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# Severity of Illness and Prognosis of Liver Transplant Candidates at Yale

Arvind Venkat

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Severity of Illness and Prognosis of  
Liver Transplant Candidates at Yale

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Arvind Venkat

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Severity of Illness and Prognosis of Liver Transplant  
Candidates at Yale

A Thesis Submitted to the  
Yale University School of Medicine  
In Partial Fulfillment of the Requirements for the  
Degree of Doctor of Medicine

by

Arvind Venkat

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## Abstract

### SEVERITY OF ILLNESS AND PROGNOSIS OF LIVER TRANSPLANT CANDIDATES AT YALE.

Arvind Venkat, Amy L. Friedman. Section of Transplantation and Immunology, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

The increasing number of patients with end-stage liver disease (ESLD) listed for transplantation has forced physicians to examine the disparities in waiting times (WT) for this procedure across the US. The debate has centered upon whether physicians within regions with longer WT, such as that of Yale, are listing patients prematurely compared to regions with shorter WT. Using regional variations in WT, per this argument, to analyze access to organs is therefore misleading. To determine the appropriateness of listing practices at Yale, the authors applied stratification guidelines for liver transplant candidates adopted by the United Network for Organ Sharing (UNOS) on 1/19/98 to patients listed for transplantation at Yale as of 11/14/97. Medical records were reviewed to confirm clinical histories, and referring physicians were contacted to obtain data from within four months of 11/14/97. Patients were reclassified per UNOS guidelines and followed until 7/1/99 to determine prognosis. Of the original cohort of 89 patients, 8 patients had died prior to reclassification; 2 had been lost to follow-up. Of the remaining 79 patients, 40/79 (50.6%) met criteria for severe ESLD, and an additional 29/79 (36.7%) met minimal listing criteria (MLC); a total of 87.3% met criteria for listing for transplantation. Of the 10 patients who did not meet MLC, by 7/1/99, 4 were listed after appeal to the regional review board under circumstances not covered by UNOS guidelines, 4 clinically worsened and were actively listed, and 2 remained clinically well. By 7/1/99, 1 patient was found to meet MLC, but was clinically too well to offer transplantation, and 1 additional patient had been lost to follow up. On 7/1/99, 3/86 (3.4%) patients in the original cohort did not meet MLC for transplantation. There is no evidence that long WT have led to premature listing of liver transplant candidates at Yale.

## Acknowledgments

Completing medical school is a daunting task.

Certainly, Yale makes life easier, but the combination of obtaining the requisite medical knowledge and learning the clinical skills necessary to become a physician while maintaining one's humanity so as to relate well to patients is a challenge to say the least.

One of the great benefits, however, of attending medical school at Yale is the opportunity to conduct independent research in the form of the thesis requirement. I came to choose the area of liver transplantation for my thesis almost by accident, after having watched, of all things, a news broadcast on the regulation of the distribution of organs. To go from this point to a thesis has required a great deal of guidance and support. As a result there are many people to thank. First, I would like to thank my advisor, Dr. Amy Friedman of the Section of Transplantation of the Department of Surgery. Over the last two years, she has been a constant source of encouragement and constructive criticism which has put me on the path to looking at my research critically and, hopefully, supporting my assertions with fact. In addition, she has been a great friend with a lot of good advice during the trials and tribulations of medical school. For that, I will always be grateful.

I would also like to thank my family, my mother, father, and younger brother, Deepak. For the past 26 years,

they have always been open minded about my interests and supportive of my educational aspirations. As I come to the end of my formal education, words cannot convey the gratitude I have for all of the sacrifices they have made for me, and while I here say thank you, it certainly is not enough.

Finally, and most importantly, I would like to thank my wife Veena for all of her love and support. As my classmates know, prior to my meeting Veena two years ago, I think that my sense of proportion about medical school was off. Since we met, I have been fortunate to have a person in my life off whom I can bounce my ideas and share my hopes, dreams, and fears about medical school. I will always cherish our relationship, and this thesis is most of all dedicated to her.

Arvind Venkat

New Haven, CT

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## *Introduction*

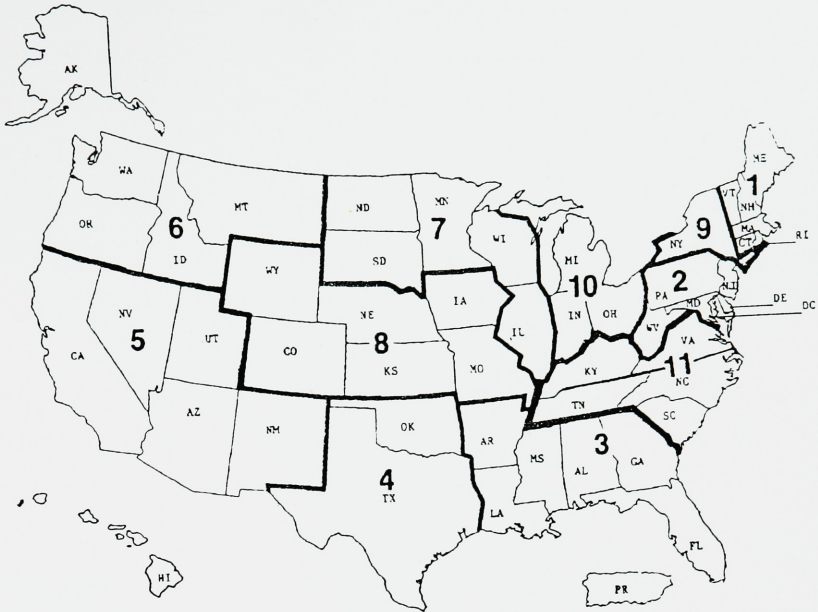
*"People are dying unnecessarily, not because they don't have health insurance, not because they don't have access to care, but simply because of where they happen to live in the country."*[1] When Secretary of Health and Human Services Dr. Donna Shalala made this statement in announcing the federal government's Final Rule, calling upon the United Network for Organ Sharing (UNOS) to devise a method of equalizing waiting times for patients listed for liver transplantation across the United States, she was capturing the heart of a dispute that has rippled through the liver transplantation community for a number of years. UNOS, a private, nonprofit organization administered by representatives of transplant centers across the nation, contracts with the federal government to coordinate the national organ allocation system under the provisions of the National Organ Transplant Act of 1984 (discussed in greater detail below). With the shortage of donated organs (4,886 livers in 1998, 2,431 through June 30, 1999)[2], the number of individuals waiting for liver transplantation has risen dramatically, from a total of 3,404 on May 31, 1994[3] to a total on December 11, 1999 of 14,349.[4]

As this number has risen, there has been increasing dispute as to what is the cause for disparities in waiting times for this lifesaving procedure. As Dr. R. Randal Bollinger, former President of UNOS, noted in 1995:

"The increasing disparity between the numbers of patients waiting for cadaveric organs and the numbers of donors in the United States is well known to liver transplant surgeons. Ever more patients will die waiting. The sense of urgency felt by potential recipients, their families, and their physicians, has led to sometimes bitter disputes about equitable allocation of this scarce human resource. Institutional concerns for the viability and effectiveness of their transplant programs have armed the protagonists with administrative, financial and legal weapons. The extreme result has been conflicts unresolvable at the organ procurement organization, local sharing level, and the filing of lawsuits in federal courts to settle such disputes." [5]

An Organ Procurement Organization (OPO) is a local affiliate of UNOS that has agreed to follow Health Care Financing Administration (HCFA) guidelines for the distribution of organs, as outlined in Attachment 2 of the UNOS By-Laws. [6] Transplant centers have agreements with OPOs for the allocation of organs in a particular locality. As UNOS states, "OPOs are nonprofit organizations that coordinate activities relating to organ procurement." [7]

According to UNOS, patients in UNOS Region 1 (Please refer to *Figure 1*), which comprises New England, who are blood type A had a median waiting time of 953 days for liver transplantation compared to those in UNOS Region 3 in the Southeast portion of the country where the median waiting time was 91 days for the period between 1994 and 1996. [8] Such disparities have sparked debate about the significance of this apparent inequity and, if it is relevant to mortality, how to rectify the geographic inequality.



**Figure 1. UNOS Regional Map**

Implemented January 1, 1991.

Source: UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, Health Resources and Services Administration, US Department of Health and Human Services, Rockville, MD. 1997. *Executive Summary. 1997 Report of the OPTN: Waiting List Activity and Donor Procurement.* 212pp.

Given the location of the Yale-New Haven Liver Transplant Center within a region of the country known to have long waiting-times for liver transplant candidates as described above, it was felt that an analysis of patients listed for liver transplantation at this center would address some of the controversy as to why these disparities in time to transplantation are occurring. Before examining

the hypothesis, methods, and results of this analysis, a thorough understanding of the history of the current organ allocation system and literature that has defined the controversy over waiting times will be critical to explaining the significance of the data collected.

### Definitions

Before beginning the literature survey, it is important to define certain terms that will appear throughout this thesis. Median Waiting Time (MWT) is defined by UNOS as the estimated number of days by which 50% of the cohort of waiting list candidates had received a transplant.[9] One criticism of this method of calculating waiting time is that the extremely long waiting times of some candidates beyond the median point of patients transplanted are not included, a fact readily acknowledged by UNOS.[10] A waiting time for the purpose of data collected for this paper from patient charts at the Yale-New Haven Liver Transplant Center is the number of days from when the patient was placed on the New England Organ Bank's active liver transplant candidate list to the occurrence of one of four events as specified:

1. Date of Liver Transplantation
2. Date of Death
3. Date on which the patient was declared inactive for transplantation for any reason
4. Date on which data was collected for all patients examined in the study who are actively listed for transplantation.

The New England Organ Bank is the OPO of which the Yale-New Haven Liver Transplant Center is a member. There are 62



OPOs operating in the United States as of December 20, 1999.[11]

### History of Liver Allocation Policies

In order to understand the current controversy surrounding geographic disparities in liver transplant waiting times, it is necessary to survey briefly the history of liver allocation policies in the United States. Prior to the Food and Drug Administration approval of cyclosporine in 1984, the allocation of non-renal organs occurred on an almost ad-hoc basis. In the late 1970s and early 1980s, there was an informal system by which transplant centers with critically ill patients would call institutions in the surrounding areas to see if an organ was available. The Southeastern Organ Procurement Foundation, which created and incorporated UNOS in January 1977, administered a computer system to coordinate the search for organs at this time.[12] The lack of safe and effective immunosuppression to control organ rejection prevented transplantation from consideration as a long-term solution for most patients with chronic liver disease.

This began to change in the early 1980s with advancements in both immunosuppression and preservation techniques of harvested organs. As Dr. Goran Klintmalm, Director of Transplantation Services at Baylor, notes:

"With the use of cyclosporine A that commenced in 1978 in Cambridge, UK, and shortly thereafter in continental Europe and the United States, a revolutionary impact on graft and patient survival rates was seen. This revolution greatly impressed the medical profession.

making physicians realize that transplantation could actually be a viable medical service.

"In the 1970s, the very few patients who sought out the possibility of liver transplantation could usually be supplied by the few donors who were available; however, results were marginal at best. Liver transplantation also became a viable option with the introduction of cyclosporine, which increased survival from 20-25% to 70-80%, and an effect similar to what happened in kidney transplantation was seen. A surge of new patients required an increase in the number of transplant centers. However, because of the lack of trained transplant surgeons and the insufficient understanding of liver transplantation's place in the treatment of end-stage liver disease, patients were initially not many. The few centers that were then established were able to serve the patients. In those days, the sharing was done on a national basis. Surgeons from the centers involved flew across the United States to where donors were available. However, as the success improved, professional recognition followed, together with increasing scientific and financial awards, and other centers opened where organs were available. This, together with the already existing kidney allocation network, instilled the 'local property' mentality, something that had not existed a few years earlier." [13]

A June 1983 National Institutes of Health consensus development conference on liver transplantation concluded, "Liver transplantation is a therapeutic modality for end stage liver disease that deserves broader application." [14]

In 1984, the National Organ Transplant Act called for the creation of an Organ Procurement and Transplantation Network (OPTN) that would administer an organ allocation system with the stated goal that, "Patient welfare must be the paramount consideration." The law called for a system to maximize organ procurement, equity in allocation, and scientific evaluation of the outcomes of organ transplantation. [15] In 1987, UNOS was granted the contract by the US Government to administer the OPTN and the

scientific registry. In October of that year, a national system of liver distribution was created that was based on the principal of local, regional, and then national allocation with consideration given to disease severity, ability to match blood type, distance from donor to recipient, and waiting time. The OPO became the unit of local organ distribution.

Allocation policies for other organs were created based on organ-specific criteria. For example, panel reactive antibody (PRA) was strongly weighted in renal allocation as sensitized patients with high levels of preformed antibodies increase the likelihood of organ rejection and make matching difficult.[16] In liver allocation, the UNOS/STAT category was intended to give priority to patients in acute fulminant hepatic failure and most urgently in need of transplantation, regardless of geographic location.[17]

It soon became apparent that this attempt at the creation of a national allocation priority for patients with the most severe form of liver disease above a system for local use of organs was problematic. As Dr. R. Randal Bollinger, noted:

"Almost immediately, the new organ allocation system created problems for liver transplant centers in the United States. Medical urgency points were the most significant factor in organ allocation, but the complex system of six levels of urgency could not be applied uniformly across the country without agreement on the definitions. Agreement could not be obtained. Without agreement on the definitions, confidence in listing practices declined, and faith in the entire system was reduced. The most difficult problem was UNOS/STAT, which allowed the entire allocation point system to be bypassed to locate and place livers for

patients with particularly urgent need for transplantation. Some centers used UNOS/STAT often, whereas others used it sparingly. There was clear disagreement about which patients should be eligible for listing in that category and to what extent the scarce resource of human livers should be allocated to the most critical patients who had lower graft and patient survival rates." [18]

These concerns led in 1991 to a revision of the organ allocation protocol put forward by UNOS. The revision eliminated the category of UNOS/STAT and instead created a four-level stratification system that included acute fulminant hepatic failure and limitations on the time period for which a patient could remain in that disease status. In addition, the new system of organ allocation placed a new priority on local and regional allocation of organs, with livers being offered first to all patients within the OPO in order of disease severity before being offered on a regional or national level to other patients who are more severely ill. [19]

#### Disparities in Waiting Times

With the creation of the new, more regionally based organ allocation system, it became apparent that waiting times were diverging based on geographic considerations. As noted in *Table 1* and *Figures 2* and *3*, the median waiting time in days for patients listed for liver transplantation between 1995 and 1997 varied considerably among UNOS regions, even though the patients compared were theoretically listed at the same point in their disease process according to UNOS disease category. As one can see, again, UNOS Region 1, which includes the Yale-New Haven

Liver Transplant Center, was at or near the top of length in waiting times, as high as 475 days for patients listed at UNOS status 3 or 4 and transplanted at status 2 compared to UNOS Region 3 with a median waiting time of 129 days. [20]

*Status 1 - Intensive Care Unit (ICU)-bound due to acute or chronic liver failure with a life expectancy without a liver transplant of less than 7 days.*

*Status 2 - Continuously hospitalized in an acute care bed for at least five days, or is ICU bound.*

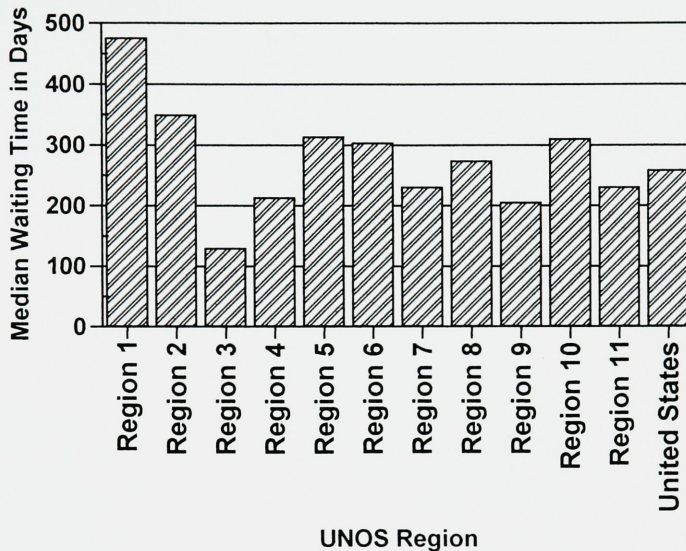
*Status 3 - Requires continuous medical care.*

*Status 4 - At home and functioning normally.*

*Status 7 - Temporarily inactive.*

**Table 1. UNOS Stratification System for Liver Transplant Candidates, 1994-1997**

Source: UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, Health Resources and Services Administration, US Department of Health and Human Services, Rockville, MD. 1997. *Executive Summary. 1997 Report of the OPTN: Waiting List Activity and Donor Procurement.* 212pp.

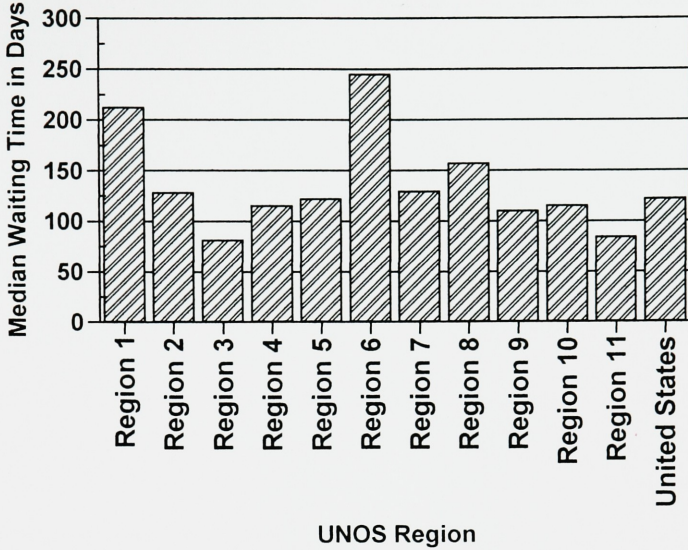


**Figure 2. Median Waiting Time in Days,  
1995-1997 Primary Liver Registrations  
Initial Status 3,4 - Final Status 2**

Source: UNOS/OPTN Scientific Registry Data.  
September 16, 1998.

Initial Status 3,4-Final Status 2 represented 3,995 new registrations for a primary liver transplant between 1995 and 1997, 22% of total (18,234).

Median Waiting Time represents time to 50% of all registrants at that status to be transplanted.



**Figure 3. Median Waiting Times in Days  
1995-1997 Primary Liver Registrations  
Initial Status 3,4 - Final Status 1**

Source: UNOS/OPTN Scientific Registry Data.  
September 16, 1998.

Initial Status 3,4-Final Status 1 represented 1,124 new registrations for a primary liver transplant between 1995 and 1997, 10% of total (18,234).

Median Waiting Time represents time to 50% of all registrants at that status to be transplanted.

The disparity in waiting times to liver transplantation became more concerning with research that confirmed that increased waiting time for liver transplantation results in higher mortality. In order to understand the role that waiting time plays in mortality, Everhart and others studied

a cohort of patients listed for liver transplantation at three large transplant centers between 1990 and 1993 with the exposure measure being ABO blood type, which, while not directly related to outcome, is a major determinant of waiting time. This is due to the fact that the O blood type organ can serve as the donor to any other blood type. In contrast, blood type O candidates can only receive blood type O organs.

As Everhart notes, during the time period of the study, 13% of type O livers went to candidates of other blood types, but only 2% of livers from other blood types went to type O transplant candidates. The authors used a logistic regression analysis to control for differences in clinical status at the time of initial listing. In this study, the type O candidates had a longer median waiting time (109 days) compared to other blood type patients (58 days) ( $P=0.001$ ), but despite having on average a better clinical status at initial evaluation, type O patients had higher pretransplantation mortality (13.3%) versus other blood type candidates (7.0%) ( $P=0.005$ ). Two year mortality was also higher for blood type O candidates (26.6%) compared to other candidates (22.1%). The authors concluded that, "Delay in liver transplantation because of prolonged waiting time caused a measurable increase in mortality." [21]

The debate on allocation of livers also began to focus on the optimal time in the patient's disease process to perform the liver transplant. At a 1994 NIH Consensus



Development Conference to address the utility of liver transplantation in specific liver ailments, a study was presented by transplant surgeons from the University of Pittsburgh analyzing their experience in transplanting patients at varying stages in their disease process as outlined by UNOS stratification guidelines of that time. Eghtesad and others stratified 1,128 liver transplant candidates according to UNOS guidelines from least ill (working) to most ill (ICU-bound or a life-expectancy of a few days without transplantation). Their study concluded that of those patients at the lowest disease status, the mortality rate while waiting for transplantation was only 3% after 229.5 days versus 28% mortality for those at the highest disease status.

In a separate analysis, they found that the best post-operative results were realized in patients transplanted at lower disease states (88% post-transplantation survival for the two lowest disease categories) versus those at the highest (71% survival). However, they concluded:

"This [the transplantation of patients at a less severe stage of their liver disease] has been justified increasingly by the argument that high-risk recipients survive less frequently after transplantation than those with lesser need. Our study has verified this conclusion, but our RR (relative risk) analysis has added the disturbing possibility that the elective use of livers for low-risk recipients could result in their net loss of life in at least a 1-yr framework while retarding the use of these organs for patients who otherwise have little hope of survival." [22]

Though limited to one transplant center, this study pointed to the growing controversy as to whether the revision of UNOS allocation guidelines in 1991 was in fact detrimental to liver transplant candidates. Indeed, a UNOS study from 1996 concluded that, "There is no net survival benefit of liver transplantation for Status 3 patients within the first two years following transplantation." [23]

Debate also focused on whether the 1991 UNOS regulations forced patients to select smaller regional transplant centers with worse overall survival outcomes. Bronshter et.al., in a review again submitted by the University of Pittsburgh transplant center, noted that the 1991 UNOS regulations led to patients being limited based on whether the centers in their region would transplant patients who were severely ill. The authors conclude:

"In this competitive interface, a syndrome of entry triage was encouraged when government agencies established minimum life survival curves as a measure of medical competence, without an attempt to stratify disease severity using the criteria of UNOS, Blue Cross/Blue Shield, Acute Physiology and Chronic Health Evaluation II score, or some other system.

"Except for those who are medically sophisticated or wealthy, such disenfranchised potential candidates can neither find treatment within nor escape from their regions. The result has been uneven quality of and access to liver transplantation throughout the United States. This heterogeneity also applies to the standards used for donor acceptance in different regions." [24]

The authors of this study do not provide data to support the argument that donor organs with minor imperfections are systematically discarded in regions of the

nation with shorter waiting times. However, there is data to support the conclusion that lower volume liver transplant centers have poorer outcomes on average. In a study reported in the *New England Journal of Medicine* in 1999, Edwards and others examined all liver transplantations that occurred between January 1, 1992 and April 30, 1994. During that time period, 47 transplant centers performed fewer than 20 liver transplants per year (837 transplants) and were defined as low-volume while 52 centers performed more than 20 liver transplants per year (6526 transplants). The authors made a distinction between low-volume centers that were sub-specialized affiliates of higher volume centers, such as pediatric programs, versus those low-volume centers which were independent. They showed that affiliated low-volume centers had a one year mortality rate of 21.8%, comparable to the 20.4% one year mortality rate of independent large-volume centers. However, the one year rate in unaffiliated low-volume centers (28.3%) was significantly higher than the combined mortality of all high-volume and affiliated low volume centers (20.1%) ( $P < 0.001$ ). [25]

Clearly, the arguments put forward in these two articles from the University of Pittsburgh are very articulate, but there is an unstated bias which also goes to the heart of the disparity in waiting times for liver transplantation across the nation, namely the struggle between large and small liver transplant centers for scarce

organs and the resources that they bring. The University of Pittsburgh is one of the largest liver transplant centers, performing 147 liver transplants in 1998 and 34 between January 1 and March 31, 1999[26] and thus has a range of patients who are often severely ill. As such, any allocation system that takes organs away from such patients is harmful to large liver transplant centers. As the review from Bronsther also notes, large transplant centers also appear to be penalized under the new system of organ allocation for having a high number of sick patients given the survival statistics that govern federal standards and thus monetary compensation from Medicare. As Bronsther states, federal guidelines for assessing the quality of transplant centers do not take into account the stratification of transplant candidates by severity of illness and the resultant difficulties in transplanting such patients.

The financial repercussions of the current system are discussed in detail in an article by Dr. Roger Evans, the former director of the National Cooperative Transplantation Study, which analyzed the costs of liver transplantation across the nation. He notes that in 1994, "The total first-year charges for liver transplantation are estimated to be \$302,900, with annual follow-up charges of \$21,900. Total five-year charges now approach \$365,000." However, Dr. Evans notes that there is a disparity in these costs as analyzed by examining eight transplant centers. Among these

centers. "One transplantation program had an average charge per case of \$409,133, but an expected charge per case of \$244,996. The least expensive center had an average charge per case of \$68,162 and an expected charge per case of \$165,215. Not surprisingly, as the charge data would suggest, there is similar extreme variation in the average hospital length of stay for patients at these eight transplant programs." [27] While the disparity in financial charges makes it difficult to state with certainty that any particular transplant or medical center is dependent upon continued increasing volumes of liver transplantation, this data does show that liver transplantation is a high-profile and potentially lucrative procedure for medical centers.

With such a clear financial incentive, it is not surprising that smaller liver transplant centers are arguing against changes in a system that keeps organs in local areas and thus makes it feasible to maintain transplant centers in small population areas. As Dr. Goran Klintmalm, the Director of Transplantation Services at Baylor, another large liver transplantation center, noted when asked about the ability of small, inexperienced transplant centers to attract patients for transplantation:

"There is no question that the availability of a short local waiting time is used as a marketing tool by many programs. We have this well documented. With the American population already well served by existing programs and new ones still springing up, it is clearly unfair to have patients waiting around the country for months on-end while available livers are used only locally, often in a setting in which donors and recipients are handpicked to produce the best possible results. These same centers do not take on the

medically and surgically difficult patients who truly need liver transplantation as their only life-saving alternative. Recipients should be considered on an equal basis and have the same risk of dying on the waiting lists around the country." [28]

Yet, there is no reason why patients should be forced to travel to other parts of the country for liver transplantation if the expertise can be had closer to home. As Dr. Maureen Martin, director of transplantation at Methodist Hospital in Des Moines, Iowa, a new and small liver transplant center (1 liver transplant in 1998, 0 between January 1 and March 31, 1999) [29], noted, "If you can develop the same expertise locally, why can't people stay in their communities? ... We've been trained by the very big centers, so the quality, expertise and talent is there." [30]

#### Standardization of Listing Criteria

In 1997, to attempt to address the issue of whether patients are being listed for transplantation or transplanted too early in their disease process, UNOS for the first time called upon the organ-specific committees of its organization to develop nationally applicable disease criteria for the listing of patients. Up to this point, listing status of patients was based on their level of clinical care, i.e., at home, hospitalized, ICU bound, or in acute fulminant hepatic failure, not on any objective scale related to the natural progression of disease which could be less influenced by the subjective clinical expertise and facilities available at any particular transplant center.

In essence, there was no means to verify that patients across the nation who were being listed at similar disease severity categories were in fact at the same point in the natural history of their disease. Instead, stratification became dependent upon the clinical acumen and expertise of each transplant center. As Dr. Byers Shaw notes in his editorial on the results of this committee report and the motivations behind it:

"The authors begin by listing several reasons for creating these criteria. Perhaps the most relevant one is the pressure that programs are under to place patients on the list to build waiting time. Although the prevalence of this practice should not come as a surprise to most of us (waiting time means everything when all else is equal), recognition of this phenomenon has caused considerable consternation within the relevant committees of UNOS." [31]

As the report of the committee sponsored by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases and supported by UNOS notes in addressing the purpose of this standardization:

"One of the principal issues in this controversy is the marked difference in the number of days on the transplant waiting list before receiving a liver transplant in different parts of the country. There are many possible explanations for these regional differences. The explanations include the possibility that the present system of donor organ identification, retrieval, distribution, and allocation results in unequal distribution of livers throughout the country. This is a contentious area, about which many interested parties, both inside and outside the transplant community, hold conflicting views. In addition, there is the possibility that patients in different parts of the country are placed on the waiting list at different points in the natural history of their diseases. This practice would result in a patient getting priority for liver transplantation based on nothing more than an accident of geography. Furthermore, there is the

concern that, because of long waiting times in certain regions, there is a pressure on transplant programs to list patients early, before they actually require transplantation, a practice referred to as 'waiting list inflation.'"[32]

One of the remarkable features of these criteria is that consensus was reached at all. For the first time, UNOS established stratification criteria for liver transplant candidates based not on level of care, but on the natural history of liver disease, using the available literature for support. The specific minimal criteria for the listing of patients for liver transplantation was based on an estimation of no more than a 90% chance of one year survival without transplantation. This stratification level was based on numerous studies of the natural history of liver disease and compared to the so-called Child-Turcotte-Pugh (CTP) Score that was created in 1973 to classify clinically patients with cirrhosis and applied in a 15 year study of the prognosis and life expectancy of chronic liver disease.

As shown in *Table 2*, the CTP score is meant to correlate specific laboratory and clinical criteria, including coagulopathy, hypoalbuminemia, hyperbilirubinemia, ascites, and encephalopathy, that develop in the natural history of patients with liver disease with their prognosis.[33] Propst and others, in their study of prognosis and life expectancy in liver disease, found that in a 15 year study of 620 patients with chronic liver disease from a variety of etiologies, including alcoholic cirrhosis, viral hepatitis, and genetic disease, prognosis



was dependent upon Child classification. Child A patients had a 95% survival probability at 180 months, Child B 45%, and Child C 5% ( $P=0.001$ ). [34]

Points	1	2	3
Encephalopathy	None	Stage I-II	Stage III-IV
Ascites	Absent	Slight - Controlled by Diuretics	Moderate - Despite Diuretics
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin Time (secs. prolonged)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Cholestatic Disease Bilirubin (mg/dl)	<4	4-10	>10

**Table 2. Child-Turcotte-Pugh Scoring System**

Source: Lucey, M.R., Brown, K.A., Everson, G.T., Fung, J.J., Gish, R., et al. 1997. Minimal Criteria for Placement of Adults on the Liver Transplant Waiting List: A Report of a National Conference Organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transplantation and Surgery*. Vol. 3, No. 6 (November): 628-37.

The selection of 90% survival at one year appears to be arbitrary. While the data regarding CTP scores supports such prognostic predictions, it is not clear why 90% likelihood of survival should serve as the cutoff at which

patients may be listed without outside review. As Dr. Shaw notes:

"In approaching this document, the temptation that many readers will have is to quibble with the 10% risk-of-death-without-transplant cut-off that the authors have chosen for entry to the waiting list. Some readers may complain that this figure represents a luxury, that they would be happy if they could get patients treated who had even a 50% chance of dying without a liver transplant. They may also assert that UNOS data show that many centers do not achieve 90% survival after transplantation, even in these relatively low risk patients ... The implied goal was to choose a degree of risk that would result in a practical degree of consensus among practicing liver transplant physicians." [35]

The panel suggested that regional review boards be created to assess the listing of patients who do not fit under CTP criteria, but have important clinical reasons to be candidates for liver transplantation. Finally, the panel noted that the CTP criteria did not definitively define all the clinical criteria of serious liver disease warranting transplantation and also suggested the inclusion of a history of refractory ascites, uncontrolled variceal hemorrhage, episodes of spontaneous bacterial peritonitis, and hepatorenal syndrome. However, the panelists reached a consensus that a CTP score  $\geq 7$  and/or the presence of portal hypertensive gastrointestinal bleeding would meet the criteria for listing for transplantation regardless of the underlying etiology of the cirrhosis. [36]

UNOS adopted these criteria in January 1998, creating a standardized way in which to determine whether patients were being transplanted or listed at earlier or later stages in

their disease process, based on studies of the natural history of a variety of chronic liver ailments, including alcohol-induced cirrhosis, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Budd-Chiari syndrome, and Wilson's disease. *Tables 2 and 3* outline the categorization system adopted by UNOS and put into effect on January 19, 1998.

*Status 1 - A patient greater than or equal to age 18 with fulminant liver failure with a life expectancy without a liver transplant of less than 7 days.*

*Status 2a - A patient in the hospital's critical care unit due to chronic liver failure with a life-expectancy without a liver transplant of less than 7 days. Patient has a CTP score  $\geq 10$  and at least one of the following criteria:*

- 1. Endoscopically confirmed active variceal hemorrhage that requires at least 2 units of blood after sclerotherapy with a contradiction to or failure of Transjugular Intrahepatic Portosystemic Shunt (TIPS).*
- 2. Hepatorenal Syndrome, defined as the presence of progressive deterioration of renal function in a patient with advanced liver disease requiring hospitalization for management, with no other known etiology of renal insufficiency, and a rising creatinine of 1.5 mg/dl (adult) or 3 times baseline in a child less than age 15. The patient should also have one of the following criteria:*
  - urine volume <500 ml/day (adult), <10 ml/kg/day (<15 years)*
  - urine sodium <10mEq/ml*
  - urine osmolality:plasma osmolality ratio >1*
- 3. Refractory Ascites/Hepato-Hydrothorax, defined as unresponsive to diuretic and salt restriction therapy, requiring paracenteses  $\geq 4L$ , or for respiratory distress more frequent than every 2 weeks with a contraindication or failure of TIPS.*
- 4. Stage III-IV Encephalopathy unresponsive to medical therapy.*

*Status 2b - A patient who has a CTP score  $\geq 10$  or a CTP score  $\geq 7$  and meets at least one of the following criteria:*

- 1. Endoscopically confirmed active variceal hemorrhage as defined under Status 2a*
- 2. Hepatorenal Syndrome as defined under Status 2a*
- 3. Spontaneous Bacterial Peritonitis, at least one episode, documented as having one of the following criteria:*
  - positive bacterial culture of ascitic fluid*
  - positive gram stain of ascitic fluid for bacteria*
  - >500 white cell count/ml or >300 PMNs/ml in ascitic fluid*
- 4. Refractory Ascites/Hepato-Hydrothorax as defined under Status 2a*

*Status 3 - A patient who requires continuous medical care and has a CTP score  $\geq 7$ .*

*Status 7 - A patient who is temporarily inactive or is temporarily unsuitable for transplantation.*

### **Table 3. UNOS Stratification System for Liver Transplant Candidates, 1/19/98**

Source: Proposed Amended UNOS Policy 3.6  
(Allocation of Livers).  
September 15, 1997.

With the adoption of these guidelines, it became necessary to see how these rules would impact upon the

current waiting list for liver transplantation. As Dr. Byers Shaw noted in his previously cited editorial on this subject:

"Now that the authors have agreed on the tools we will use to estimate the risk of death without transplantation for various diseases, why don't we apply those criteria to the existing waiting list at all of the US centers and see where everyone falls out? This would be the first step in determining what level of risk we are willing to tolerate for patients admitted to the waiting list." [37]

In essence, the creation of this standardized criteria for the listing of patients for liver transplantation has given researchers the opportunity to assess whether patients across the nation are being listed in an appropriate manner or whether regions with long waiting times are listing patients too early in their disease process and regions with short waiting times are transplanting patients earlier in the natural history of their ailment.

### *Statement of Purpose*

The Yale-New Haven Liver Transplant Center is located within a region of the nation known to have extremely long median waiting times for patients listed for liver transplantation. Therefore, it was felt that an examination of the medical history of patients listed for liver transplantation at Yale could reveal whether patients were being listed too early in their disease process so as to accumulate waiting time. Such premature listing would result in their not meeting the new minimal listing criteria. However, if patients are being appropriately

listed and thus meet new minimal listing criteria, this would point to the inequity of organ allocation by geography. A hypothesis is made that patients are being listed appropriately under agreed upon disease status criteria at the Yale-New Haven Liver Transplant Center, indicating the need to reexamine how organs are allocated across the nation by UNOS.

### *Methods*

The medical records of all patients listed for liver transplantation at the Yale-New Haven Liver Transplant Center on November 14, 1997 were examined by the author of this thesis. The new minimal listing and disease status criteria adopted by UNOS in January 1998 as outlined in *Tables 2* and *3* were applied to classify each patient. If not apparent in the chart, the author of this thesis contacted primary care and specialist providers for the patient to obtain laboratory data on liver function and clinical history from within four months of November 14, 1997, the date of chart examination. Patients were then reclassified to new UNOS disease status categories based on their chart and updated laboratory and clinical history. Based on this reclassification, it was determined whether patients met the minimal listing criteria for liver transplantation or criteria for severe liver disease.

In addition, taking advantage of the statutory obligation of UNOS to track information about liver transplantation through the OPTN scientific registry, the

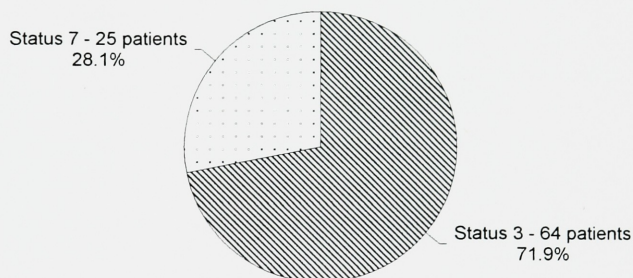
author of this thesis asked for and acquired data regarding liver transplantation of patients across the nation related to waiting time, disease status, and UNOS region both prior to and after the 1998 changes in UNOS listing criteria. These data were used to understand whether the new allocation guidelines had modified waiting times to and disease status at transplantation after January 19, 1998.

Finally, on July 1, 1999, 18 months after the implementation of the revised UNOS listing criteria, the author of this thesis received data accumulated by Dr. Amy Friedman, Director of Liver Transplantation at Yale, as to the current clinical condition and transplantation status of the patients examined, i.e., whether the patients were still alive, had been transplanted and if so at what UNOS disease status category, or had died pre- or post-transplantation. These data were used by the author of this thesis to assess the prognosis of the patients initially examined, i.e., whether candidates were being transplanted or dying over the 18 month time period and at what UNOS disease status.

### *Results*

As of November 14, 1997, there were 89 patients listed for liver transplantation at the Yale-New Haven Liver Transplant Center. Under the previous UNOS listing criteria described in *Table 1*, no patients were listed at UNOS Status 1 or 2. Sixty-four patients were listed at UNOS Status 3, signifying an active candidate with chronic liver disease

eligible for transplantation, and 25 patients were listed at UNOS Status 7, signifying an inactive candidate for liver transplantation despite a history of chronic liver disease (Figure 4). Table 4 outlines the clinical reasons for which the 25 patients listed at Status 7 in November 1997 were classified in that way.



**Figure 4. UNOS Status of Liver Transplant Candidates at the Yale-New Haven Liver Transplant Center on November 14, 1997**



<b>Clinically Well</b>	<b>10 Patients</b>
<b>Died prior to Re-examination</b>	<b>5 Patients</b>
<b>Hepatoma</b>	<b>1 Patient</b>
<b>Broncheictasis/Active Lung Infection</b>	<b>1 Patient</b>
<b>Too Ill to Transplant</b>	<b>1 Patient</b>
<b>Active Infection</b>	<b>1 Patient</b>
<b>Breast Biopsy Pending</b>	<b>1 Patient</b>
<b>HTLV 1 or 2 (Infectious Disease Consult Pending)</b>	<b>1 Patient</b>
<b>Chronic Rejection of Previous Liver Transplant, Currently Stable</b>	<b>1 Patient</b>
<b>Actively Drinking</b>	<b>1 Patient</b>
<b>Unknown</b>	<b>2 Patients</b>

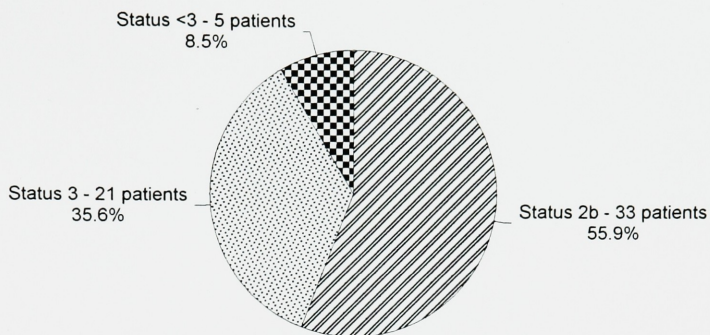
**Table 4. Rationale for UNOS Status 7 Classification of Patients at the Yale-New Haven Liver Transplant Center November 14, 1997**

Of these 89 patients, 10 patient records were not reviewed. Of these patients, 5 patients were listed at UNOS Status 7; their records were not examined as it was discovered that they had died prior to the November 14, 1997 patient reclassification date. The remaining 5 patients were listed at UNOS Status 3, two of whom had died prior to

November 1997, one of whom had been transplanted elsewhere prior to the study period and subsequently died shortly after the start of the study period, one of whom had been lost to follow-up, and one for whom records were not available.

#### Results of January 19, 1998 Reclassification

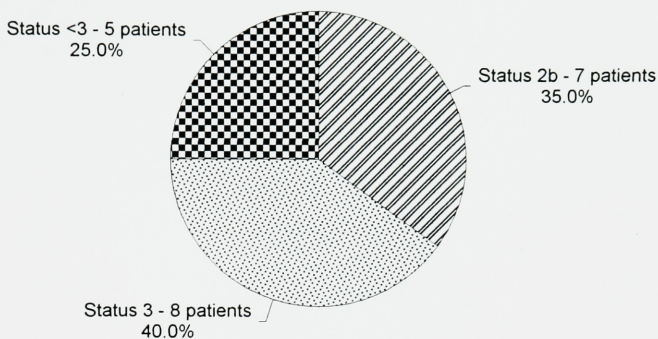
Of the 79 patients that remained for chart examination, 59 patients were originally categorized as UNOS Status 3. Reclassification according to UNOS guidelines for status stratification of liver transplant candidates that went into effect on January 19, 1998 revealed that 33 patients or 55.9 percent met criteria for the new UNOS Status 2b that defined severe chronic liver disease. Twenty-one patients or 35.6 percent met criteria for the new UNOS Status 3 that defined minimal listing standards for transplantation. Five patients or 8.5 percent did not meet minimal listing criteria as defined by CTP score and clinical criteria of liver disease outlined in the new UNOS guidelines (*Figure 5*).



**Figure 5. Results of Reclassification of UNOS Status 3 Patients, January 19, 1998**

Note: Status <3 indicates patients who did not meet minimal listing criteria per revised UNOS guidelines, 1/19/98 .

Of the 20 status 7 patients studied for reclassification, 7 or 35 percent would have been classified as UNOS Status 2b based on their clinical history of liver disease and most recent relevant laboratory data if their clinical reason for being listed as inactive for liver transplantation were resolved. Eight patients or 40 percent would meet minimal listing criteria and be classified as UNOS Status 3. Five patients or 25 percent would not meet minimal listing criteria as outlined by UNOS (*Figure 6*).

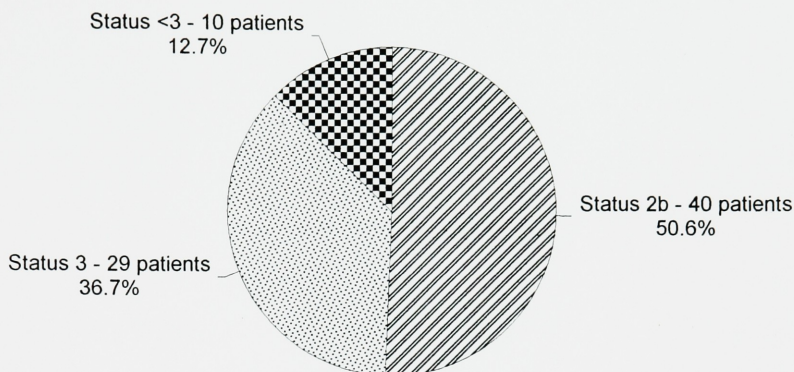


**Figure 6. Results of Reclassification of UNOS Status 7 Patients, January 19, 1998**

Note: Status <3 indicates patients who did not meet minimal listing criteria per revised UNOS guidelines, 1/19/98.

Overall, 40 of 79 patients listed for transplantation at the Yale-New Haven Liver Transplant Center who were reclassified per the most recent UNOS guidelines for status stratification, or 50.6 percent, met criteria for severe chronic liver disease or UNOS Status 2b. Twenty-nine of 79 patients or 36.7 percent met minimal listing criteria for liver transplantation or UNOS Status 3. Ten of 79 patients or 12.7 percent did not meet minimal listing criteria for liver transplantation according to CTP score or other clinical situations recognized by UNOS.

Thus 69 of 79 patients, or 87.3 percent, under accepted criteria for the listing of patients for liver transplantation, were appropriately listed at the Yale-New Haven Liver Transplant Center for this procedure. If one considers the 7 patients who died prior to examination of patients in November 1997 and the 1 patient who was transplanted elsewhere and subsequently died as having been appropriately listed but having died while either waiting for transplantation or soon after transplantation, 77 of 87 patients listed for transplantation as of November 14, 1997 (not including two patients who though listed as status 3 had been lost to follow-up or for whom records were unavailable) or 88.5 percent of all patients within the original cohort met minimal criteria for liver transplantation (*Figure 7*).



**Figure 7. Results of Reclassification of Transplant Candidates at the Yale-New Haven Liver Transplant Center, January 19, 1998**

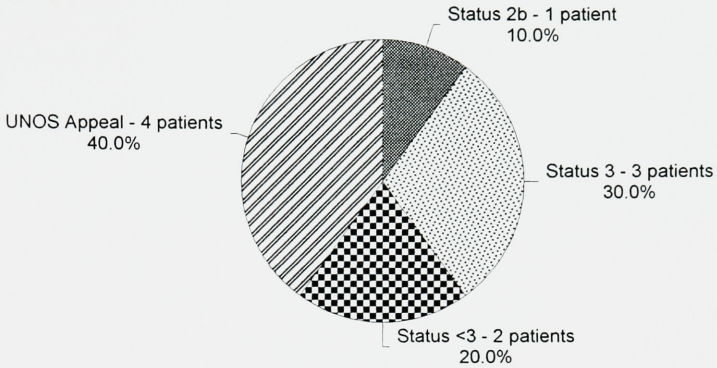
Note: Status <3 indicates patients who did not meet minimal listing criteria per revised UNOS guidelines, 1/19/98.

#### Results of Follow-Up to July 1, 1999

The 10 patients who did not meet listing criteria as of January 19, 1998 when the new UNOS regulations went into effect were followed along with the other 69 patients over the next 18 months and reassessed on July 1, 1999. Of the 10 patients who did not meet minimal listing according to UNOS guidelines in January 1998, 4 patients were permitted to be listed for transplantation after approval of the UNOS Region 1 Review Board. This procedure was incorporated to

accommodate those patients with circumstances that do not fit clearly under established guidelines. Three of four patients had been transplanted before and had suffered from postoperative and immunological complications that threatened the graft; all were clinically stable as of July 1999 and are listed at UNOS Status 7 today. One patient has Hepatitis C and Hemophilia A and, though clinically stable, is listed at UNOS status 3 given his age (under 18) and that a liver transplant would effectively treat both his primary liver disease and his hereditary coagulopathy.

Three patients showed progression in their liver disease to the point that they met minimal UNOS listing criteria or UNOS Status 3 as of July 1, 1999, and one patient with Primary Biliary Cirrhosis who had been previously listed as UNOS Status 7 after having refused transplantation, had progressed to the point of meeting UNOS Status 2b listing criteria for severe chronic liver disease. Two patients, as of July 1, 1999, both of whom had been UNOS Status 7 in November 1997, as they were clinically well and did not meet minimal listing criteria on reclassification, remained clinically well and were listed as UNOS Status 7 (*Figure 8*).



**Figure 8. Results of Follow-Up of Patients who did not meet UNOS Minimal Listing Criteria in January 1998, July 1, 1999**

Note: This figure specifically addresses those 10 patients who did not meet UNOS minimal listing criteria per guidelines adopted on January 19, 1998. Status <3 in this figure indicates that reassessment as of July 1, 1999 showed that those patients continued to not meet UNOS minimal listing criteria at that point in time.

Of the 33 patients who were listed in November 1997 at UNOS Status 3 and were reclassified as UNOS Status 2b, as of July 1, 1999, 17 (52 percent) were still alive at Status 2b, 11 (33 percent) had received transplants[38], 4 (12 percent) had died awaiting transplantation, and 1 (3 percent) had shown some clinical improvement and was listed at UNOS Status 3.



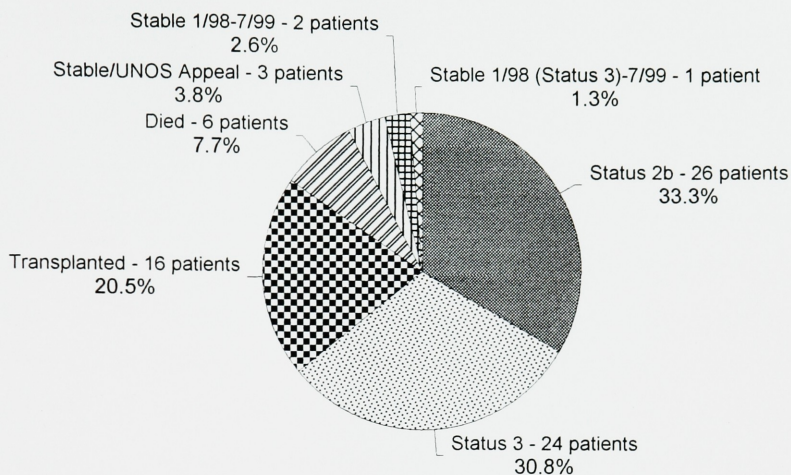
Of the 21 patients who remained at UNOS Status 3 after reclassification in January 1998, as of July 1, 1999, 13 (62 percent) were still alive at Status 3, 4 (19 percent) had received transplants[39], 3 (14 percent) had progressed in their disease to UNOS Status 2b and were alive, and 1 (5 percent) had died.

Of the 7 patients who were listed at UNOS Status 7 in January 1998, but would have qualified for UNOS Status 2b by accepted listing criteria, as of July 1, 1999, 4 (58 percent) had seen resolution of the clinical issue requiring inactive status and were actively listed at UNOS Status 2b[40], 1 with previously clinically stable alcoholic cirrhosis (14 percent) met UNOS Status 3 listing criteria, showing improvement above previous laboratory and clinical findings, but no longer clinically inactive, 1 (14 percent) received a transplant at another institution after developing a hepatoma at status 2b and subsequently died, and 1 (14 percent) was lost to follow up.

Of the 8 patients who were listed at UNOS Status 7 in January 1998, but would have qualified for UNOS Status 3 by accepted listing criteria, as of July 1, 1999, 5 (63 percent) were actively listed at UNOS Status 3[41], 1 (12.5 percent) had died of Methotrexate induced cirrhosis after having been previously clinically well, 1 (12.5 percent) had seen progression of Hepatitis C from having been clinically stable to now meeting criteria for UNOS Status 2b, and 1

(12.5 percent) was still clinically well and was listed at status 7.[42]

Overall, after 18 months follow-up to July 1, 1999, of the 79 patients reclassified in January 1998 and followed over the time period, 1 patient was lost to follow-up, leaving 78. Twenty-six patients (33.3 percent) were alive at UNOS Status 2b, 24 (30.8 percent) were alive at UNOS Status 3, 16 (20.5 percent) had received transplantation (all at UNOS Status 2b or 2a), 6 (7.7 percent) had died awaiting transplantation (an additional 7 patients died prior to the study period, and one patient died after transplantation elsewhere prior to the study - a total of 14 (16 percent) of 86 patients not lost to follow-up), 3 (3.8 percent) were listed after approval from the UNOS Region 1 Review Board, but are now stable, 2 (2.6 percent) were clinically well in January 1998 and did not meet minimal listing criteria at that point in time and in July 1999, and 1 (1.3 percent) who was clinically well, but would have met minimal listing criteria in January 1998, remained clinically well in July 1999 and was continued as UNOS Status 7. Overall, of the 86 patients followed from November 1997 to July 1999, 3 patients (3.4 percent) did not meet minimal listing criteria in January 1998 and/or July 1999, were clinically well, and showed no clinically significant progression in the nature of their liver disease warranting later listing for liver transplantation (*Figure 9*).



**Figure 9. Results of Follow-Up of Liver Transplant Candidates at the Yale-New Haven Liver Transplant Center, July 1, 1999**

Note: Stable indicates Status 7 according to clinical evaluation in either January 1998 and/or July 1999.

### *Discussion*

This study attempted to address one of the hypotheses surrounding the disparity in waiting time to liver transplantation of patients with chronic liver disease, namely that patients across the nation are not being listed at equal and appropriate times in their disease process, thus making it invalid to compare waiting times across the nation. As was noted in the introduction, the creation of standardized criteria for the evaluation and stratification

of patients with liver disease by UNOS was meant to rectify the possibility of disparities in the listing of transplant candidates across the nation.

Application of these guidelines to the patients listed for liver transplantation at the Yale-New Haven Liver Transplant Center in November 1997 reveals that patients generally have not been listed prematurely in their disease process. On the date of implementation of the new UNOS guidelines on January 19, 1998, 88 percent of patients met minimal criteria for eligibility for transplantation, and 51 percent of patients met criteria for severe chronic liver disease. When the cohort of patients were followed to July 1, 1999, only 4 percent of patients studied did not meet minimal listing criteria or were ineligible for listing through an appeal to the regional review board. Only 1 percent of the patients reviewed would have met minimal listing criteria by the new UNOS criteria as of January 19, 1998, but was too well clinically at that date and at July 1, 1999 to warrant listing for transplantation.

These results indicate that the premature listing of patients does not significantly contribute to the long waiting times of liver transplant candidates at Yale. In addition, there is no evidence from this study that the classification system adopted by UNOS in January 1998 results in the acceptance of candidates for transplantation for which the procedure is not clinically warranted, i.e., that the standards are too low for listing patients for this

procedure: only 1 percent of patients studied would have met minimal listing criteria, but was determined to be too well clinically to warrant transplantation after follow-up to July 1, 1999.

The January 1998 UNOS guidelines were based on studies that validate the use of CTP scores and other clinical criteria to evaluate the severity of a variety of chronic liver diseases. Furthermore, there is an increase in mortality of patients who wait longer for liver transplantation. Therefore, it can be fairly concluded that the disparity in waiting times that now exists among UNOS regions for liver transplantation is of severe detriment to those patients who are in areas of the country with longer waiting times through an accident of geography.

There are limitations, however, to this statement. First, and perhaps foremost, this study only closely examines those patients at the Yale-New Haven Liver Transplant Center. It is possible that other centers in UNOS Region 1 and other regions with long waiting times are listing patients inappropriately under current guidelines. The only true method to evaluate this hypothesis is to do a comparable study at other centers.

Similarly, it is possible that a retrospective application of the January 19, 1998 UNOS listing criteria to the patients studied at their time of initial listing for transplantation would reveal that many were classified as transplant candidates prematurely by current standards. At

the same time though, an advantage of this study is that it closely follows the policy evolution that has taken place within UNOS. The new listing criteria adopted in January 1998 were not meant to be applied to when patients were originally listed, but rather to patients currently listed as a way to stratify patients more appropriately. If the transplant candidates at Yale in November 1997 were inappropriate candidates for liver transplantation, this analysis should have shown a larger percentage of patients not meeting minimal listing criteria under the January 19, 1998 guidelines.

Another important conclusion of this study is that any premature listing that might have occurred at Yale has not resulted in patients being transplanted at a lower than average UNOS status. One would expect that patients listed earlier who accumulate waiting time would be transplanted at a comparable disease stage as those who are transplanted in regions with shorter waiting times. In other words, the listing of patients at an earlier stage or prematurely should benefit patients in that they are transplanted at a comparable disease severity to patients around the country.

This is not borne out by data accumulated by UNOS since the implementation of the standardized criteria for evaluating and stratifying patients for transplantation. If one looks at the percent of patients transplanted between January 19, 1998 and April 1, 1999, only 4.7 percent of all transplants in UNOS Region 1 were occurring in patients at

Status 3, the second lowest region after UNOS Region 9. In contrast, UNOS Region 1 had the second highest percentage of patients, 27.5 percent, being transplanted at UNOS Status 2a, again second only to UNOS Region 9. Finally, UNOS Regions 1 and 9 are the only two parts of the nation which fall below the average national percentage for transplantation at UNOS Status 2b, the status at which most patients received liver transplantation in the time period in question, and also fall below the national percentage for liver transplantation at Status 3 (Figure 10). [43]

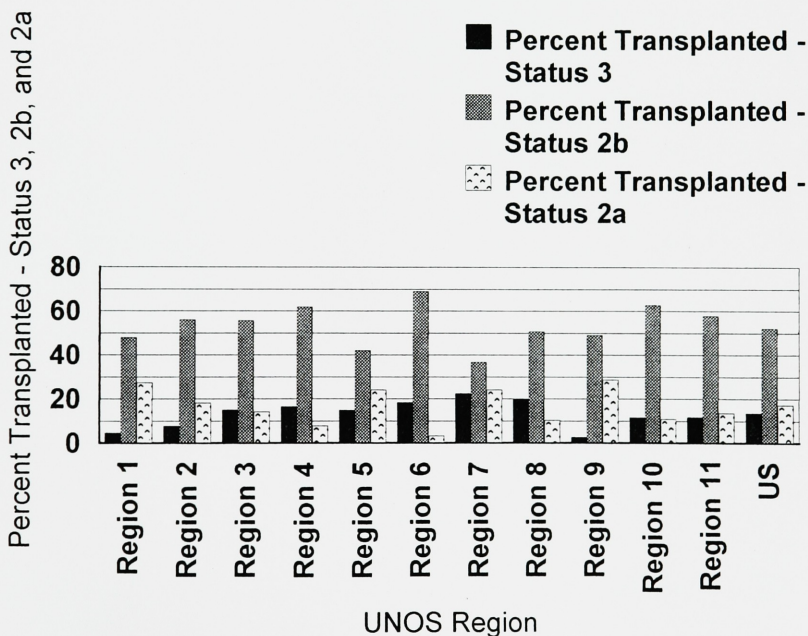


Figure 10. Percent of Liver Transplants Performed in the United States by UNOS Status, 1/20/98-4/1/99

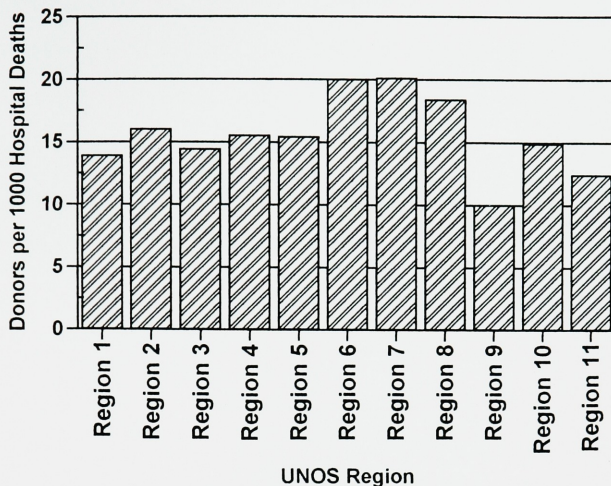
Source: UNOS/OPTN Data. July 26, 1999.

These statistics are reflected in the patients studied at Yale, where all of the 16 patients transplanted received their graft at either UNOS Status 2b or 2a. Clearly, the listing of patients prematurely in their disease process, if it is occurring, is not benefiting patients in terms of being transplanted earlier in their disease process. If anything, patients in UNOS regions 1 and 9 are waiting longer on average than the rest of the nation.

#### Potential Reasons for Disparities in Waiting Times

Another limitation of this study is that it does not address why the waiting time to liver transplantation is in fact longer for patients in certain parts of the country, if patients are not being listed too early in their disease process. The most obvious reason is that the relative availability of cadaveric donors of livers is lower in certain regions of the country. Between 1994 and 1996, according to UNOS, Region 1 had the third lowest number of organ donors per 1000 hospital deaths at 13.9 (*Figure 11*). [44]





**Figure 11. Number of Cadaveric Donors per 1000 Hospital Deaths, 1994-1996**

Source: UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, Health Resources and Services Administration, US Department of Health and Human Services, Rockville, MD. 1997. *Executive Summary. 1997 Report of the OPTN: Waiting List Activity and Donor Procurement.* 212pp.

Note: Based on service areas designated by the Health Care Financing Administration for the 1994-1995 OPO assessment process and mortality data from the Centers for Disease Control.

But one cannot draw the conclusion that organ donation rates alone are responsible for the discrepancy in liver transplant waiting times. As shown in *Figures 2.3, and 11*, there are exceptions to the correlation between organ donation and median waiting time to liver transplantation. UNOS Regions 9 and 11 had lower organ donation rates than UNOS Region 1 between 1994 and 1996, but had shorter median

waiting times than Region 1 between 1995 and 1997. There are, however, limitations to such a comparison. First, the time periods in question do not overlap completely, making correlation difficult. Second, as noted in the introduction, median waiting time is a limited measure to use in comparing regional variation in waiting times to transplantation as it does not take into account outlying candidates who wait for time periods well beyond the median. As also noted in the introduction, prior to January 19, 1998, listing criteria for liver transplant candidates were more subjective, based on level of medical care, as opposed to the more objective criteria adopted on that date that were based on the natural history of liver disease. Finally, *Figure 11* does not show how many cadaveric donors did or did not donate a liver as there may have been patients who donated only particular organs and not all possible.

While organ donation rates may play a role in the disparities in waiting times for liver transplantation, a carefully constructed study is needed to establish whether liver donation rates since the adoption of the January 1998 UNOS guidelines for listing transplant candidates correlate most significantly with the disparity in waiting time to and disease status at liver transplantation across the nation. Other confounding factors may include a higher density of patients with liver disease per population unit and/or a greater referral rate of patients with liver disease in UNOS

regions with longer waiting times than in others. This study does not address these variables, but rather shows that, at least at Yale, patients being listed prematurely is not an important factor in the disparity in waiting times to liver transplantation.

#### Policy Proposals to Address Waiting Time Disparities

The third limitation of this study is that it does not point to any clear solution as to how to address the disparities that exist in waiting times for liver transplantation, how to create a more equitable system. Ideally, more organs would be procured, decreasing the scarcity of this valuable resource. But until that time, there is a need to find new ways to distribute fairly organs for transplantation. As was cited in the introduction, in March 1998, Secretary of Health and Human Services Donna Shalala directed UNOS to change the current system of liver allocation such that geographic disparities no longer exist. This directive, the Final Rule, created immediate controversy within the transplant community. As noted in the introduction, mortality is higher post-transplantation when the procedure is performed in severely ill patients, though they individually gain the greatest survival benefit when liver transplantation is successful. Similarly, though preservation of livers has been reported up to 20 hours, the standard of care is to transplant the organ within 12 hours of procurement since prolonged preservation is associated with sinusoidal and endothelial injury, especially to the

biliary tract.[45] The implementation of the Final Rule to create a national allocation system is unrealistic given the current inability to maintain donated livers consistently for more than 12 hours; a regional system of some sort is needed for this reason alone.

Finally, the change to a more national system of liver allocation would also seem to favor larger programs with broader national reputations, perhaps depriving local communities of a valuable resource, forcing patients to travel to remote areas of the country to be eligible for transplantation. Indeed, the debate over the Final Rule led Congress to delay the implementation of the regulation until October 1, 1999 pending study of its impact by the Institute of Medicine. In addition, a number of states in regions with shorter waiting times, such as Louisiana, Oklahoma, South Carolina, and Florida, have passed legislation to bar the transportation of organs across their borders until they have been offered to local patients first.[46]

In response to the geographic disparities that exist, UNOS has implemented changes in allocation policy that would give priority to Status 1 patients throughout the region before less ill patients locally. But this change did not affect the vast majority of patients in that only 14.5 percent of donated livers go to Status 1 patients today.[47]

In the late summer of 1999, the Institute of Medicine report on the potential impact of the Final Rule was provisionally released. This report makes three important

conclusions. First, it concurs with most studies that the current system is equitable for patients with Status 1 or 2a liver disease, who though the most severely ill patients, represent together only 11% of all patients registered for liver transplantation between January 20, 1998 and January 19, 1999.[48]

Second, it notes clearly that the greatest heterogeneity is in waiting times for Status 2b and 3 patients, which is confirmed by data in this study. Moreover, it notes that rather than use overall median waiting time as a measure of disparities in transplantation rates across the nation:

"Status-specific rates of pretransplantation mortality and transplantation are more meaningful indicators of equitable access."

Again, this study shows that status-specific transplantation rates are indicative of the geographic disparities that exist in transplantation. The report also notes most intriguingly that there is a sub-population of Status 2b and 3 patients who though remaining long on the waiting list for liver transplantation neither receive this procedure nor die. The authors of this study state:

"It may be that some patients are put on waiting lists at an early stage in their disease condition to accumulate waiting time and move up the priority list."

While this study seems to disprove this contention at least at the Yale-New Haven Liver Transplant Center, there is merit in the notion that, "An appropriate medical triage

system should be developed to ensure equitable allocation of organs to patients in these categories." [49]

The Institute of Medicine analysis of the DHHS Final Rule argues that the potential premature listing of patients, again brought into question by the results of this study, is being countered by physicians selecting which patients in each disease status should receive a transplant. As the report states regarding patients listed at Status 2b:

"Finally, significant time effects on both transplantation and pretransplantation rates were observed, indicating that the longer patients are listed as status 2b, the lower is their likelihood of either dying or receiving a transplant. This finding suggests that there is heterogeneity in the population of status 2b patients, with a subgroup who need transplantation more quickly or they will die after a relatively short time on the status 2b waiting list. By contrast, those patients who remain on the list for more than 4 months have considerably decreased risk of pretransplantation mortality or transplantation. It may be that the treating physicians are aware of this heterogeneity and effectively screening the more severely ill status 2b (and status 3) patients for early transplantation." [50]

This conclusion points to an important limitation of this and any study that attempts to draw conclusions based on an analysis of the stratification by disease status of candidates for liver transplantation. In essence, the fact that there is often a discordance between how physicians classify patients and how long they are both expected to and actually survive points to a limitation of our current understanding of medical science regarding liver disease. Until more is understood and a more accurate classification system can be developed, it may be inevitable that

disparities exist in transplantation rates across the country. At the same time, there has to be some type of classification system in order to triage access to the scarce resource of liver transplantation. The key then is further research into the pathophysiology and natural history of liver disease.

In the mean time, a more immediate solution is needed to address the disparities that do exist across the nation for liver transplantation. As long as transplant candidates and physicians see patients who are supposedly at the same severity of disease being transplanted at differing times, there will be, if nothing else, political pressure to create equity in the organ allocation system. The solution put forward by the Institute of Medicine report is to establish organ allocation areas of at least 9 million people, a number that by their analysis would increase the number of UNOS Status 1, 2a, and 2b patients receiving transplants without increasing pretransplant mortality for UNOS Status 3 patients.[51] This compromise between a national allocation system and the current local and regional system may be the first step towards addressing the needs of all appropriately listed liver transplant candidates, both here at Yale and across the nation.

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[38]3 of these patients had progressed to UNOS Status 2a at the time of transplantation, which meant that they were in the Intensive Care Unit secondary to chronic liver disease with a life expectancy of less than 7 days. Two of these patients died post-transplantation. 8 patients received transplantation at Status 2b.

[39]3 of these patients had received transplantation after progressing to UNOS Status 2b. 1 patient received a transplant at Status 2a and died subsequently

[40]1 patient no longer had an active infection. 1 patient was listed after consultation with infectious disease specialists regarding infection with HTLV 1 or 2. 1 patient

has autoimmune hepatitis that is no longer in remission, and 1 patient is no longer actively drinking alcohol.

[41] 1 patient had a negative breast biopsy, 1 patient was listed for Tylenol toxicity pending follow-up of liver function at which point the patient might be moved to Status 7, 1 patient who had been too sick to transplant had recovered enough to be re-listed, 1 patient had a worsening of previously stable Hepatopulmonary Syndrome, and 1 patient had been listed as Status 7 in January 1998 for unknown reasons.

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