CURRENT ALLOCATION POLICIES AND DISPARITIES WITHIN LIVER AND KIDNEY TRANSPLANTATION

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ABSTRACT

Through wide-spanning policy changes, disparities in access to transplantation and transplantation rates have been created, in both the past and current liver and kidney transplant allocation systems. These disparities mainly affect women and minorities, and can be lessened, and in some ways eliminated, through concentrated efforts by policy makers and public health officials. The current waitlist burdens, allocation policies and transplantation rates, are described in this essay with the purpose of identifying weak areas in the current system where policy amendments and public health interventions would be most beneficial. Proposed changes to the current allocation policy in liver and kidney transplantation include the redrawing of borders in which organs are shared and altering the MELD score for women to better reflect smaller physical traits of women, in the liver allocation system, and expanding the role of kidney paired donation in renal transplantation. In conjunction with policy changes, interventions that increase education and awareness of the need for living donor organs and the importance of decreasing Hepatitis C transmission can be directed to problematic communities. While the solutions for observed disparities in both liver and kidney transplantation may not be obvious, understanding the epidemiologic factors that lead to observed disparities in organ allocation systems for liver and kidney transplantation are of paramount public health importance because they have the potential to limit millions of people from obtaining a life-saving therapy.

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LIST OF COMMON ACRONYMS AND ABBREVIATIONS

ACE – Angiotensin-converting enzyme

ARB – Angiotensin receptor blockers

BMI – Body Mass Index

CKD – Chronic kidney disease

CLD – Chronic liver disease

CPRA – Calculated panel-reactive antibody

DSA – Donor Service Area

ECD – Expanded Criteria Donor

EPTS – Expected Post Transplant Survival

ESLD – End Stage Liver Disease

ESRD – End Stage Renal Disease

GFR – Glomerular filtration rate

HCC – Hepatocellular carcinoma

HCV – Hepatitis C virus

HHS – Health and Human Services Department

HLA – Human leukocyte antigen

HRSA – Health Resources and Services Administration

ICU – Intensive Care Unit

INR – International normalized ratio

KAS – Kidney Allocation System

KDPI – Kidney Donor Profile Index

KDRI – Kidney Donor Risk Index

KPD – Kidney paired donation

MELD – Model for End-Stage Liver Disease

NEPKE – New England Program for Kidney Exchange

NOTA – National Organ Transplant Act

OPO – Organ Procurement Organization

OPTN – Organ Procurement and Transplantation Network

SRTR – Scientific Registry for Transplant Recipients

UNOS –United Network for Organ Sharing

USRDS – United States Renal Data System

1.0   INTRODUCTION

1.1   END-STAGE RENAL DISEASE

The kidneys are two bean-shaped organs located on either side of the spine behind the upper abdominal organs and play a critical role to normal physiology. Using tiny structures called nephrons and glomeruli, they kidneys filter the blood of waste products that can become toxic if allowed to accumulate; remove excess fluid around the heart and the lungs; return nutrients to the blood stream; and help regulate blood pressure and prevent anemia. Most kidney diseases assault the nephrons. Chronic kidney disease (CKD) gradually damages the nephrons over several years. It is characterized by declining kidney function, assessed by the glomerular filtration rate (GFR) of kidneys, and is divided into five stages of increasing severity.[1] In normal functioning kidneys, GFR exceeds 90 mL/minute/1.73m^3. As GFR decreases, the severity of CKD increases by increasing stages of disease.[1] End-stage renal disease (ESRD) develops when the kidneys fail to function at the level required for normal physiology, i.e. when the GFR falls below 15 mL/minute/1.73m^3.[1] ESRD poses significant burden to the society. It accounts for 4.9 deaths per 100,000 in the United States and it is the ninth leading cause of death.[2]

Risk factors for ESRD

The main causes of ESRD are diabetes and high blood pressure.[1, 3, 4] People at increased risk of developing ESRD include those with a family history of kidney disease, history of hypertension or diabetes, and persons that belong to populations that are more likely to have the former risk factors (i.e. Blacks, Hispanics, Asians, and Native Americans).[1]

Prevalence and incidence of CKD/ESRD in the United States

Currently, 26 million adults are estimated to have CKD in the United States.[1] In adults over the age of 30 years, the estimated burden of CKD is 13.2% and is expected to increase to 14.4% by 2020 and to 16.7% by 2030.[5] For age groups 30-49, 50-64 and ≥65, the lifetime incidence of CKD is 54.13%, 52.01% and 41.8%, respectively. The incidence of end stage renal disease is much lower for these groups and is estimated to be 3.17% for the 30-49 age group, 3.31% for the 50-64 age group, and 2.63% for adults over the age of 65 years. The most common stage of disease is Stage 3 of CKD where the GFR is functioning at 30-59 mL/minute/1.73m^3.[5]

Racial/ethnic differences exist in CKD. Thus, although the prevalence of CKD in adults older than 30 years and in those >65 is similar between blacks and non-blacks (estimated at 13.2% and ~40%, respectively), blacks have a higher prevalence among 30-49 year olds (5.6% versus 3.8%) and in the 50-64 age group (13.62% versus 9.42%).[5] The lifetime incidence of ESRD is also higher in blacks compared to non-blacks in the 30-49 age group (6.56% vs. 2.73%), the 50-64 age group (8.45% vs. 2.72%) as well as in adults over 65 years (7.22% vs. 2.22%).[5]

Treatment options for ESRD

ESRD prevention in early stages of CKD includes limiting salt intake to prevent hypertension and decreasing the risk of diabetes through balanced dieting and exercise. In addition, avoiding the overuse of non-prescription pain relievers and limiting the intake of alcoholic drinks are steps to ensuring a healthier lifestyle and preventing chronic kidney disease from occurring.[1] Once ESRD has occurred, however, dialysis, an artificial means of filtering the blood, is required for these patients. There are two types of dialysis: hemodialysis, in which an artificial kidney is used to filter the blood, and peritoneal dialysis, in which a special cleaning solution (dialysate) passes into the abdomen via a catheter to filter the blood.[6] A disadvantage of kidney dialysis is that it involves strict scheduling and lifestyle modifications which may interfere with the patient's ability to work and/or continue with other daily activities. An alternative treatment option of replacing kidney function is by kidney transplantation.

1.2   END STAGE LIVER DISEASE

The liver is a large organ mainly located in the upper right quadrant of the abdomen. The liver performs a multitude of critical functions relating to digestion, metabolism (including of drugs), detoxification, immunity and the storage of energy. Chronic liver disease (CLD) involves the progressive destruction of liver tissue over time. It is a term that is applied to various clinical disorders that cause the liver to fail to perform its functions and it can vary from mild liver test abnormalities to end stage liver disease (ESLD), which is the most severe form of liver disease. Cirrhosis is an irreversible, life-threatening condition in which liver tissue is replaced by scar, non-functioning, tissue.[7] A decrease in liver function usually occurs when more than 75% of liver tissue is affected by disease and 80-90% of liver tissue needs to be destroyed before any clinical

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signs of liver failure.[8] Unlike chronic kidney disease, there is no definitive event such as the drop in GFR for ESRD, that occurs in chronic liver disease to signify that a patient has CLD; therefore, assessing the prognosis of liver disease is extremely difficult from patient to patient.

Causes and risk factors for ESLD

An extensive list of conditions is associated with CLD. The most common cause of liver disease in the United States is alcohol abuse.[7] Other common causes of CLD include viruses (e.g. hepatitis B and C, cytomegalovirus, and Epstein Barr virus), genetic predispositions, disorders of the immune system (e.g. autoimmune hepatitis), reactions to medications or toxins, and unhealthy lifestyle choices relating to illicit drug use and risky sexual behaviors, where hepatitis C (HCV) can be transmitted. Severe scarring of the liver, or cirrhosis, can result from these causes and cirrhosis can lead to liver cancer or hepatocellular carcinoma (HCC).[7] Cirrhosis does not present equally in every patient and does not always lead to carcinoma, which makes diagnosis of ESLD and subsequent estimation of burden of ESLD very challenging. Other consequences of as a result of liver disease are premature death, esophageal bleeding, liver transplantation and liver cancer.[7]

The populations at the highest risk of CLD are minorities, the poor, uninsured, former or current drug users and alcoholics. The primary cause of end stage liver disease is hepatitis C infections (HCV) followed by malignancies that could potentially overlap with HCV.[7] Prevention of chronic liver disease includes a balanced diet, abstaining from illegal drug use and the sharing of needles, safe sexual practices, and drinking alcohol in moderation.[7]

Prevalence of ESLD

The burden of liver disease is difficult to estimate because CLD encompasses many disorders of the liver without one specific, defining event being able to accurately and consistently predict that a patient is undergoing liver damage.[7] Nevertheless, in a recent report using data from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2010, the prevalence of cirrhosis was estimated to approximate 0.27%, a higher proportion than previously anticipated.[9] This proportion would correspond to 633,323 adults in the United States being afflicted with cirrhosis of the liver based on 2010 US census data. Study investigators noted a bimodal age distribution in cirrhosis prevalence, with peaks during the fourth and fifth decade as well as after 75 years.[9] In multivariable logistic regression, men were greater than two times more likely to be affected by liver cirrhosis, as were individuals with a diabetes diagnosis. Blacks and Hispanics also had greater odds of liver cirrhosis although the results did not reach statistical significance. Alarmingly, 70% of these individuals reported being unaware of having liver disease.

Treatment options for ESLD

Although liver damage from cirrhosis is not reversible, depending on the cause and stage of liver cirrhosis, treatment could stop or delay further disease progression and prevent or minimize complications. Improvements in lifestyle factors such as diet and weight reduction, treatment of alcohol dependency, adherence to medication regimen for hepatitis control, may minimize liver damage in early stages of cirrhosis.[10] However, in cases of advanced liver disease, where the liver ceases to function, a liver transplant may be the only available treatment option. The chapters to follow will focus on this well-established form of treatment, the shortage of donor organs and unintended disparities in accessing this treatment option created by organ allocation systems.

1.3   TRANSPLANTATION OVERVIEW

Better surgical technique, perioperative care and major advancements in immunosuppression have transformed the field of transplantation from an experimental procedure to wide acceptance as an effective and life-saving method for treatment of ESRD and ESLD.[11-14] While wide-spanning policy changes have been successful in increasing access to transplantation therapy and in improving allocation of organs, unintended disparities in access to transplantation and transplantation rates have been created, in both the past and current liver and kidney transplant allocation systems. These disparities mainly affect women and minorities and could be lessened, and perhaps even eliminated, through concentrated efforts by policy makers and public health officials. The current waitlist burdens, allocation policies and transplantation rates, are described below with the purpose of identifying weak areas in the current system where policy amendments and public health interventions would be most beneficial.

In 1984, with the passing of the National Organ Transplant Act (NOTA), the United States Congress established the Organ Procurement and Transplantation Network (OPTN) which was to be headed by a private, non-profit organization, the United Network for Organ Sharing (UNOS), with federal oversight by the Health Resources and Services Administration (HRSA) of the Health and Human Services Department (HHS). This act came in response to the nation's erratic transplantation climate, caused both by a critical organ donation shortage; as well as problems in the matching and allocation processes. Both of these processes were plagued by "privileged access" by certain patient demographic groups, while transplant therapy remained hindered for many other patient populations.[15, 16] As part of this network, the United States was divided into 11 regions, grouping several states, in order to create OPTN regions; these regions are further divided into Donor Service Areas (DSAs) that are defined as the areas from which Organ

Procurement Organizations (OPOs) collect and allocate organs to transplantation centers (Figure

1). Since its beginnings, the goals of UNOS have been to balance utility and equity, in the

allocation of deceased donor organs through efforts in the form of both broad and selective policy

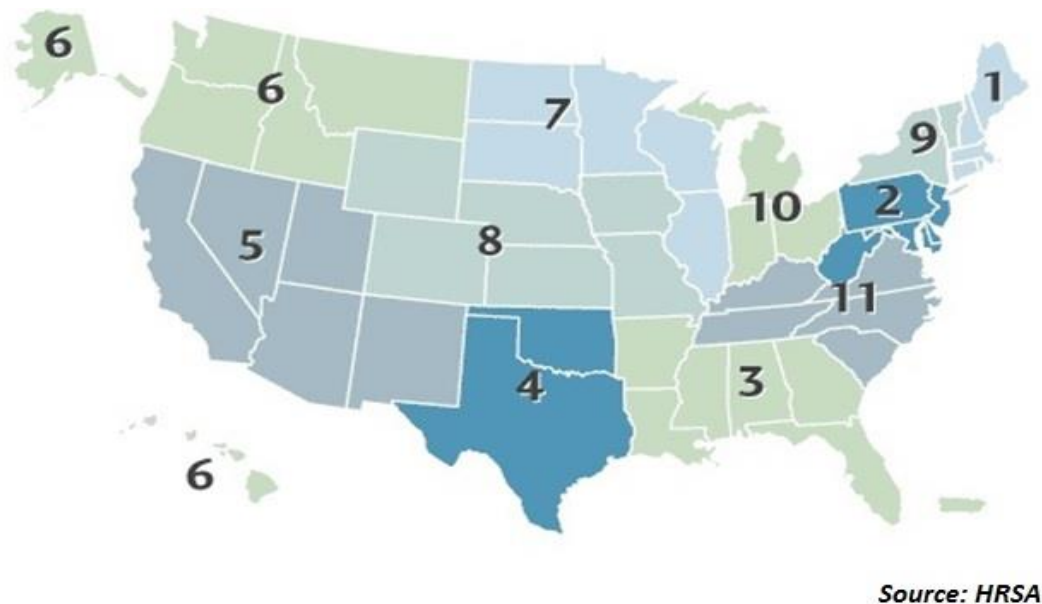changes, in order to optimize allocation to meet these often competing goals.

Source: HRSA

Figure 1. OPTN Regions [17]

Wide spanning policies have been the primary vehicle for permanent change in the

allocation system for all organs. Allocation policies in the liver have moved away from a wait time

designation to addressing more urgent cases of ESLD based on a calculated score (Model for End-

Stage Liver Disease – MELD score) that predicts the three month survival of a particular patient

if they would not receive a transplant. MELD score ranges from 6-40 with higher MELD scores

indicating a higher chance of mortality due to ESLD.[12, 18] While the MELD score is an accurate

predictor of survival, there exists no database of people diagnosed with ESLD that can verify the

extent to which this measure is precise. Such a database exists within the United States Renal Data

System for ESRD and it tracks all patients from the start of dialysis.

In renal transplantation, the snowball effect of "baby boomers" on the health care system has overwhelmed the waitlists and created an even more desperate need for organs.[19] Allocation systems that had been previously based on human leukocyte antigen (HLA) matching have transformed into allocation systems based on waiting time, and even more recently as of December 2014, it has turned into an allocation system based on a refined metric (Kidney Donor Profile Index – KDPI) for assessing how long a kidney is expected to function post-transplantation.[18] With the exception of this new renal allocation system, policy changes in renal and liver transplantation are responsible for the most current reports regarding the transplantation rates in the US and the waitlist burdens for ESLD and ESRD patients.

1.4   WAITLIST BURDENS IN LIVER AND KIDNEY TRANSPLANTATION

In liver transplantation, data from 2013, the most recent and fully-completed year, estimates the waitlist burden to be 15,027 candidates awaiting transplantation, including 12,407 candidates in active status. Overall, in 2013, and there were 5,921 transplants performed and it was shown that 1,767 candidates died on the waitlist while 1,223 were removed from the list for being too sick to undergo transplant.[20, 21] The highest proportion of those waitlisted are aged 50-64 (61.5%), white (70.7%) followed by Hispanics (16.9%), males (65.9% of all transplants), most candidates have MELD scores 15-29 at the time of transplant and hepatitis C infection is the leading cause of ESLD (29.3%). The majority of deaths prior to transplant occur in individuals older than 65 years.[20, 21]

Despite the increased and continuing need for transplantable organs, the number of living donor donations has decreased. A partial explanation for this decline is the observation of an increase in living donor readmissions to the hospital in the first year after transplantation. These readmissions are largely due to biliary and vascular complications. More studies in living donors need to be done in order to elucidate these findings and this should be done prior to the publication of the annual report for 2014. In contrast to the increased complication rates among living donors, outcomes for deceased donor recipients have continued to improve over the years. The highest survival rates are in recipients in the 35-49 age group and lowest in adults over the age of 65 years.[20, 21]

Renal transplantation mirrors the burdens of liver transplantation and over the past decade, little has changed in terms of total numbers of transplants. Yearly, the total number of candidates on the waiting list increases and in the most recent report for 2013, the waitlist for kidney transplantation was estimated to be over 97,000.[3, 4] The highest proportion of all transplants

occurred in candidates aged 50-64 with organs from both deceased donors and living donors.[3, 4] In addition, a greater proportion of renal transplants has been reported among males (51.8% of all transplants), whites (65.8% of all transplants), and the primary cause of ESRD has been reported to be diabetes (29.3%).[3, 4] Like in the liver, outcomes in kidney transplantation have improved tremendously with advances in immunosuppression.[11] However, graft failure and return to dialysis increases as the transplant recipient furthers away from the date of transplantation. Graft survival from living donors is higher than graft survival from deceased donors and overall survival is almost identical among by race, except for a sharp decline that has been observed in blacks within 60 months after transplantation.[3, 4]

These current rates are the end result of numerous policy changes that have been put forth by UNOS in order to solve the issue of the growing waitlist and the shortage of organs. While allocation in the U.S. does help to transplant many individuals, epidemiologic factors such as race, age, gender, socioeconomic status and geographic variation create disparities in both liver and renal transplantation and hinder the current allocation systems from making organs available for the greatest number of people.

2.0   LIVER TRANSPLANTATION: HISTORICAL PERSPECTIVE AND CURRENT

STATUS

Prior to the introduction of the MELD score, there were unequal transplantation rates between minorities and whites, and between genders. Subjective criteria were used to prioritize and evaluate whether a patient was eligible for transplantation.[12] Early allocation was based on location (outpatient setting, hospital ward or intensive care units—ICUs) in order to account for the urgency in which transplantation was needed. This led to large groups of candidates, in ICUs for example, remaining poorly differentiated and it increased the discrepancies in transplantation rates among all patient demographics. Blacks had more advanced disease at the time of wait-listing and were more likely to die while waiting for a graft.[22, 23] At listing, blacks tended to be younger and presented with worse disease than whites.[22] There was a significant discrepancy in the transplantation rate between whites and blacks, with whites being more likely to obtain transplantation once waitlisted. Blacks remained on the waitlist for longer periods of time and underwent prolonged dialysis.[22, 24] Gender discrepancies existed prior to the MELD score as well, however, this disparity is still continuing today, albeit to a lesser extent.[22, 25, 26] Prior to the institution of the MELD score, women were more likely to die or become too sick to transplant within three years of being added to the waitlist and they were less likely than men to undergo transplant.[25, 26]

In 2003, MELD score became the basis of the allocation system after efforts were set to ensure a fair distribution of organs in the system to those with the greatest need: the sickest patients. MELD is based on three laboratory tests: international normalized ratio (INR) of the prothrombin time, total serum bilirubin and serum creatinine.[18] It is a reliable clinical tool for consistent and

accurate estimation of three month mortality for a wide range of chronic liver disease patients based on objective criteria.[12, 27-29] Under the MELD system, priority is given first to acute liver failure candidates who face the risk of mortality within hours or days of diagnosis. These patients are designated status 1A and livers are offered to them, first at the local level and then to status 1A candidates at the regional level. Next, status 1B patients who are very sick, chronically ill pediatric patients, are offered livers first at the local level and then at the regional level. Prioritization is then designated by MELD score ≥15, first locally then regionally. If the liver is not accepted by any of the above, the liver is then offered to MELD ≤15 candidates first at the local level then regionally. Lastly, the liver is offered sequentially to 1A, 1B and all others prioritized by MELD at the national level.[12, 18, 30] MELD scores ≥18 have been found to be significantly associated with benefit in transplantation therapy and studies have shown that increasing MELD scores are proportional to benefit of transplantation therapy.[31] MELD scores 15-17 represented a transition point where there was much ambiguity about the benefit of transplantation and MELD scores lower than 15 had a higher benefit without transplantation. For candidates with MELD scores less than 15, the benefit was greater without transplantation because these patients still had longevity with their own grafts.[27, 31]

The current allocation policy offers organs to those that gain the most benefit from transplantation or candidates with MELD ≥15 first at the local level then regionally to increase benefit of transplantation.[18] There is a large geographic component to this. Previously, organs were being offered in descending order of MELD scores within the same OPO leading to high rates of transplantation in MELD scores less than 18, which decreased the benefit of transplantation therapy in these individuals.[31] In the older system, many OPOs were doing transplants in MELD scores lower than 15, where some were transplanting patients as low as

MELD 7.[32] The allocation policy has since been updated and as was previously stated, organs are offered by MELD score first locally then to candidates with the same MELD score at the regional level before this organ would be offered to a candidate with a lower MELD score.[18] In the current policy, scoring changes as the disease progresses and the score is updated during the course of ESLD treatment. Certain diseases are eligible for MELD score exceptions that award higher points to candidates. Hepatocellular carcinoma (HCC) patients are given a MELD exception and are automatically given higher scores (i.e. 20-22) in order to reach the top of the transplant list for transplantation to occur before the carcinoma is able to spread to the surrounding lymphatic system.

The effectiveness of MELD scoring is invalidated by the diseases that are granted an exception to calculated MELD scoring, due to the fact that MELD scores are unable to accurately predict the urgency in which transplantation therapy is needed. In the example of HCC patients, urgency of the need for transplantation cannot be calculated before the cancer is able to spread. In the current system, additional MELD exception points are given to HCC patients with tumors meeting the Milan criteria of a single tumor no more than 5cm in diameter or fewer than three tumors each no more than 3cm in diameter in order to move these patients further up the waitlist.[18] HCC patients were initially and arbitrarily given MELD scores ranging from 24-29 in order to help predict the urgency of the disease, however, in 2003, this was modified to MELD 20-22.[12, 23, 27] Rates of transplant in HCC patients immediately rose and disparities were reduced across races and genders.[23, 33] Even though the assignment of MELD scores for HCC patients is arbitrary and represents a failure of the MELD system to predict urgency of disease, the reduced differences in transplant rates of patients diagnosed with HCC represents the efficiency of the MELD system to identify the sickest individuals.[23, 27, 34]

This new scoring system has also helped to diminish disparities in transplantation by race and gender. In the pre-MELD era, blacks were less likely to receive a liver transplant than white patients within three years of registering on the waiting list; whereas post-MELD, race was no longer significantly associated with receipt of a liver transplant. Blacks had a 20% increased risk of death in the pre-MELD era if listed without HCC and an equal risk in the post-MELD era compared with white men.[23] Likewise, women listed without HCC had a higher risk of dying or becoming too sick to transplant while on the waitlist in the pre-MELD era. However, after the implementation of the MELD score, men and women both had high rates of transplantation if listed with a diagnosis of HCC (72.2% vs 74.0%, respectively) although, women had a higher risk of death than men if listed without an HCC diagnosis.[23]

Recently, however, there has been a slight decline in the overall number of livers transplanted in HCC patients. While it is still greater than the number of transplants, in this population, prior to the implementation of the MELD based allocation system, the rates of transplant were somewhat decreased between the years 2009-2010.[35] In one study by Halazun *et al*, it was found that transplantation rates varied greatly by region in the amount of time that HCC patients spent on the waitlist.[36] In regions where the waiting time was short, HCC patients had worse overall survival than HCC patients in regions where the wait time was longer. It was also found that being listed and transplanted in regions with short waiting time was an independent predictor of poor patient survival on multivariable analysis.[36] In addition to decreased rates in HCC patients, minorities were significantly less likely to undergo liver transplantation during this same time period.

When comparing between DSAs among all 11 OPTN regions, there exists great variation in organ access, which leads to varying risk of death for a liver transplant candidate.[37] Ideally,

a candidate has the highest likelihood for transplantation in areas where the waitlist is short and the availability of organs is high. Geography-associated imbalance in organ availability is largely demand driven, and demand is proportional to increasing populations. In large metropolitan areas, demand is especially high and it is in these same areas that minority populations are large.[37] This recent decline in transplantation rates of HCC patients does not indicate that the MELD system has failed to work in the HCC population; rather, it directly shows the great need of organs for these very sick patients.[35]

As it was briefly mentioned above, after the introduction of the MELD score, disparities in liver transplantation were decreased and, in some cases, eliminated. Once waitlisted, blacks had the same transplantation rates as whites despite having higher MELD scores at listing.[22-24] Blacks had a lower mortality than whites while on the waitlist, as well.[24, 38] Shorter waiting times were observed for higher MELD scores.[12, 23, 24] Women were still less likely to undergo transplantation than men; however, this disparity was attenuated with the introduction of MELD.[23] Disparities within blood group ABO continued in the MELD era. In the donor pool, there are more blood type O donors than waitlisted recipients. Type-O candidates remain on the waitlist longer than others in both pre- and post-MELD eras.[39] Graft survival is higher in identical ABO matching and slightly lower when blood types are compatible. Type-O organs are disproportionately going to compatible recipients rather than blood type O recipients.[39]

Aimed at increasing transplantations and further decreasing disparities, several policy changes have been put in place in order to improve components of the MELD system. Due to the arbitrarily drawn regional borders of the OPTN, many livers were transplanted locally into recipients with lower MELD scores even when candidates with higher MELD scores were still on the waitlist in neighboring OPTN regions and its DSAs. In 2005, Share 15 policy was implemented

in order to improve organ allocation for local and regional candidates with MELD scores ≥15. If

an organ became available at the local level and it did not match any candidates with MELD ≥15,

the policy allows for the organ to be offered at the regional level for any potential matching

candidate with MELD ≥15. [40] Outcomes of this policy were positive: there was a drop of 26%

of livers being offered to candidates with MELD <15, where the benefit of transplantation was

low, and there was a reduction in variability of MELD scores at the time of transplantation across

the country.

There is great variability among regions with respect to the number of applications for

exception points to Share 15 (i.e. requests for points to increase MELD scores for patients to better

account for the urgency in which they need to be transplanted), which resulted mainly from a lack

of standardization and oversight.[41] The proportion of DSAs where at least 90% of all liver

transplants were done on candidates with MELD ≥15 increased significantly.[40] Exception point

applications did not differ by center competition for organs in the DSA. More than half of all

applications were approved (64.5%) and candidates were transplanted with a deceased donor organ

even when an astonishing 80.2% of these patients had a MELD score of less than 15. [41] Given

the fact that MELD scores 15-17 represent a transition point where scores less than MELD 15 have

a lower survival benefit, it is surprising that such a high proportion of applications were accepted

for MELD exception points. This example clearly shows the influence that individual physicians

have regarding the transplantation process for candidates. Certain physicians or transplantation

centers might be more inclined to apply for exception points and there could be a selection bias

for candidates for which physicians are willing to submit these applications.

Along the same lines as Share 15, another policy change came into effect in 2013. Share

35 is aimed at increasing transplantations in liver transplant candidates with MELD scores higher

than ≥35 which identified very ill candidates with ESLD whose survival benefit of transplantation is much higher than that of remaining on the waitlist.[27, 42] Share 35 is successful and is associated with more transplants and lower waitlist mortality, without having much effect on the early outcomes after transplantation surgery.[40, 42]

Despite policy updates and creation of a prognostic tool to treat all patients with ESLD equally, differences in outcomes exist. Blacks have worse graft and patient survival after liver transplantation in comparison to whites.[43-47] Whites have an overall advantage over blacks but there is no advantage over Hispanics.[46] Survival rates decrease as recipients further away from the date of transplant. At 10 years post transplantation, survival rates were highest in those whom were transplanted as children (overall survival is 77% within one year of transplantation, 79% survival 1-5 years post transplantation, and 81% survival 6-11 years after transplantation).[43] One year graft survival was highest in ages 1-50 (90%), and lowest in children under the age of one (83%) and in older adults over the age of 65(81%). [43]

Since the prevalence of depression is high among candidates while they are still on the waitlist (60%), the treatment of depression after liver transplantation was shown to be a better predictor of long-term mortality than MELD score, HCV status and donor age.[48] After transplantation, the prevalence of depression among patients is curbed but not eliminated (prevalence rate 30-40%).[49, 50] A study by Rogal *et al* showed that there was a difference in ten year overall survival between patients that were treated and not treated for depression after transplantation. Patients that were treated for depression after surgery had a slightly lower overall survival percentage compared with non-depressed recipients (52% versus 56%, respectively). Survival in those whom were inadequately or not given treatment for depression was found to be 32% at ten years post transplantation.[48]

Living donors had bad outcomes as a result of biliary, re-hospitalizations due to initial transplant and donor suicides within the first year post transplantation.[20, 21] Based on the results from the aforementioned study, intervention could be focused on the prevention of suicides in living donors through advocacy for increased monitoring and screening prior to and post organ donation. Finally, there is large variability in graft outcomes and the location of where the transplantation was performed and this has been determined to be an independent predictor of graft loss.[51] Variability exists in the way that centers manage complications after surgery; complications can be lessened by carefully evaluating donors prior to transplantation in order to make sure that they are healthy enough to tolerate such a demanding surgery (i.e. evaluating donor BMI, blood pressure, age among other factors). In addition, elimination of complications can also be accomplished through skillful surgical technique and attentive follow-up care.[52, 53]

3.0 KIDNEY TRANSPLANTATION: HISTORICAL PERSPECTIVE AND CURRENT STATUS

Since the establishment of the OPTN and UNOS, like in liver transplantation, there have been many allocation systems tried in renal transplantation to increase equality and utility. The renal allocation system was first based on HLA matching which was aimed at increasing long term graft survival [54] and then it switched to a system based on calculated panel reactive antibodies (CPRA). In December 2014, a new allocation system was implemented based on the Kidney Donor Profile Index (KDPI) which is derived from data from donors in the previous 12 months, making the system incredibly up to date and better able to predict matching between recipients and donors.

The formerly mentioned HLA based system awarded points based on number of matches in the HLA-A, HLA-B, and HLA-DR loci. The system was flawed due to natural variation in HLA genotypes between different racial groups.[19] Blacks were poorly served by this system due to the natural heterogeneity at these loci, in this population.[12, 19, 54] As was discussed earlier, blood group ABO matching continued to create disparities. Graft survival was higher in exact ABO matches and worse in compatible matches (type-O as the universal donor for A, B, AB, O). In this system, AB (the universal recipient) had the shortest wait time on the transplant list and donor type AB organs were discarded at a higher rate than any others. Since the largest proportion of donors were and are currently in the type-O blood group, in the HLA-based system type-O organs were being offered to compatible recipients, rather than solely to type-O recipients. As a result, type-O candidates had longer waiting times and had lower rates of transplantation.[55, 56]

Allocation policies in renal transplantation then increased use of predictive tools that intended to calculate the most appropriate organs for recipients, through matching, by taking into

account the recipient's own biological and epidemiologic characteristics. In order to better estimate the proportion of deceased organ donors that would cross match, the calculated panel-reactive antibody measure (CPRA) was created. CPRA took into account the HLA frequencies and characteristics of the entire donor pool that had been entered into the OPTN registry and was used to predict matching between transplant candidates and potential donors.[12, 57] The higher the percentage, the more unsuitable organs there are in the donor pool for that individual because the recipients antibodies reacted to the antigens of a potential donor, much like they would if the organ would be transplanted into that candidate.[57] Using this measure, priority was first assigned to recipients receiving multiple organs, secondly priority was given to recipients of cadaveric kidneys where there was zero antigen mismatch with the donor, and thirdly, priority was given to ABO compatible recipients and the six HLA A, B, DR antigens.[12] Next, all candidate were ranked by their CPRA percentage much like the MELD score that was previously discussed, and organs were first distributed locally, regionally, and lastly, nationally. Organs were first offered to CPRA ≥80% at the local, regional, and national level before they were offered to CPRA 20-79% in this same geographic sequence because the higher the CPRA the harder it is to find suitable organs for these candidates. If they matched to a particular donor, they were given priority.[12] In order to help rank patients within each level of CPRA, candidates were given points. Those who have waited the longest were assigned one point and the rest were given fractions of points relative to that individual who had waited the longest.[12]

In order to improve the aforementioned disparities in transplantation rates that had been created by this system, attention was focused on prioritizing candidates based on the amount of net lifetime benefit that they would receive from the graft.[58] HLA-A and HLA-B matching were eliminated because they did not show significantly greater benefit to recipients. This allowed for

many more recipients to be matched to potential donors due to the fact that they were being matched only at the HLA-DR locus. Matching at this locus proved to be essential for graft survival.[59] In addition, elimination of compatible matching between blood groups increased transplantation rates in type-O candidates. These major revisions of the allocation policy were responsible for a sharp increase in transplantation rates for minorities and decreases in disparities based on race and blood group.[12, 55, 59, 60]

Despite successful policy changes, limitations to the HLA based system existed. The system was not able to differentiate the ability of candidates to survive on the waitlist, and it did not match donor and recipient characteristics to optimize survival after transplantation. Organs from younger donors were being transplanted into older individuals even when these older individuals would not get the maximum benefit from the grafts due to their older age. Many were dying of other comorbidities with functioning transplanted grafts.[12] Furthermore, HLA matching was creating differences in transplantation rates between whites and blacks because it did not account for the extensive HLA variation in blacks where extremely rare HLA genotypes exist. Caucasians make up the majority of the donor pool thus HLA matching systems naturally favor white recipients.[61] In addition, minorities make up the majority of the type-O blood group and since compatible matching allowed for type-O organs to be distributed to blood group compatible individuals, this caused a shift in organ distribution away from the blood type-O group.[39, 61] The cumulative incidence of graft failure was higher among blacks and Hispanics than whites. They were more likely to develop acute rejection despite modern immunosuppression.[26, 45, 62-65] Furthermore, black race was associated with a higher risk of biopsy proven acute rejection at one year post transplant.[63, 65] In a study by Rhee *et al*, rejection rates across all age groups were studied, and it was found that rejection rates were significantly

higher in blacks older than 40 but rates for blacks 18-40 were similar to those of whites. They also found that Hispanics experienced lower rejection rates than whites.[62, 66] Graft failure was found to be highest in recipients who live in poorer areas. This highlights a possible disparity in access to healthcare, socioeconomic factors that may play a role in follow-up maintenance and decreased monitoring which lead to higher rates of rejection.[44, 63, 67-69]

In December 2014, UNOS implemented a system based on Kidney Donor Profile Index (KDPI) which is a numerical measure based on the Kidney Donor Risk Index (KDRI). The KDRI takes into account the relative risk of kidney failure after transplantation in an adult recipient from a particular deceased donor based on average donor characteristics.[18] KDPI takes into account 10 donor factors and summarizes the potential risk of graft failure after kidney transplantation. The KDPI ranges from 0% to 100% and the lower the KDPI value, the higher the expected longevity is after transplantation therapy and vice versa. The new kidney allocation system (KAS) was developed to address the issue of inadequate longevity matching and variability in transplantation rates for candidates with high CPRAs. In the new system, all adult kidney candidates receive an Expected Post Transplant Survival (EPTS) score which is based on four medical factors: age, time on dialysis, current diabetes status, and whether the candidate had a previous solid organ transplant. Lower scores are associated with more benefit from longevity kidneys. This would likely be a score given to younger candidates. Again, KDPI scores are assigned to donors and EPTS scores to recipients in order to achieve better longevity matching so that grafts from younger donors would be transplanted in age-matched recipients rather than patients that do not have a high predicted longevity. Candidates with CPRA scores greater than 98% are given increased priority in the region and nationally. Total dialysis time even prior to wait listing will be taken into account for all recipients. This prioritizes patients that have been on dialysis for a long period of time and

may impact older recipients by decreasing their survival post transplantation because in addition to being on dialysis for the duration of the waiting time, these candidates would be given grafts from age-matched donors that would not perform as well as grafts with low KDPI scores. Nevertheless, this would decrease unrealized life years from younger grafts being transplanted into older candidates. Simulation modeling has predicted that the new KAS will result in over 9,000 additional life years achieved annually from the current pool of deceased donor kidneys.[70] Furthermore, the new system will attempt to address the geographic variation in access to transplantation by high CPRA candidates. More organs are expected to be offered at the regional and national level.

Three monitoring reports have been issued by OPTN HRSA databases since the implementation of the new Kidney Allocation System (KAS).[71] Three main differences have been observed since the implementation of KAS relative to previous rates: there is a seven-fold increase in transplantation of candidates with CPRA 99-100%, an increase in non-local transplants from previously reported 20% to 35%, and a drop in the number of age mismatched (i.e. longevity mismatched where recipients and donors differed by 15 years) transplants from 50% to 41.7%.[71] These changes were expected due to the way in which KDPI and EPTS are calculated in order to increase longevity matching, the built-in sliding CPRA scale and the broader sharing of organs for highly sensitized patients. A high number of candidates with CPRA 99-100% were expected to be transplanted initially creating a spike in the number of transplants in this cohort. Many of these candidates have been on the waitlist for quite some time and their rates of transplantation will decrease due to regional and national priority for CPRA 99-100% patients. In addition to these trends, there was an observed increase in transplants in age groups 18-49 and decreases in transplants among persons aged 50 and older as well as a decrease in transplantation from 5% to

2.2% in pediatric candidates. Likewise, the number of waitlist registrations has also decreased slightly in the weeks prior to KAS implementation; the number of registrations in the KAS period was 2802.9 compared to the average registration of 3119.7, a drop of 3% from the immediate pre-KAS period.

The second and third reports issued by OPTN HRSA in February and March 2015, respectively, mirrored the same three trends regarding high rates of transplantation of candidates with CPRA 99-100%, decreases in the number of non-local transplants and decreases in age-mismatched transplants. Significantly fewer zero-mismatch transplants (about 5%) have been performed in the first month post-KAS since prior to KAS (about 8%).[72, 73] The same decrease in pediatric candidates was observed and it can somewhat be explained by the elevated prioritization for very high CPRA patients after KAS implementation. The distribution of transplants by candidate age has continued the shift away from candidates over the age of 50 towards candidates aged 18-49. In addition to these known trends, the proportion of blacks undergoing transplantation has increased significantly; they represent 39% of all transplant recipients post-KAS implementation.[72, 73] It is possible that this is the result of KAS awarding points to time spent on dialysis prior to listing since the waitlist time is known to be higher in this group.[12, 19, 61, 74-76]

Since it is known that transplant rates vary by OPTN region but are relatively fair at the level of OPO, these data warrant a look at the level of DSA and OPO in order to determine if real changes in transplantation are present and if known disparities in access to waitlist, transplantation of ABO blood groups and differences in outcomes persist in the new KDPI based system.[61]

4.0   UNDERLYING DISPARITIES IN LIVER TRANSPLANTATION

Liver and kidney transplantation rates are impacted greatly by epidemiologic factors that cause previously mentioned disparities throughout the entire transplant process. Liver transplantation is impacted by age, race, gender, and varying geographic factors. In the liver, the MELD based allocation system changes in favor of wait time are impacting older candidates negatively.[11, 19, 51] Older individuals are remaining on the waitlists longer due to longevity matching that was previously discussed which leads to lower survival rates after transplantation due to age-related comorbidities.[77] The race disparity is less pronounced in the MELD system as opposed to the pre-MELD era.[24, 34, 77] Whites are typically older and have a higher socioeconomic status than blacks and Hispanics at the time of listing, yet their MELD scores are lower at transplantation.[46] Blacks and Hispanics are more likely to be insured by the government which impacts their likelihood for evaluation and wait-listing for transplantation.[38, 44, 46, 51] Access to wait-listing is disproportionately lower in blacks and after wait-listing, their median MELD scores are higher than their white counterparts. This suggests that blacks are sicker upon listing.[23, 24, 38, 77] HLA matching continues to be an important factor in hindrance to transplantation in minorities.[39, 61] There is extensive variation in HLA genotypes in blacks and since the majority of the donor pool is made up of whites, matching tends to favor white recipients.[61] There are discrepancies in the literature regarding death while on the waitlist for blacks. Studies have shown that blacks are more likely to die while on the waitlist which likely corresponds to a sicker population being listed, as described by higher MELD scores upon listing, lower access to healthcare for ESLD management, and likely confounding by geographic area of study.[22, 23, 38, 46] In contrast, Mathur *et al* reported that blacks had a 37% lower mortality rate

than whites while active on the waitlist and that removal from the waitlist did not differ by race.[24] It is evidenced by these discrepancies in the literature that geographic variation is a large confounder of transplantation rates.[24, 44, 52, 66, 74, 78, 79] Equal rates of transplantation have been observed between the larger OPTN regions but differences in the population make up of regions will produce differences within regions because minorities are not equally distributed among the 11 OPTN regions.[24] When relative transplant rates were compared between blacks and whites registered in the same quadrant of the country (grouped contiguous OPTN regions: northeast, southeast, northwest, and southwest), blacks had a significantly lower adjusted transplant rate versus whites.[23] Similarly, blacks and whites in the same OPTN region had differing rates of transplantation but at the level of DSA, the differences disappeared.[23, 24] Again, no statistically significant differences were found among the 11 OPTN regions.[23, 24, 38, 52] Once waitlisted, blacks have the same likelihood of undergoing transplantation as whites.[24, 34, 38]

Much like in blacks, race disparities exist in the Hispanic population as well. Hispanics have overall lower rates of transplantation and wait-listing despite high rates of referral for evaluation for transplantation than whites.[39, 44, 51] This population has high rates of co-morbidities such as diabetes, hypertension and obesity which leads to high rates of ESLD in this population.[46, 51] Hispanics make up the highest proportion of candidates with blood type-O which continues to be a limitation to transplantation due to the fact that type-O organs are disproportionately given to compatible recipients, thus creating longer waitlists and wait-times for type-O candidates.[39] Hispanics are overrepresented at low and medium performing transplantation centers and their waitlist time tends to be long because tend to transplant patients with higher MELD scores.[51] Populations that are more concentrated in certain parts of the

country end up in similar performing centers and are subject to the waitlist disparities at that given location.[24, 51] In addition to black and Hispanics, Native Americans had the lowest rates of wait-listing prior to and after the introduction of the MELD system whereas the disparities in transplantation rates for Asians decreased with the introduction of MELD scores.[26]

Women face a large disparity in access to transplantation, despite being listed three times as often as males.[26, 77] This disparity existed even when women and men were given the same MELD score at listing in the same center. Since there is greater benefit of transplantation in MELD ≥15, women at these high MELD scores are especially vulnerable to becoming too sick to transplant or dying while still on the waitlist. This disparity was measured to be 20% in MELD scores 20-29 and it was 12% in MELD scores 30-40. In lower MELD scores, the transplantation rates are equal.[26] It is possible that MELD scoring could be a poor predictor of disease severity in women because it is based, in part, on serum creatinine levels. Women are naturally smaller and have less muscle mass which could account for lower levels or creatinine.[26, 80] Creatinine levels do not account for all of the disparity in transplantation rates of women because these disparities existed prior to the adoption of the MELD score as a prognostic tool. Before MELD scoring was the used as the main measure, the difference in transplantation rates between women and men was more than 14% lower, but still existent.[26] Given the fact that women have a 9% lower removal rate than men from the waitlist due to factors other than transplantation, it is possible that they are disproportionately surviving on the waitlists.[26] It is possible that the assigned, calculated MELD score could be overestimating the severity of disease in women if they have a higher chance of survival on the waitlists.

Geography not only affects disparities faced by women, but also it affects race, socio-economic status, and age related disparities that were previously mentioned.[34] Local

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environments of the transplant centers play a big part in transplant rates. This is especially important in minorities because if one race or group of people is more highly concentrated within a region and within the borders of a particular OPO, this can lead to higher rates of transplantation in these individuals.[61, 81] This accounts for the great variation in candidates per deceased donors among the 63 DSAs in the US and it demonstrates why the waitlist removal rates vary greatly.[44, 81] Transplant recipients at high-volume centers had lower MELD scores and recipients at high-volume centers also experienced shorter waiting times.[34] High performing centers tended to use expanded criteria donor (ECD) organs that carried a higher risk of graft failure due to donor specific characteristics such as obesity, diabetes, and hypertension among other factors. In other words, the donors might have been on the path to declining liver function themselves. The use of extended criteria donor grafts has been reported in centers that are in direct competition with each other within the same DSA.[82-84] Centers that use more livers offered at the national level, which have been rejected both at the local and regional levels, are likely to have large waitlists and patients with high MELD scores, high transplant volumes and be located in competitive DSAs where organs are even more scarce due to population demand. Center competition is a direct result of the patient volume and center specific motivation to decrease waitlist burdens. Patient outcomes are worse in these centers due to use of marginal organs.[83, 84] Competition for organs exists at the patient level as well. Candidate listing at more than one DSA is allowed by law and many patients list in DSAs with shorter waiting times with transplantations occurring at lower MELD scores. The patient demographic that tends to multiple list are individuals that are privately insured, college educated, white males with blood type O.[78] For those that can afford to travel, double listing greatly increases the likelihood of transplantation.

5.0   UNDERLYING DISPARITIES IN KIDNEY TRANSPLANTATION

The same epidemiologic factors that affect liver transplantation are apparent in kidney transplantation. Minorities have a large socioeconomic disadvantage compared to whites, leading to lower rates of transplantation, lower rates of wait-listing, decreased availability of living donation, and higher discrepancies in HLA matching.[13, 61, 67, 68, 85, 86] It has been reported that as neighborhood poverty increases, the likelihood of wait-listing decreases for blacks compared to whites. Blacks living in poor neighborhoods (i.e. where more than 20% of the population lived below the federal poverty line) had a two-fold lower difference in access to the waitlist than their white counterparts.[62, 67] Black ESRD patients are 67% less likely to be placed on the deceased donor waitlist.[67, 68, 86]. In this population, failure to complete standard requirements for transplantation was higher in blacks and a significant portion of individuals reported psychosocial reasoning for failure to complete requirements.[68] A greater portion of blacks did not even start the evaluation process.[62, 67, 68] Blacks face greater barriers to wait-listing than whites.[13, 67, 68, 87-89] Those able to be waitlisted for a transplant, have longer waiting times, and tend to be younger and female. Blacks are 38% less likely to receive deceased donor transplants due to disparities in HLA matching that have been previously discussed. They have a survival advantage on dialysis and they remain on dialysis therapy for longer periods of time due to longer wait times to transplantation.[90] Prolonged exposure to dialysis before transplantation and black ethnicity are known risk factors for acute rejection and graft loss in kidney transplant recipients.[91, 92] This could be an explanation for the higher death rate seen in blacks at 60 months post transplantation that was previously mentioned. Graft outcome and overall patient survival are shorter for blacks compared to whites.[62, 63]There is greater heterogeneity

in this population that complicates matching. However, with the policy to eliminate HLA-B matching after the publication by Roberts *et al*, the disparity in matching decreased by 15% and blacks were only 23% less likely to receive transplantation therapy.[59, 60, 93]

Hispanics experienced similar disparities as blacks in access to kidney transplantation therapy.[61, 62, 66, 87, 94] Hispanics make up the largest minority group in the US and are twice as likely to develop ESRD at a younger age compared to whites, due to high rates of hypertension and diabetes in this population.[66] While this population is equally as likely to be referred for transplant therapy, they are waitlisted at a lower rate than whites.[61, 66] This may imply that Hispanics are a healthier cohort of people.[61, 66] Graft failure is lower in Hispanics than whites, as well.[62] As was the case in the Hispanic population, Native Americans were also more likely than whites to be identified as possible candidates for renal transplantation, however they were less likely to be listed than whites.[94]

Geographic differences account for large proportions of the disparities in transplantation rates in blacks and Hispanics. Local organ availability is limited by population concentrations, Greater demand for transplantation in regions where there is limited organ availability will affect access to transplantation.[61] For example, rapidly growing Hispanic populations seem to be concentrated in highly populated OPOs in certain regions of the country (i.e. Florida, New York, Texas, and California).[61, 66] OPO of listing was found to be the single most important contributor of disparities faced by minorities. Nationally, there is greater variability in disparities, but at the level of OPO, small differences exist.[61] This national variability will continue to exist so long as allocation follows arbitrarily drawn OPTN regional borders.

A possible way to decrease discrepancy in these minority populations is to increase their rates of living donation. Since 1988 living donation had steadily increased in all OPTN regions of

the U.S. until 2004. Reasons for such high donations include advances in HLA matching, less invasive laparoscopic surgery techniques, greater public awareness of the need for transplant and less strict donor eligibility criteria.[76, 95] Research on appropriate donor criteria has shown that careful evaluation prior to donation needs to be done. Therefore, this relatively recent decline in living donor donations could be the result of shifting donor criteria towards healthier donors with lower rates of pre-existing conditions and obesity.[75] Furthermore, increased oversight and low performance ratings of centers have had an impact on donation rates. In centers that received low performance ratings, there was a decrease of 22 transplants compared to an average decrease of eight over study period ranging from 2007-2010.[85] Increases in oversight have led to suppression of innovation of surgical technique, decline in use of novel therapies, and increases in the use of more conservative policies.[85]

Currently, women are more likely than men to be living donors [76] and they were less likely to want living donation kidney compared with men.[96] Living donation is very low in blacks and minorities.[61, 62, 67, 68, 75, 93, 97-100] Studies have found that more individuals in this population might be in the early stages of living donor donation that are characterized by increasing willingness to learn more about the process. Patients in later stages reported having significantly more knowledge of transplantation, increased willingness to talk to family members about donation, and fewer concerns about the process.[99] Research has shown that the more trust there is in healthcare, the higher the donation rate.[98, 101] Other barriers to donation in blacks include financial barriers, as out of pocket costs of donation average to $5,000 due to travel and lodging, and lost wages during recovery.[98, 102] The same barriers were observed in Hispanics, citing lack of knowledge about the transplant process, family dynamics where certain members discourage donation, and financial barriers to donation and fear of being unable to work.[103]

Among all living donors, women, Hispanics, and blacks have higher incidence of hospitalizations, diagnoses of hypertension and depression, and variable insurance status.[104]

6.0   PROPOSED WAYS TO DECREASE AFOREMENTIONED DISPARITIES

Transplantation therapy has come a long way since its beginnings in the early 20th century; however, improvements in policies and education continue to be important ways of decreasing disparities between transplant recipient demographics. In liver transplantation, although the MELD system is working well, minorities and blacks continue to have difficulty in obtaining access to the waitlist. Arbitrarily drawn OPTN regions dictate the flow of organs within large metropolises, small towns and rural areas.[16] In one model, re-drawing of the regions to account for large populations of possible donor and recipient matches, has increased the intraregional number of transplants by more than 130.[105] Redrawing of OPTN borders is an important step to improving allocation because the current system is not based on any measureable statistic for effectiveness in allocation of organs.[16]

Another important step in improving liver allocation is the creation of an analogous registry for all patients diagnosed with chronic liver disease that can be linked to the Scientific Registry for Transplant Recipients (SRTR) in order to facilitate development of allocation policy through better estimates of ESLD burden. There is a desperate need for a better defined set of guidelines for non-hepatocellular carcinoma patients that can be used in order to better characterize and evaluate candidates for transplantation. There is no definitive event that occurs to signify that a person has ESLD, therefore a possible step to creating a database is to have healthcare providers report incidences of liver related diseases or mentioning transplantation therapy to their patients. Possibly adding ESLD or the mentioning transplantation therapy to patients to the list of reported diseases could be a way of obtaining the true rate in the population. This on-going reporting would not mean that all of the identified patients are eligible for transplantation therapy, but it would give

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a rough estimate of the disease burden of ESLD, in the United States. Some have argued that a minimum MELD score for listing needs to be created.[31, 32] While this would certainly reduce transplantation in individuals with low MELD scores, in whom the benefit of transplantation therapy is lower than the benefit without the new graft, this change would restrict data gathering on waitlist mortality and other factors in this group.[32] These individuals with low MELD scores serve as one of the best populations to study in order to determine the burden of ESLD in the nationwide population.

To address the disparity between genders in access to liver transplantation both in the pre-MELD and the worsening disparity in the MELD era, the MELD score could be adjusted for women to account for the naturally low titers of serum creatinine, a large component of MELD score calculations.[80] Furthermore, better treatment of depression in post-transplant populations would increase and help to better predict overall survival.[48] Continuous screening of patients for depressive symptoms after transplantation therapy is a way of increasing survival by possibly improving adherence to antirejection medication regimens and post-operative follow-up. In addition, better post-operative depression treatment would likely result in lower rates of inactivity and weight gain that are associated with depression, leading to better rehabilitation after surgery.[48]

Alongside these policy changes, public health intervention should focus on vaccinations against Hepatitis A and B as well as education efforts to promote healthy lifestyles in order to prevent progression to ESLD. Since hepatitis C is the leading cause of ESLD in the U.S., increasing education efforts regarding the modes of transmission of the virus is an important step to curbing infections. Hepatitis C is spread through blood-to-blood contact and a leading way of transmission is through intravenous drug use.[106] The community resources that would be most valuable are:

school administrators, parents of those that have died or gotten sick as a result of intravenous drug use, nurses and doctors, people working in clinics, sheriffs/local police department and current and past intravenous drug users themselves. School administrators are an invaluable part of designating drug free areas and making sure that schools have a zero tolerance policy. They could provide insight about after-school programs that aim to keep kids off of the streets and providing them with anti-drug education so that they do not become the next wave of users. Intervention methods relating to intravenous drug use have been studied in adults, however, the same strategies might not work well in adolescents and young adults due to differing developmental stages.[106] More research is needed in this field.

As in liver transplantation, policy changes and increasing education efforts through public health interventions are possible ways of decreasing observed disparities in kidney transplantation. Redrawing of OPTN regions could possibly increase the number of kidney transplants, in the U.S., in the same way that was observed after liver allocation remodeling.[105] Likewise, increase living donation through policy changes, in particular expanding kidney paired donation (KPD) nationally will result in more transplants being done. In practice, KPD is when two pairs of donors and recipients are incompatible with their intended recipients. If the donors are both compatible with the recipient from the other pair, kidney paired exchange may occur if all parties are willing to participate.[18] Currently, the rates of KPD are low largely due to ethical and legal barriers, but efforts are still being directed to implementing a National KPD program. In 2005, the New England Program for Kidney Exchange (NEPKE) began incorporating donor and recipient pair data into a large database that would be able to successfully predict matching pairs, eventually increasing matching to three-way paired exchange and even longer chains. The NEPKE computer algorithm identifies recipients who are ABO compatible with the donor pool; if an incompatibility is found,

this donor is eliminated from the results. Long transplant chains can be built if there is an altruistic donor present who is not paired with a recipient. This donor starts a chain by donating an organ to a matched pair whose donor will eventually give to another pair and the chain will continue until it breaks.[107] Breaks in the chain result from either the recipient or donor wishing to no longer participate, or the recipient denying the organ which has been offered. Even though kidney paired exchange is an effective way of increasing living donor transplants, it is somewhat unreliable because the identified pairs could change their minds regarding surgery and affect many other candidates. To minimize possible breaks, the new system for allocation of kidneys has limited chains to 20 donor recipient chains.[18] Despite this drawback of relying on patients to make clinical decisions, in 2010, UNOS piloted the National KPD program where four coordinating centers were charged with enrolling patients into the paired exchange database. The eventual goal is to link these databases to the main UNOS database that links all OPOs and transplant centers and allow for any transplant center to participate in KDP program.[107]

In conjunction with wide-spanning policies, increasing knowledge of the transplantation process through education efforts from community wide interventions is a method for not only increasing living donation rates in blacks and minorities, but also decreasing barriers to wait-listing by possibly making these populations more likely to initiate conversations regarding transplantation with their physicians. This intervention could potentially introduce increases in available organs for transplantation and decrease the exponentially growing waitlist. Together with these community wide interventions, public health intervention should focus on increasing education on the leading causes of ESRD: hypertension, diabetes, and obesity. Promotion of physical activity and healthy diets are key. Walking paths, bike lanes and farmers markets could be incorporated into communities with high rates of obesity in order to increase physical activity

in these populations. Furthermore, healthcare providers can initiate more conversations with patients regarding these pre-cursors to ESRD, or, provide information to family members so that the conversations regarding healthy living can be initiated at home.

The solutions for observed disparities in both liver and kidney transplantation are not obvious. Effective policy changes in conjunction with educational efforts relating to greater public health have the potential to ameliorate observed health differences between populations and, in some cases, eliminate the progression to ESLD or ESRD altogether. For those patients who progress to the point of needing transplantation therapy, these same policy changes have the potential to bring a lifesaving therapy to many more individuals than the current system supports.

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