

Chapter 2

Redesigning Organ Allocation Boundaries for Liver Transplantation in the United States

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Abstract Geographic disparities in access to and outcomes in transplantation have been a persistent problem widely discussed by transplant researchers and the transplant community. One of the alleged causes of disparities in the United States is administratively determined organ allocation boundaries that limit organ sharing across regions. This paper applies mathematical programming to construct alternative liver allocation boundaries that achieve more geographic equity in access to transplants than the current system. The performance of the optimal boundaries were evaluated and compared to that of current allocation system using discrete event simulation.

2.1 Introduction

Existing studies of organ transplant report various disparities in access to and outcomes in transplantation. Disparities have been found in terms of race, socioeconomic status, insurance type and the location of candidate's residency. While

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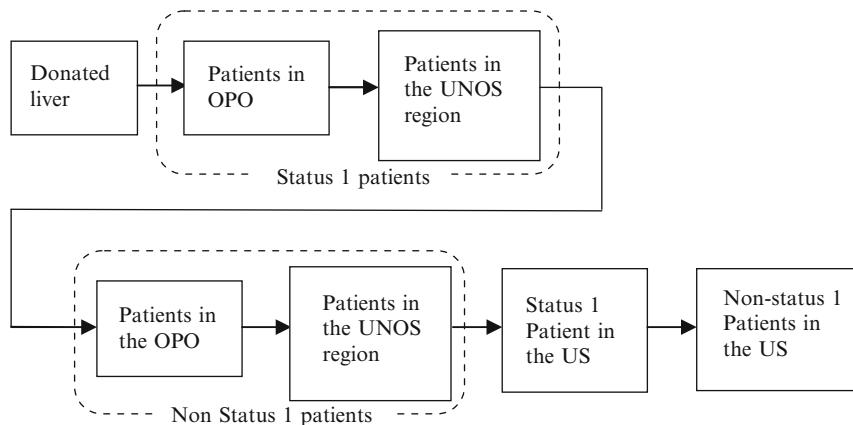
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these disparities tend to coexist, disparity associated with candidates' locations or "geographical disparity" is the first and foremost discussed. Researchers worldwide have repeatedly confirmed that the likelihood of receiving a transplant as well as pre- and post-transplant mortality rates vary significantly from region to region [1–10]. Geographic disparity in transplant access in the US has been a persistent issue ever since organ allocation became a regulated process in 1984 under the National Organ Transplant Act (NOTA). As the most important act in the history of US transplantation, NOTA created the Organ Procurement and Transplantation Network (OPTN), a public-private network of regional organ allocation offices known as Organ Procurement Organizations (OPOs) [6]. NOTA also authorized the Department of Health and Human Services (HHS) to contract with the United Network for Organ Sharing (UNOS) as the only administrative entity to govern the OPTN. At first, all organs were distributed within each OPO's service area (ibid) in order to limit cold ischemia time (CIT), i.e. the interval between organ retrieval and the time of transplantation during which an organ is preserved in a cold perfusion solution. Allocation of organs within each OPO was solely based on the length of time that each candidate had spent waiting for an organ since initial referral. In response to the concern that the waiting time varied significantly by OPO, HHS introduced a new regulation known as the "Final Rule" (42 CFR Part 121) in 1998 to "assure that allocation of scarce organs will be based on common medical criteria, not accidents of geography" (HHS, 1998b) (ibid).

As per the directives of the Final Rule, the allocation mechanism for a number of vital organs has been rectified to address the criterion of medical necessity. For liver allocation, HHS revised the Code of Federal Regulations legislating organ allocation process and, in 2002, the Model for End-Stage-Liver-Disease (MELD) scoring system was launched as a way to prioritize the candidates with a higher medical urgency. Since then, the harvested adult livers had been distributed, in principle, based on the algorithm summarized in Fig. 2.1. Thus the current organ allocation system consists of three hierarchical, geographic levels: the OPOs (a.k.a. the Donor Service Areas), the UNOS regions and the National level.

While several changes in allocation rules have been introduced to address discrepancies, transplant researchers still report that a number of key elements that determine equity in transplantation vary significantly depending on the location of a patient. This study thus developed a mathematical programming model to redesign liver allocation boundaries. The optimal boundaries were derived to maximize geographic equity in access to a transplant while maintaining efficiency in outcomes in transplantation. The model was also used to analyze which existing "kidney-only" transplant centers could be activated to improve the current liver allocations. Finally, discrete event simulation was applied to evaluate the performance of the optimal boundaries in comparison to that of the existing boundaries.

The primary data used for the analyses is UNOS's Standard Transplant Analysis and Research (STAR) Dataset that records clinical, administrative, demographic and locational information of over 40,000 adult liver transplant candidates and recipients who appeared on the wait list between 2003 and 2010.



- Status 1 patients refer to those with fulminant liver failure with a life expectancy without a liver transplant or less than 7 days.
- Within each category of patients (i.e. Status 1, MELD scores ≥ 15 , MELD score < 15), a liver is offered, in principle, in the descending order of first MELD score and then waiting time.
- Extra points are added to the MELD score for those patients whose blood type is compatible to that of the available liver and those with specific clinical circumstances such as Hepatocellular Carcinoma (HCC).

Fig. 2.1 Current liver allocation system

2.2 Model Description

2.2.1 Mathematical Model

The mathematical programming approach has the twofold objective of: (i) identifying optimal locations for liver transplant centers and (ii) identifying new OPO boundaries that replace existing OPO's boundaries, which are mainly defined by political issues. Two mathematical models are proposed to achieve these objectives. Both models are described next, but, due to the current page limit, we present the mathematical formulation of only the second model.

The first model (Model 1) addresses the problem of: (a) selecting a fixed number p of transplant centers to be opened among a possible set of candidates and (b) associating a subset of donor hospitals (that define the organ acquisition area of the center) and a subset of counties (that define the service area of the center) with each opened transplant center. The model ensures that each donor hospital and each county are associated with exactly one transplant center. Moreover, the distance between a donor hospital and the associated transplant center is such that the corresponding travel time is within the CIT of the organ, and finally, the distance between the centroid of a county and the associated transplant center is not

greater than a predefined maximum threshold. The proposed model is similar to the mathematical model proposed by Bruni et al. [11] in that each selected transplant center is associated with an acquisition area and a service area. However, unlike Bruni's model, we consider an additional set of constraints to ensure that, for each opened transplant center, the ratio between the available organs (coming from the associated acquisition area) and the total number of recipients (coming from the associated service area) is greater than or equal to a fixed threshold α . The objective function of the model is the minimization of the total distance between the set of donor hospitals and the associated transplant centers plus the total distance between the county centroids and the associated transplant center.

Model 2 addresses the problem of clustering a set of transplant centers that are selected for activation (as a result of Model 1) into a predefined number of clusters. Each cluster represents an OPO. The resulting OPOs are defined so that they are balanced both in terms of the supply/demand ratio of organs and in terms of total number of transplant centers that belong to the OPO. The boundary of each OPO is determined by the union of the service areas associated with the transplant centers that belong to the OPO. Hence, one important constraint to take into account when defining the cluster is contiguity of the service areas. To achieve this aim, Model 2 takes a graph $G = (V, E)$ as an input where each vertex $i \in V$ is associated with a transplant center and there is an arc $(i, j) \in E$ between vertex i and vertex j if the corresponding service areas have a common border. Two weights are associated with each vertex i of this graph: w_i and h_i representing, respectively, the total supply and the total demand associated with the transplant center represented by the vertex. A super vertex s is added to the graph and is connected with each vertex of the graph by the set of arcs (s, i) , $\forall i \in V$. Hence, the resulting graph is such that the total number of vertices is equal to $p + 1$ and the total number of arcs depends on the solution returned by Model 1.

Model 2 looks for a spanning tree T_s of G rooted in s such that the total number of children of the root is equal to the total number of clusters that need to be defined. In this way, the vertices of each subtree T_i rooted at vertex i (i.e., one of the children of the supervertex s) represent the set of transplant centers that belong to the cluster. Connection of the subtree ensures contiguity of the service area associated with the cluster. Moreover each subtree is such that the ratio between the sum of the weights w_i associated with the vertices of the subtree and the sum of the weights h_i associated with the vertices of the subtree is greater than or equal to a predefined threshold α . The objective function of the model is the minimization of the maximum number of vertices in each of the resulting subtrees, ensuring that the resulting clusters are also balanced in terms of total number of transplant centers that belong to them.

Let $O = \{1, 2, \dots, l\}$ be the index set of the clusters that need to be defined. Then the proposed formulation is a Miller-Tucker-Zemlin (MTZ) formulation [12] where we considered the following set of variables:

- Variable y_{ik} is a binary variable that is equal to one if vertex $i \in V$ belongs to cluster $k \in O$ and is equal to 0 otherwise;

- Variable x_{ijk} is a binary variable that is equal to one if arc $(i,j) \in E$, that connects vertices i and j in the cluster k , is selected to be in the spanning tree and is equal to 0 otherwise;
- Variable u_i , defined on each vertex $i \in V$, assigns a label to each vertex of the graph. In particular, such a labeling ensures any directed arc that belongs to the optimum spanning tree goes from a vertex with a lower label to a vertex with a higher label.

Hence, variables y_{ik} are used to define the clusters, while variables u_i and x_{ijk} are used to define the final spanning tree.

The resulting Model 2 is the following:

$$\min \max \left(\sum_{i \in V} y_{ik} \right) \quad (2.1)$$

$$\sum_{(s,j) \in E} x_{sjk} = 1 \quad \forall k \in O \quad (2.2)$$

$$\sum_{k \in O} \sum_{(i,j) \in E} x_{ijk} = 1 \quad \forall j \in V, j \neq s \quad (2.3)$$

$$\sum_{k \in O} x_{ijk} \leq 1 \quad \forall (i,j) \in E \quad (2.4)$$

$$x_{ijk} \leq y_{ik} \quad \forall (i,j) \in E, i \neq s, \forall k \in O \quad (2.5)$$

$$y_{ik} \leq \sum_{(i,j) \in E} x_{ijk} \quad \forall i \in V, i \neq s, \forall k \in O \quad (2.6)$$

$$u_s = 0 \quad (2.7)$$

$$1 \leq u_i \leq p \quad \forall i \in V, i \neq s \quad (2.8)$$

$$(p+1)x_{ijk} + u_i - u_j + (p-1)x_{jik} \leq \forall (i,j) \in E, i \neq s, \forall k \in O \quad (2.9)$$

$$\sum_{k \in O} y_{ik} = 1 \quad \forall i \in V, i \neq s \quad (2.10)$$

$$\sum_{i \in V, i \neq s} w_i y_{ik} \leq \alpha \sum_{i \in V, i \neq s} h_i y_{ik} \quad \forall k \in O \quad (2.11)$$

$$\sum_{i \in V, i \neq s} y_{ik} \geq 1 \quad \forall k \in O \quad (2.12)$$

The objective function [1] minimizes the maximum cardinality of the resulting clusters. Constraints [2] ensure that the total number of children of the root s is equal to the total number of clusters that need to be defined. Constraints [3] ensure that each vertex has exactly one entering arc. Each arc can be associated with at most one cluster, which is ensured by constraints [4]. Constraints [11] and [12] are logical constraints linking the binary variables. The spanning tree is defined by the classical MTZ constraints [13, 5]. Constraints [6] ensure that each vertex belongs exactly to one cluster. The structure of the cluster is defined by constraints [14] and [15]. In particular, each cluster must not be empty (constraints [15]) and total supply/demand ratio at each cluster must be greater than or equal to a predefined threshold α (constraints [14]).

Our model extends a handful of studies [11, 14, 16, 17] that investigate optimal boundaries for organ allocation using a mathematical approach. Most previous models [14, 16, 17] are based on a set covering mathematical formulation of which feasible sets are represented by all possible regional configurations resulting from different clusters of OPOs. This approach tends to be computationally very demanding. The MTZ formulation we proposed for Model 2 solves a constrained version of a spanning tree problem. This approach enabled us to solve the problem to optimality through the available commercial solvers, Cplex and Gurobi, in a reasonable amount of time. In this study, all mathematical formulations were coded in AMPL and solved using CPLEX 11 and Gurobi 5.1 on a 2.4GHz Intel Core2 Q6600 processor.

2.2.2 Discrete Event Simulation

A discrete event simulation (DES) was run to evaluate the performance of the boundaries developed by the mathematical model. The key events and the parameters used to frame the simulation were: (i) patient arrival rate; (ii) length of time registered as a transplant candidate; (iii) rates of death and drop-out while waiting for an organ; (iv) rate of candidates receiving a transplant and (v) liver arrival rate. Both livers and patients enter the system with certain characteristics used in “match-run”, the process to match a donor to a recipient. Those characteristics included blood type, MELD score and the category and age.

The usefulness of DES in evaluating organ allocation policies/scenarios is already well established [13, 15, 18, 19]. In fact, DES-based simulation software, SAM (Simulated Allocation Model), was developed by the Scientific Registry of

Transplant Recipients (SRTR) and has been used by UNOS to evaluate the impacts of various organ allocation policy alternatives. However, SAM and other existing DES models does not allow for the explicit consideration of geography thereby limiting the simulation of the impacts of boundary changes. Our study developed a simulation model that simulates various allocation boundary scenarios in a more direct and overt manner.

The first task of the baseline simulation modeling was to generate recipient and donor data. As described above, each OPO is comprised of a set of counties, each of which is identified using a unique FIPS code. Each county is characterized by the historical patterns of recipient and donor counts per year and the arrival rates per day of the year, which also follows the historical proportions. Using the historical numbers and proportions from 2003 to 2009, the simulation was able to generate both recipient and donor data for 2010, which was then validated using the actual data from 2010.

The next step was to allocate organs to recipients using the current UNOS and OPO boundaries and using the new OPO boundaries obtained from Model 2. First, candidates waiting as of January 1st 2010 were generated from the actual STAR data. This data was used to initialize the simulation of liver allocation. Livers were then allocated using the current system of allocation in which Status 1 patients were given the top priority followed by patients with MELD > 15 and MELD < 15 (Fig. 2.1). The performance metrics were the waiting time for transplants for status 1, MELD < 15 and MELD > 15 transplant recipients and the geographical disparity measured in terms of the mean squared error, which is calculated as the deviation of the supply/demand ratio of the OPOs from the mean supply/demand ratio. Since there were about 12,000 candidates in the waitlist on Jan 1st 2010 and about 10,000 candidates joined the list in 2010, the supply/demand ratio for 5,000 donors in 2010 is about 0.23. After accounting for death while waiting (12.8 %), the supply/demand ratio is about 0.25 (including both waiting list and new candidates in 2010). The simulation was written and run in MATLAB.

2.3 Results

2.3.1 *Results of the Mathematical Model*

The Model 1 analysis revealed that opening additional 103 liver transplant centers at kidney-only transplant centers, while ensuring equity in terms of provided service, would marginally increase the efficiency in liver transplantation of the current system. In contrast, the result suggested that opening 61 new liver programs at existing kidney-only transplant centers while keeping 62 of the existing 123 liver transplant centers can substantially reduce waiting time and graft failure.

Model 2 clustered the existing 123 transplant centers into 58 OPO clusters. Figure 2.2 shows the current OPO boundaries in color and the new OPO boundaries

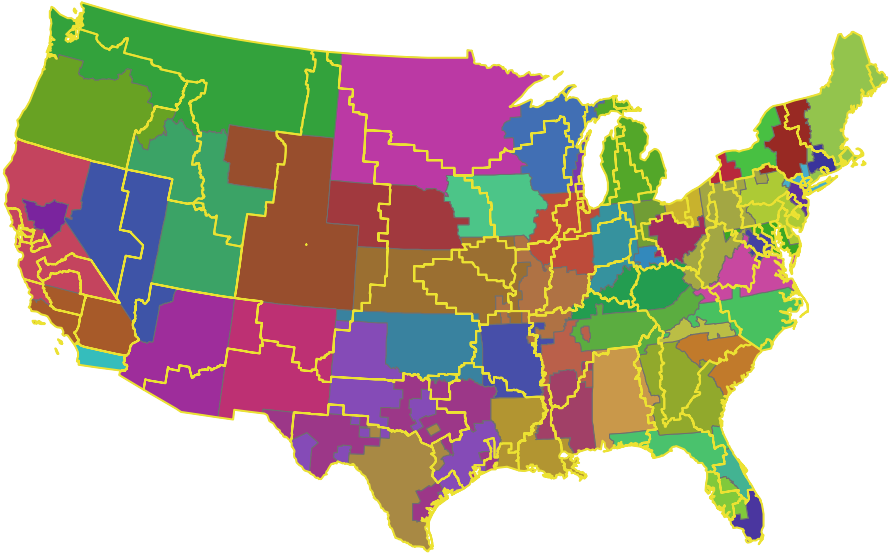


Fig. 2.2 Current (in *color*) and optimal (in *yellow lines*) OPO boundaries

suggested by the model in yellow lines. The resulting boundaries differ considerably from the actual boundaries although, in several OPOs, the boundaries coincide with actual boundaries fairly well.

2.3.2 Results of the Discrete Event Simulation

Figure 2.3 presents the actual and the simulated numbers of recipients per county arranged in ascending order in OPO #12 in 2010, which was randomly picked among other OPO's. The figures show a great deal of similarity, which was verified using the Kolmogorov-Smirnov test for equality of the probability distributions. Likewise, every OPO's recipients and donors were simulated for each county, and the characteristics described above were assigned.

Following the common simulation practice, 30 simulations were run to obtain the performance metrics of the current allocation scheme under each set of the OPO boundaries. Our simulation analysis indicates that it leads to sufficiently tight confidence interval for the estimation. Figures 2.4 and 2.5 show the distributions of the (a) number of counties per OPO, (b) donor counts or supply of liver per OPO, (c) candidate counts or demand of liver per OPO, and (d) supply/demand ratio per OPO for both the current and the new OPO boundaries respectively. Comparison of (b), (c) and (d) in the two figures reveals that, under the current boundaries (Fig. 2.4), there are several OPOs in which the supply/demand ratio was disproportionately higher than that in other OPOs. This is one of the primary causes of geographical

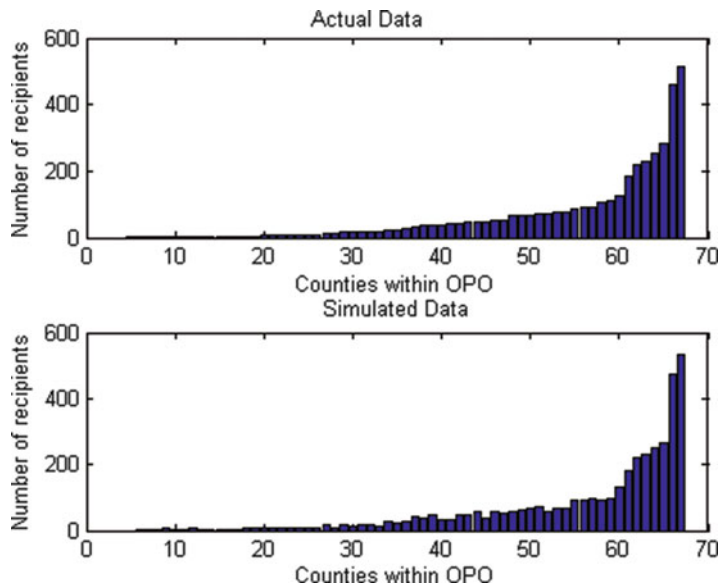


Fig. 2.3 Actual and simulated number of recipients per county for OPO #12 in 2010

disparity. With the new boundaries (Fig. 2.5), the number of instances of such a disproportionate supply/demand ratio is less frequent due to the balancing of supply/demand ratios across OPOs.

Table 2.1 indicates that the distribution of the supply/demand ratio is statistically more uniform with the new OPO boundaries. The mean supply/demand ratio is much closer to the total supply/demand ratio of 0.25 under the new boundaries. The standard deviation of the ratios dropped in the new boundary supporting the claim that the new OPOs have a more uniform supply/demand ratio. The mean square error, which is the mean of the squared deviation of errors (error in ratio of OPO i = supply/demand ratio of OPO i – mean supply/demand ratio of all OPOs) was also 15 % less with the new boundaries.

Table 2.1 presents waiting time for a transplant under the current and the new OPO boundaries. Waiting time is presented for each severity category, i.e., for status 1, MELD <15 and MELD >15. As the table shows, mean and median wait time decreased with the new boundaries, most of which is attributable to the wait time among status 1 and MELD < 15 candidates. Mean and median wait time slightly improved for the MELD > 15 category of candidates. However, neither the mean nor the standard deviation was statistically significantly different from that obtained under the existing boundaries. In terms of the number of transplants, MELD > 15 candidates had the highest number of transplants, accounting for about 85 % of the recipients of the 5,000 donors appeared in 2010. One can conclude that the new OPO boundaries are successful in alleviating geographic disparity while reducing wait time significantly among status1 and MELD < 15 candidates.

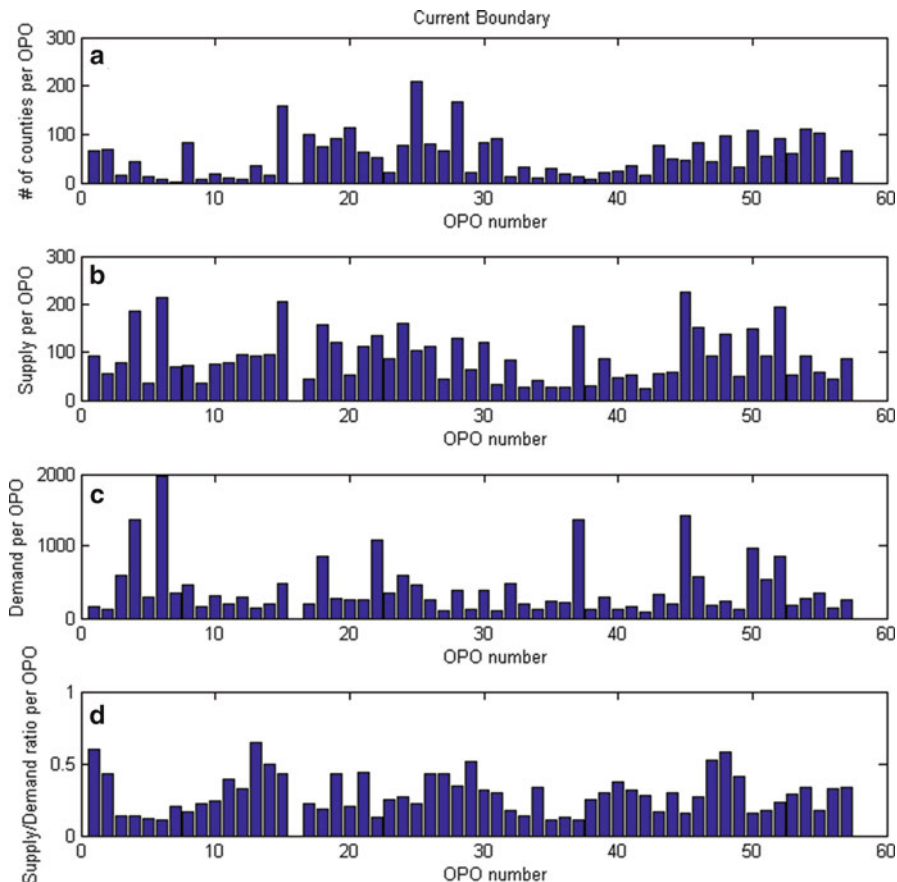


Fig. 2.4 Current boundaries: (a) number of counties per OPO, (b) supply per OPO, (c) demand per OPO, and (d) supply/demand ratio per OPO

Figures 2.4 and 2.5 shows that some of the new OPOs are larger containing more counties. The observation corresponds to the map in Fig. 2.2 in which some of the new OPOs are larger, especially in the mid-west region of the US.

2.4 Conclusions

Mathematical programming was used to derive new liver allocation boundaries that maximize geographic equity in access to liver transplant. Our study extended past studies on this topic by introducing MTZ formulation, which enabled us to solve the problem of optimality through the available commercial solvers in a reasonable amount of time. Our study is also different from past studies in that the performance

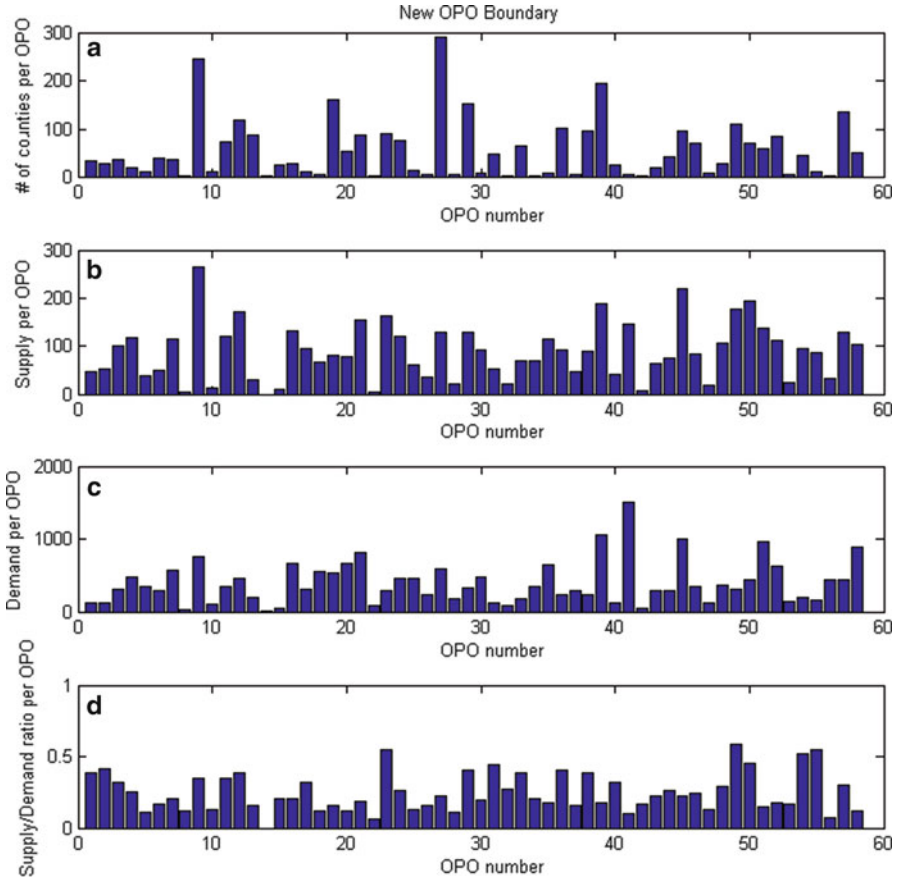


Fig. 2.5 New boundaries: (a) number of counties per OPO, (b) supply per OPO, (c) demand per OPO, and (d) supply/demand ratio per OPO

of new boundaries was evaluated dynamically using discrete event simulation. The boundaries derived from the mathematical model differed significantly from the current boundaries and our simulation results confirmed that the new boundaries could achieve a more equal supply demand ratio across OPOs and reduction in waiting time.

We note several directions for future research. First, it would be interesting to explore different equity measure definitions both for Model 1 and Model 2 in order to take into account additional aspects such as those considered by Kong et al. [14] and by Demirci et al. [16]. We are also interested in exploring the possibility of adapting our Model 2 to solve the problem of clustering the OPOs into UNOS regions so that the final allocation system represents the hierarchical system as presently implemented.

Table 2.1 Performance metrics

Performance metric	Current OPO boundaries	New OPO boundaries	Percentage change (%)	Increase/decrease
Waiting time for Transplant (in days)				
Status 1				
Median	1	1	0.1	Same
Mean	2.3	1.4	39.1	Decrease
Standard deviation	4.8	2.4	50.0	Decrease
MELD<15				
Median	1,139	940	17.5	Decrease
Mean	1,211	1,073	11.4	Decrease
Standard deviation	944	831	12.0	Decrease
MELD>15				
Median	300	278	7.3	Decrease
Mean	508	506	0.4	Decrease
Standard deviation	561	572	−2.0	Increase
Geographical disparity				
Supply/demand ratio among 58 OPO				
Median	0.2700	0.2034	24.7	Decrease
Mean	0.2801	0.2453	12.4	Decrease
Standard deviation	0.1442	0.1330	7.8	Decrease
Maximum	0.6479	0.5803	10.4	Decrease
Mean squared error	0.0204	0.0174	15.0	Decrease

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