whether there was a correlation between a better GHS severity score prior to transplantation and a better GHS severity score after transplantation. Finally, an analysis of covariance was used to determine variance in the GHS severity score between age, gender, race, and comorbidities, and a generalized linear regression model was used to identify which variables were associated with the outcome, which was GHS severity scores. Severity scores were built using RStudio, version 3.1.3. Descriptive statistics, *t*-test, Spearman's rho, and analysis of covariance tests were performed using SAS, version 9.4.

3 Results

The final sample consisted of 109 recipients. A full description of the sample is in Table 1. The mean age was 57.05 years with a standard deviation of 8.06 years. The majority of the sample was male (n = 73, 66.97%) and Caucasian (n = 100, 91.74%). The mean GHS severity score pretransplantation was 0.05 and the mean severity score posttransplantation was 0.15. When testing for independence of samples between recipients who were included with recipients who were excluded, there were significant differences between these groups based on age (p = 0.01) and race (p = 0.001).

	Included (<i>n</i> =109)		Excluded (<i>n</i> =234)		sig		
Variable	n/µ	%/sd	n/µ	%/sd			
Gender					0.45		
Female	36	33.03	67	29			
Male	73	66.97	167	71			
Race					0.001		
Caucasian	100	91.74	183	78			
Non-Caucasian	9	8.26	51	22			
GHS Pre-LT	0.05	0.87	-0.02	1.06	0.48		
GHS Post-LT	0.15	0.30					
Age	57.05	8.06	54.36	10.6	0.01		
Comorbidity Severity Scores							
Blood	1.16	0.21	1.19	0.20	0.13		
Circulatory	0.87	0.34	0.89	0.33	0.57		
Endocrine	0.97	0.27	1.01	0.26	0.23		
Gastrointestinal	0.85	0.18	0.83	0.18	0.64		
Kidney	0.91	0.17	0.94	0.17	0.08		
Biliary	0.99	0.20	1.01	0.20	0.27		
Respiratory	1.14	0.10	1.16	0.10	0.20		
Musculoskeletal	0.99	0.25	0.97	0.25	0.81		

Table 1: Descriptive Statistics and Sensitivity Analysis for Included and Excluded Sample.

Results indicate that our hypothesis that GHS would improve after transplantation when comparing recipients' pretransplantation GHS with their post-transplantation GHS was not supported. However, GHS severity scores posttransplantation (sd = 0.30) were less variable than GHS scores pre-transplantation (sd = 0.87), which are illustrated in Figure 2. The paired *t*-test demonstrated that GHS severity scores post-transplantation did not statistically improve when compared to GHS severity scores pre-transplantation (p = 0.26). The Spearman's rho did not show a correlation between a better GHS severity score prior to transplantation and a better GHS severity score after transplantation (p = 0.27).

The analysis of covariance demonstrated statistically significant variance in GHS (p = 0.03) between pre- and posttransplantation GHS, when considering age, gender, race, and comorbidities. The generalized linear regression model demonstrated statistically significant associations between worse post-LT GHS and gender and kidney severity scores, but did not demonstrate statistically significant associations between worse post-LT GHS and age, race, or any other comorbidity severity scores. There was a statistically significant association between female gender (p = 0.01) and worse post-LT GHS. The kidney severity score (p = 0.02) was the only comorbidity severity score to demonstrate a statistically significant association with worse post-LT GHS. The results of the analysis of covariance are summarized in Table 2.

Variable	DF	MSE	F	sig
Age	1	0.00	0.00	0.99
Gender (Female)	1	0.54	6.26	0.01
Race (Non-Caucasian)	1	0.30	3.47	0.07
Kidney Severity Score	1	0.51	5.96	0.02
GHS Pre-LT	1	0.14	1.62	0.20

Table 2: Analysis of Covariance Between Liver Transplant Recipient Characteristics Pre- and General Health Status Score Post-Transplantation.





Figure 2. General health status scores are less variable two years after transplantation than general health status scores pre-transplantation.

4 Discussion

The results of this study suggest that GHS does not have a statistically improvement overall two years after LT. However, there are groups of recipients who share characteristics pre-LT who demonstrate worse GHS post-LT. Specifically, female LT recipients appear to have worse outcomes after transplantation, as well as recipients with kidney comorbidities pre-transplantation, which suggests that female gender and kidney disease are statistically significant risk factors for worse GHS post-LT.

Results suggest that GHS does not statistically improve after LT when compared with GHS pre-LT. Similarly, better GHS prior to LT is not associated with better GHS after LT. Although the relationship between GHS pre- and post-LT was not statistically significant, GHS after transplantation was less variable than GHS before transplantation (Figure 2), which has clinical significance, where LT has the potential to improve patients who have worse GHS before.

However, our results did not demonstrate a trend in improvement in GHS or a trend in worsening of GHS. More recipients had GHS scores closer to zero following transplantation. When examining the data from which the GHS scores were derived based on the functional status, physical capacity, work status, and employment description of recipients with the scores closest to zero, most carried out activities of daily living with effort, were unable to do active work, had no mobility limitations, and were not currently working due to disability. This clinical picture suggests that more recipients have GHS that is neither improved nor worsened after transplantation. This can possibly be attributed to the high demand of the LT surgical procedure and that it may take longer than two years to see statistically significant improvement in the GHS.

When examining the functional status, physical capacity, work status, and employment description of recipients with the worst GHS scores, most required assistance with activities of daily living, had major mobility limitations, and were not currently working due to disability or retirement. When examining the functional status, physical capacity, work status, and employment description of recipients with the best GHS scores, most carried out activities of daily living with effort, were unable to do active work, had some mobility limitations, and were not currently working due to disability. Overall, this suggests that even the recipients with the greatest improvement in GHS after transplantation still have limitations in the health and security dimensions of wellbeing.

Finally, we found that there are recipient characteristics, specifically gender and kidney comorbidities, that are associated with worse GHS after LT. First, the results suggest that female gender is associated with worse GHS after LT. This finding is comparable to several studies that have examined the relationship between gender and GHS variables in the LT population. Studies that suggest that female LT recipients have worse functional status and physical capacity than male LT recipients include studies that have demonstrated higher physical functioning scores on the SF-36 among male LT recipients [Bianco *et al.*, 2013; Desai *et al.*,

2008; Kotarska *et al.*, 2014; Saab *et al.*, 2008]. Of note, Duffy *et al.* [2010] did not find a statistically significant association between gender and the physical functioning domain of the SF-36. In a study that examined the relationship between gender and scores on the Karnofsky Performance Status scale after transplantation, Cowling *et al.* [2004] found that male LT recipients had statistically significant higher scores immediately following LT and two years after LT, but did not find a statistically significant difference in scores one-year post LT.

Studies that compare employment pre- and posttransplant using the same data suggest that rates of unemployment after transplantation are high, with some estimating as high as 55%, which is much higher than the United States national unemployment rate of 4.8% [Åberg *et al.*, 2016; Huda *et al.*, 2012]. The lack of improvement in general health status in this study could in part be explained by the results of studies that have examined employment in the LT population, which suggest that rates of employment are low after transplant. Of note, this study included employment description options of homemaker, retired, and student, which are not always included in studies that examine employment in the LT population, and may provide a more realistic reflection of the employment status, and consequently, the general health status of LT recipients.

The results of this study suggest that there are recipient characteristics, specifically female gender and kidney comorbidities are associated with worse general health status after LT. First, the results of this study suggest that female gender is associated with worse general health status after LT. This finding is comparable to several studies that have examined the relationship between gender and general health status variables in the LT population. Studies that suggest that female LT recipients have worse functional status and physical capacity than male LT recipients include studies that have demonstrated higher physical functioning scores on the SF-36 among male LT recipients [Bianco et al., 2013; Desai et al., 2008; Kotarska et al., 2014; Saab, Ibrahim, et al., 2007]. Of note, [Duffy et al. 2012] did not find a statistically significant association between gender and the physical functioning domain of the SF-36. In a study that examined the relationship between gender and scores on the Karnofsky Performance Status scale after transplantation, [Cowling et al. 2004] found that male LT recipients had statistically significant higher scores immediately following LT and two years after LT but did not find a statistically significant difference in scores one-year post LT.

Studies also suggest that male LT recipients have higher rates of employment after LT. A review conducted by [Åberg *et al.*, 2016] found that male gender was a predictor of employment after transplant, but suggested that this may be due to many studies not categorizing homemakers as employed. Also, [Cowling *et al.*, 2004] found higher rates of employment among male LT recipients one year after transplantation but found no significant difference two years after transplantation. Despite the inclusion of homemakers in employment description data in this study, the association between female gender and worse general health status suggests that rates of employment among female LT recipients may be lower than rates of employment among male LT recipients, which is similar to the majority of findings from the literature.

Second, the results of this study suggest that kidney comorbidities pre-transplantation are associated with worse general health status. The comorbidities that were included in the kidney severity score were pre-LT dialysis, kidney dysfunction without dialysis, pre-renal acute kidney injury due to hemorrhage, and the presence of a benign, uninfected kidney mass or cyst. Previous studies that have examined the association between kidney diseases pre-transplant with outcomes post-transplant have found that kidney disease increases the risk of mortality, but it is less clear how kidney disease is associated with the health and security dimensions of wellbeing after LT [Weber et al., 2012. Potential reasons for the association between kidney comorbidities pretransplant and worse general health status post-transplant could include the increased risk for continuing kidney disease after transplantation and the potential impact of renal dysfunction on recipients' ability to carry out activities of daily living, participate in physical activity, and maintain employment.

Limitations include the retrospective, single cohort approach with a secondary analysis of data, which could lead to biased findings that are not generalizable to the national LT population. However, our sample characteristics was similar to the national sample of LT patients. Additional limitations include the small number of Non-Caucasian recipients in the study sample and the exclusion of recipients who died. Exclusion of recipients who died and recipients who did not have follow-up data before and after two-year post-LT does not account for attrition and could potentially alter the results of the study. However, the sensitive analysis did not demonstrate statistically significant differences in the majority of characteristics between recipients who were included and recipients who were excluded.

5 Conclusion

In conclusion, using a summative score to demonstrate GHS as a holistic measure, results of this study suggest that GHS does not statistically improve after transplantation and that better GHS pre-transplant is not statistically associated with better GHS post-transplant. However, GHS is less variable after transplantation, meaning more LT recipients have GHS scores closer to zero following transplantation than prior to transplantation. This suggests that the health and security dimensions of wellbeing of LT recipients neither improve nor worsen after transplantation, and at some point, the LT procedure places patients with both worse and better scores pre-LT at the same GHS two years after LT. In addition, there are recipient characteristics, specifically female gender and kidney comorbidities, which are associated with worse GHS. Additional studies should focus on investigating how long after transplantation GHS would improve and if there were additional conditions to consider when analyzing GHS improvement for this population.

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