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Waiting for liver transplantation in Canada: waitlist history 2000–2004 and sensitivity analysis for the future

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Abstract This study comprises a historical review of liver transplants performed in Canada during 2000–2004, and sensitivity analyses to assess the impact of possible changes in the operation of the waitlists. In the first part, overall statistics are reported, and the notable impact that blood type plays in affecting waiting time is discussed. Waiting times and numbers of transplants are also reported by gender, age, and geographic region (waitlist), and statistical analyses of the patient placement and cadaveric donations processes are performed. These analyses establish that the service times of an appropriate queuing model are closely approximated by an exponential distribution. Consequently, the resulting distribution for the waiting time from placement until transplant is well described by a different exponential distribution. The GI/M/1 queuing model is then used to perform a number of sensitivity analyses. The sensitivity analyses attempt to quantify the impact of no change in policy via a lottery system, and likely increases in cadaveric and/or living donor sources that would be needed to bring stability to the system. The results can be used by relevant authorities, together with information on success rates for publicity campaigns and living donor matching campaigns, to assess where further efforts should be made to reduce waiting times.

Keywords Waitlist · Liver transplantation · GI/M/1 queue · Sensitivity analysis · Statistical analysis · Historical analysis · Living donor · Deceased donor · Waiting time

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1 Introduction

Liver transplantation is the primary therapy for patients with chronic end stage liver disease. Unfortunately, there is a shortage of deceased donor organs, which means that there is often a significant waiting period for patients requiring transplantation. Similar to other transplantable organs and/or other jurisdictions (a selection of such references is [4, 5, 9, 10]), our study of liver transplantation in Canada 2000–2004 has revealed an increasing demand for livers as the median population increases. Meanwhile, the availability of cadaveric organs has remained essentially constant. This continues a previously reported trend. [1]

This study comprises two parts: a historical review of liver transplants performed in Canada during 2000–2004, followed by sensitivity analyses to assess the impact of possible changes under two scenarios. In the former part, overall statistics are reported, and the notable impact that blood type plays in affecting patient waiting time are discussed. Waiting times and numbers of transplants are also reported by gender, age, and geographic region (waitlist). Following this, statistical analyses of the patient

placement rate, the rate of cadaveric donations, and the number of living-related donations are presented.

The latter part of this study attempts to quantify the impact of no change in policy via a lottery system. It also suggests likely increases in cadaveric and/or living donor sources needed to bring stability to the system. The paper ends with a discussion of the results.

2 Background

Organ transplant allocation systems have evolved since the 1960s, and are usually based on time waiting with a modification for medical urgency. In Canada, there are six regional centres that perform liver transplants, each with its own waitlist (or "queue"). These six queues generally operate independently, allocating donated organs from within their specific geographical range to patients on its own waitlist. Patients on the waitlist are classified by blood type and priority status group. Status is based on a patient's hospitalisation situation; if it changes, their priority is updated immediately. Statuses are assigned as follows (from highest priority to lowest):

4F	acute liver failure, intubated in ICU
4	intubated in ICU
3F	acute liver failure in ICU
3	in ICU
2	in hospital (not ICU)
1T	at home with tumour
1	at home

For our data analysis, we have aggregated the groups as urgent (3F, 4 and 4F) and non-urgent (1, 1T, 2, and 3). Within status groups, organs are allocated based on waiting time, with whoever has been waiting the longest receiving the next appropriate organ.

The exception to the independent operation of the queues occurs when there is an urgent patient. If a regional queue with no urgent patients obtains a liver from a deceased donor, the liver is "shared" to a nearby region with an urgent patient. If there is more than one urgent patient, the liver is allocated to the patient who has been waiting the longest.

Approximately 90% of liver transplants in Canada are allocated on the basis of waiting time alone. [2] There are concerns that patients who might have benefited from liver transplantation have died before allocation, while others received a transplant but did not benefit by transplantation at that particular time. In the USA this concern caused a change in policy, so that time waiting no longer determines organ allocation priority which is now dependent on a liver disease severity score (known as MELD or model of end-stage liver disease). [3] The presence of a different system of organ allocation has stimulated interest in analysis using models and simulations. [4] We are unaware of any description or analysis of organ allocation models for liver transplantation in Canada.

3 Methodology and adjustments

The data was obtained from the Canadian Organ Replacement Registry (CORR), a division within the Canadian Institute for Health Information (CIHI). Data was also obtained from the national waitlist housed at the London Health Sciences Centre (LHSC). The data collected consisted of all waitlist activity for liver transplants in Canada from January 1, 2000 to December 31, 2004. Follow up data was obtained until December 31, 2005. Information about activity on the waitlist was available from the LHSC data, while information about transplants was obtained from the CORR data.

The most common challenge faced was missing data. In most cases we were able to match the record based on transplant date with the LHSC data, and fill in the missing field, e.g. date of listing, or diagnosis for liver failure. In the data set from CORR, records for patients with multiple transplants during the time period under study had some errors where the listing date occurred after the transplant date. These were corrected wherever possible by comparing to the LHSC data. Any records that could not be corrected or where the listing date was missing were removed from the analysis.

For a period during this study, transplant services for patients from Atlantic Canada were provided by the London Health Sciences Centre. Both the recipients and the donor organ were flown to London, Ontario from Atlantic Canada for transplantation.

Arrivals to the queue occur when a patient is added to the waitlist. Service is considered to be complete when a patient receives a transplant from a deceased donor. Departures from the queue occur upon transplantation or removal from the queue. For our project we have treated transplant by living donation as a removal from the queue before service (abandonment). Living donations are matched to specific patients, and do not increase the rate of availability for others. Reasons for abandonment also include death while waiting, becoming too sick to undergo transplant, becoming too healthy to benefit from transplant, and other causes. Data from each of these sources were reviewed, compared and reconciled. A description of waitlist activity was generated and analysed according to certain factors. Waitlist activity during this period was also analysed according to the principles of Queuing Theory to determine its amenability to subsequent modelling.

4 Results of the wait list study

4.1 Overall descriptive statistics

Data analysis was performed using R software for statistical computing (Table 1). The total number of records for cadaveric liver transplants during the period of study was 1,812. The following graphs and table describe general characteristics of the data for all of Canada.

4.2 Impact of blood type on waiting time

Blood type has a significant impact on the delay prior to transplant (see Table 2). Since blood type O is the universal donor type, an O type liver can be transplanted into patients of any blood types. Similarly, since blood type AB is the universal recipient blood type, an AB patient can receive the liver of any donor type. Each of blood types A and B can receive an O organ, and donate to an AB patient. Typically, attempts are made to match donor and recipient blood type, except in urgent cases.

The donor and recipient blood types in Fig. 1 below are consistent with this reality. There are more O type donors than recipients, while there are more A and AB recipients than donors. The number of type B recipients is essentially the same as the number of donors, suggesting that the number of B livers allocated to AB patients is offset, essentially, by O livers allocated to B patients.

Overall, the Canadian population comprises 46% blood type O, 42% type A, 9% type B, and 3% type AB [8]. Figure 1 reveals that the proportion of donors by blood type is roughly in keeping with the distribution of blood type in the population at large. The figure also reveals that the distribution of recipients by blood types is different: most notably, there are more type A recipients than type O recipients, and in fact more A, B, and AB recipients than donors (although the numbers of type B donors and recipients is quite close). Hence there is a migration of blood type O livers to other blood types, and a notable net positive difference between the number of type O livers received by type A patients, and the number of type A livers received by type AB patients. Finally, we note that the number of type AB recipients is significantly larger than the number of type AB donors, and that in percentage terms, the ratio of received livers to donated livers of the same blood type is greatest for blood type AB. Based on these facts, one might expect that blood type A and especially type AB recipients would see reduced delays due to their increased share of received livers, that type B recipients would see delays worse than type A and type AB but better than type O, and that type O recipients would see the worst delays as they require a type O organ.

These expectations are borne out in the results of Table 2 below, which quantifies the waiting time prior to transplant by blood type. While the overall average waiting time is slightly less than 8 months, it is an average of 10 months for type O recipients, who can access 46% of organs (ignoring Rhesus factor). This figure drops to just over 7 months for type B patients who have access to 55% of organs, and 6 months for type A, who have access to 88%. Type AB transplant recipients who have access to 100% waited an average delay prior to transplant of just 3 months.

The field in Tables 2 and 3 denoted “n” includes patients who were on the list prior to January 1, 2000 and not yet transplanted as of that date, plus those added to the waitlist during the period of study. This includes patients added to the list and then subsequently removed before transplant for any reason (death, recovery, etc) and patients who received a living donation. The first two columns (‘*n*’ and ‘Deaths on the waitlist’) are taken from the LHSC data set because CORR does not collect information on patients prior to transplantation. The data in the third through seventh columns are from the CORR data.

4.3 Characteristics of transplants by gender, age, and waitlist

The figures and the tables display summary statistics calculated by group. Figure 2 below reveals a net transfer of about 150 livers from female donors to male recipients. Figure 3 seems to suggest that patient health remains relatively stable between listing and transplant; but this ignores deaths prior to transplant, and patients removed from the queue.

5 Three approaches to address system instability

In order to achieve timely transplants for all patients deemed to be able to benefit from them, the long-run rate at which livers become available for transplant must, to start with, exceed the patient placement rate. This in itself is not sufficient to ensure timely treatment for all patients, due to randomness inherent in waitlists: substantial variation exists not only in the times between patient placements, but also in organ availability.

Table 1 Overall statistics

Variable	Mean	Standard Deviation
Recipient age (year)	47.8	16.0
Donor age (year)	42.0	18.3
Waiting time (day)	231.8	296.9

Table 2 Transplant results by blood type

Blood Type	*n*=# on the List During the Study period	Number of Deaths on the Wait List	Number of Cadaveric Transplants	Average Waiting Time (days)	Average Age of Recipient (years)	Average Age of Donor (years)	Number of Deaths First Year Post Transplant
O	1,500	255 (17.0%)	708	309.4	47.6	43.6	97 (13.7%)
A	1,253	137 (10.9%)	779	184.6	47.5	40.6	105 (13.5%)
B	426	64 (15.0%)	215	219	50.2	43	33 (15.3%)
AB	139	17 (12.2%)	108	87.5	47.2	38.4	15 (13.9%)

As the following tables establish, however, none of the six regional waitlists even meet the necessary first step: the patient placement rates exceed the rates at which organs become available in all parts of the country. It is intuitively clear as well that in a stable environment, as the capacity of the system in terms of available organs grows well beyond the demand in terms of placement rate, the delays would be expected to decrease accordingly.

In order to address the inherent system instability due to the fact that demand continued to outstrip supply throughout the study period, and this tendency had in fact worsened over this period of time, we formulated three strategies to bring about stability. The first assumes that one must curtail the demand to less than existing system capacity, while the latter two look at ways to increase supply to meet existing demand:

A) Lottery system:

It is required ethically and legally of an allocation system for a scarce life saving resource to be transparent and fair. It has been suggested that allocation of scarce resources by lottery is the only way to avoid bias. [7] This approach has not been applied because its arbitrary nature implies that other systems can do better. Current allocation systems are based on time waiting, modified for medical urgency. Sensitivity analysis using random allocation of organs is useful to provide a control against which other systems may be measured.

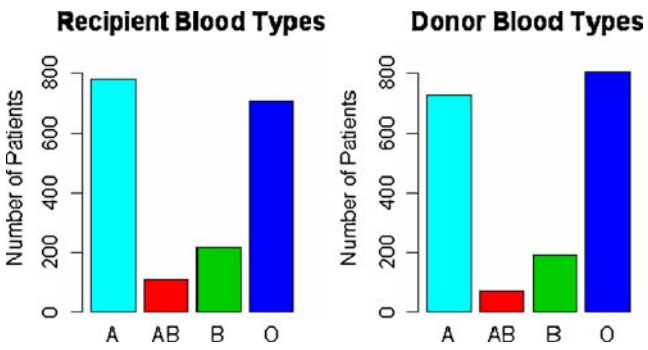

Fig. 1 Blood types of donors and recipients

B) Increased living donations:

The liver is the one organ capable of regenerating itself, when a portion is removed. Consequently it is possible to perform transplants of a section of an adult liver, typically to a compatible relative. As so-called "living-donor" transplants become more and more common, they represent one source of hope for reconciling a growing patient placement rate with a stable rate of cadaveric donations.

On April 10th 2007, the Ontario provincial government indicated it is taking a "good look" at a policy already implemented in British Columbia, where living donors are reimbursed for lost wages and travel expenses during the period of assessment, surgery, and recovery. The B.C. program offers up to $5,500 in compensation per donor. Therefore, we considered it timely to assess the number of living donors that would be required to bring stability to the transplant systems in Ontario as well as nationally.

C) Increased cadaveric organ availability:

The other option to an increase in the living-related rate would be an increase in the cadaveric donor rate, and of course the two options can be pursued in tandem. The primary means of increasing the cadaveric donor rate is by a campaign to increase the degree to which donors sign cards. In Ontario, a private member's bill sponsored by MLA Frank Klees in 2007 proposed that all residents of Ontario would be reminded about the matter of organ donation whenever their provincial health cards come up for renewal.

It seems that there have not been many studies as to the degree to which donor cards have been signed among the adult population, and we are unaware of any. Similarly, regional variations in willingness to sign a donor card do not appear to have been studied. In the course of our research, values ranging from 20% signing rate to 60% have been suggested. One study suggests an upper bound of 95% might be the limit of an achievable signing rate.

6 Modelling the waiting times

The two alternatives available to assess the efficacy of these three methods to rectify system instability are 1) a detailed

Table 3 Transplant results by various other factors

	n=# on the List During the Study Period	Number of Deaths on the Wait List	Number of Cadaveric Transplants	Average Waiting Time (days)	Average Age of Pecipient (years)	Average Age of Donor (years)	Number of Deaths First Year Post Transplant
Age							
Adult	3,062	456 (14.9%)	1,671 (54.6%)	237.2	51.3	43.4	230 (13.8%)
Child <18	228	15 (6.6%)	141(61.8%)	167.3	6	24.9	20 (14.2%)
Gender							
M	1,897	259 (13.7%)	1,163 (61.3%)	232.5	48.8	43.2	149 (12.8%)
F	1,086	173 (15.9%)	649 (59.8%)	230.5	46.1	39.7	101 (15.6%)
Province of Wait List							
BC	282	51 (18.1%)	168 (59.6%)	162.6	49.7	38.5	24 (14.3%)
AB	508	49 (9.6%)	298 (58.7%)	172.8	46.6	37.8	39 (13.1%)
ON	1,609	275 (17.1%)	703 (43.7%)	340.2	46.3	42.6	60 (8.5%)
QC	737	77 (10.4%)	529 (71.8%)	151.1	50	45.1	110 (20.8%)
NS	177	21 (11.9%)	114 (64.4%)	193.3	47.6	39	17 (14.9%)

simulation reflecting all or the most relevant influencing factors, and 2) a relevant theoretical model that reflects the key aspects of the system. While the former alternative is something we are pursuing currently, this is a time-consuming process; meanwhile, a great deal of relevant information can be gleaned by modelling the waitlist as a queue, which requires much less effort.

Queues have been used extensively in models of health care systems. In this journal, the literature review in a recent paper [12] includes an excellent discussion and a list of more than two dozen papers where mathematical models have been used to address issues related to health care resources. In particular, Cipriano et al. [12] states that "Queuing theory has been applied to many aspects of heath care including emergency rooms [72, 73], cardiac catheterization [74], drug treatment [75], organ transplantation [76–79], and total joint replacement [35]."

It has been suggested that the proper application of a pertinent mathematical model is like a good caricature [13]. In the latter case, the image that results from the use of a small number of well-drawn pen strokes manages to convey the identity of the intended individual. In the former case, selection of a pertinent model based on most of the most important factors at play, when evaluated based on good data estimates, manages to provide useful insight about the real phenomenon.

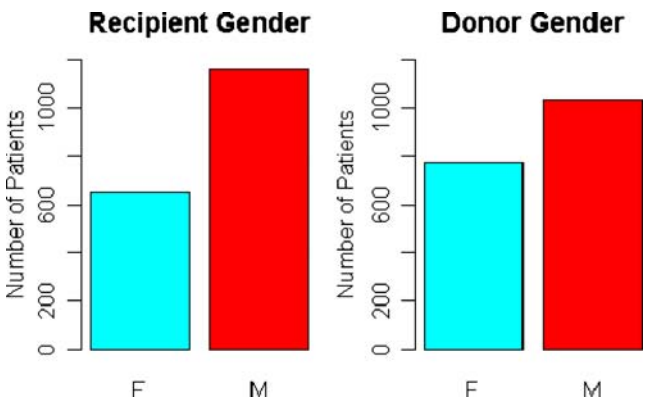

Fig. 2 Donor and recipient gender

The key questions that decision makers of waitlists need to address are the following: How many patients roughly can a waitlist handle, and is their time until transplant likely to be on the order of weeks or months? What are reasonable estimates of the proportion of patients who will wait in excess of a specified time interval? Queuing models that assess system performance under the three suggested approaches can provide appropriate answers to these order of magnitude questions, especially as we will establish the appropriateness of the exponential service mechanism in the next section.

In order for the queuing model to be relevant, the list of important factors to be considered includes the number of servers available, the customer arrival process and the service time distribution, the service discipline, and whether the overall arrival and service rates are changing or relatively static. The present work proposes a GI/M/1-type queue model (a first-come, first-served single server queue with exponential service); areas where the model diverges from reality will be discussed shortly.

Queues are used to model congestion due to random demand for a limited resource. The limiting factor in a transplant setting is practically never the availability of the surgeon or operating theatre; rather, it is the availability of the organ. Consequently, the arrivals to the queue comprise the patients being placed on the waitlist, whereas the service time represents the interval between successive livers becoming available. The best-known model of the single server queue presumes that customers arrive according to a Poisson process and that service times are

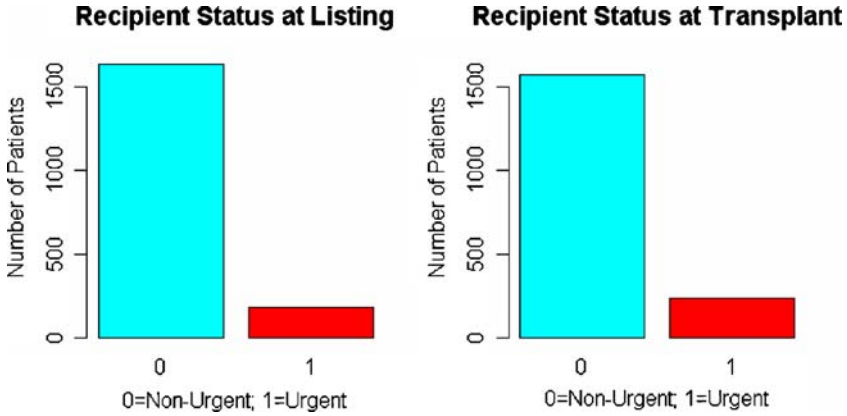

Fig. 3 Recipient status at time of listing and time of transplant

exponential. Of the two, the more important assumption is the exponential service assumption, as we will see two sections hence. The goal of the next section is to assess the conformity of the data to these distributional assumptions. Following statistical analysis of the data at hand, we initially focus on the key role exponential service plays in this regard, following which other issues such as server discipline are discussed.

7 Statistical analysis of patient placement and organ availability

7.1 Description of the queue properties

The stability of the waitlists is indicated by the ratio ρ (rho) of the net arrival rate λ (lambda) to the service rate μ (mu). Here, the "arrival rate" equals the patient placement rate minus the rate of living-related donations. Formally, by "stability," we mean the ability of the waitlist to catch up eventually to any random burst of arrivals. The condition for stability is $\rho=\lambda/\mu<1$; failing this, the waitlist is bound to grow over time, unless patients die off or abandon for other reasons. In fact, one expects the length to grow by $(\lambda-\mu)t$ patients after t time units. We discount by the living-related transplant rate, as the recipients of living donations are removed from the waitlist once a match is found. In contrast, the availability of a deceased-donor organ remains a random event. Therefore, the "service rate" is the rate at which cadaveric livers become available. The numbers in this table should be considered as approximate because of data quality issues. During the 5 year study period, from January 1, 2000 to December 31, 2004, there were 3,320 patients already on or added to the waitlist for liver transplant. According to the CORR data (records with missing transplant dates or list dates removed), there were 2,011 liver transplants performed between Jan. 1, 2000 and Dec. 31, 2004. Of these, 1,812 were cadaveric organs and 199 were living related donors. Of the 3,320 patients on or added to the list during this time period, 471 died before receiving a transplant. Four hundred and thirty-four patients were removed for miscellaneous reasons.

As measured by ρ, Table 4 indicates that none of the waitlists is stable in the sense of a queue. Deaths and abandonment can make a system appear stable, but these are not desirable ways to achieve stability. In fact, the queues we have observed have grown over time, which is consistent with the unstable scenario reported by Howard [4]. The national ratio during the 5-year study period is 1.55, indicating a net patient placement 55% higher than the rate at which cadaveric organs become available. Broken down by region, ρ varies from 1.29 in Quebec to a high of 1.78 in Ontario. The variation in organ availability rate reflects a host of causes, most notably differences in population, but also including, possibly, differences in accident rates and differing degrees to which donor cards are signed.

7.2 Distribution of arrivals to the queue

As noted in the last section, the classical models of queues assume that customers arrive according to a Poisson process, and that service times are exponential. The assumed distributions are frequently different from those observed in the area of application. It is generally assumed that the greater the degree of deviation from reality, the less reliable the inference from the queuing model. Hence it is quite relevant for us to address here the nature of the arrival and service time distributions.

7.2.1 Tests on the data at the national level

First of all, inspection of the data showed an increasing trend of yearly arrivals to the waitlist. This was confirmed using linear regression analysis. Since the yearly arrivals of patients on the waitlist are "count" data, a square root transformation was performed on the data before doing the regression analysis. Transformations are required to satisfy

Table 4 2000–2004 patient placement, organ availability, and living donation rates

	Rates
National rates	
Previously waiting	311
Placements on waitlist (λ)	3,009
Total	3,320
Cadaveric organs available (μ)	1,812
Living donor transplants	199
Abandonment (includes Living donors)	1,104
British Columbia rates	
Previously waiting	12
Placements on waitlist (λ)	270
TOTAL	282
Cadaveric organs available (μ)	168
Living donor transplants	10
Abandonment (includes Living donors)	102
Alberta rates	
Previously waiting	13
Placements on waitlist (λ)	495
TOTAL	508
Cadaveric organs available (μ)	298
Living donor transplants	34
Abandonment (includes Living donors)	168
Ontario rates	
Previously waiting	212
Placements on waitlist (λ)	1,397
TOTAL	1,609
Cadaveric organs available (μ)	703
Living donor transplants	143
Abandonment (includes Living donors)	620
Quebec rates:	
Previously waiting	60
Placements on waitlist (λ)	683
TOTAL	743
Cadaveric organs available (μ)	529
Living donor transplants	1
Abandonment (includes Living donors)	164
Nova Scotia rates	
Previously waiting	14
Placements on waitlist (λ)	164
TOTAL	178
Cadaveric organs available (μ)	114
Living donor transplants	6
Abandonment (includes Living donors)	47

the requirement of constant variance for regression. The analysis showed that the slope was positive, suggesting an increasing trend, with a p value of 0.007. Therefore we concluded that the number of patients arriving to the waitlist is indeed increasing yearly.

Initial analysis using a chi square goodness-of-fit test demonstrated that the arrivals of patients onto the waitlist, considered as national aggregate data, during the time period Jan 1, 2000 to Dec. 31, 2004, did not follow a Poisson distribution. It is likely that physician intervention, based on their knowledge of the status of the waitlist, affects the placement of patients; other factors may influence this outcome as well.

7.2.2 Regional data

Since the queues actually function as six individual queues (with minimal sharing), considering a national waitlist is somewhat artificial. Analysis of the individual regional queues showed that none of the queues experienced a Poisson distribution for arrivals to the queue. However, we found that the arrivals of patients to the larger regional waitlists were adequately described by a geometric distribution. For example, considering the Quebec queue, there were 680 arrivals in 1,827 days. A chi square goodness-of-fit test for the Geometric distribution (with parameters μ= 0.372 and p=0.729) showed a p value of 0.836. This means that we cannot reject the null hypothesis that the arrivals for the Quebec queue follow a geometric distribution. The arrival of patients to the queue for London also appears to follow a geometric distribution with parameters μ=0.241 and p=0.806.

7.3 Distributions of service time

As noted above, we are in fact dealing not with one national queue, but rather six regional queues. When considered on an individual basis, analysis of the service time for the regional queues by means of the chi square goodness-of fit test showed that the larger centres do in fact satisfy the Poisson model for organ availability. This is in fact not surprising, in that the source of cadaveric donations is the result of rare events occurring over a large population, such as severe accidents or medical events such as aneurisms. The Poisson distribution has often been used to model such phenomena. Consequently, we feel it is reasonable to work with the classical assumption of exponential service times in our sensitivity analyses that follow.

In summary, we observe that the assumption of exponential service times appears to reflect reality, and this result has important consequences for us. In particular, it is the assumption of exponentially-distributed service times that leads to exponential distributions for the time a customer spends in a single server queue, as we show in the next section. The greater amount of deviation between theory and reality lies in the area of the arrival mechanism.

8 Pertinent results from the theory of M/M/1 and GI/M/1 queues

The most widely-used single-server model is the M/M/1 queue, which assumes both Poisson arrivals at rate λ and

exponential service at rate μ. For $\lambda>\mu$, we have shown that the queue length will tend to grow over time. So long as $\lambda<\mu$, the system can keep up with the demand in the long run. For an M/M/1 queue with $\lambda<\mu$, it is well-known (see for instance Gross and Harris [6], p 64–68) that

Average waiting time (from arrival to departure)
$= 1/(\mu - \lambda) = 1/[\mu(1-\rho)]$,

Probability that an arrival will wait more than t time to complete service $= e^{-(\mu-\lambda)t}$.

What is particularly appealing about these formulas is their simple dependence upon the arrival and service rates. It is a well-known queuing-theoretic result (see for instance, Gross and Harris [6], section 5.3) that it is the exponential service assumption that leads to the simple form of these formulas. In fact, the single-server, exponential-service queue with a general, independent renewal process for the inter-arrival times (denoted the GI/M/1 queue) has the following equivalent forms for the performance measures (see ref. 6, pp. 252–253):

Average waiting time (from arrival to departure)
$= 1/[\mu(1 - r_0)]$,

Probability that an arrival will wait more than t time to complete service $= e^{-\mu(1-r_0)t}$,

where the root r_0 is the unique solution in the interval (0,1) of a fixed point equation entailing the Laplace–Stieltjes transform of the interarrival-time distribution. This root can be found by factoring a quadratic equation in certain circumstances, and numerically by successive substitution otherwise. In contrast, without the exponential service assumption, these simple forms do not apply even when the arrival process is a Poisson process. In the so-called M/G/1 queue, while the mean waiting times can still be found easily (see ref 6, p.212), the exact expression for the waiting time distribution for even some simple non-exponential cases like the M/D/1 queue are quite complicated (see ref [14]). In fact, the M/D/1 waiting time distribution does not appear in the standard references on queues.

8.1 Justification for (and implementation of) a GI/M/1 type model

The use of the GI/M/1 model is typically hampered by the fact that Poisson arrivals tend to occur more frequently in reality than exponential service. In the transplant setting, the situation is reversed: the availability of deceased-donor livers is either described adequately by a Poisson process, or its deviation from it is relatively minor. Below, we will describe our proposal for handling the deviation of the patient placement process from the Poisson process in our GI/M/1 model.

There are still two other notable deviations of the actual waitlists from the queuing model we are proposing for them. The former of these is the question of blood type. The blood type of a deceased donor liver will determine who can get it, and who is likely to, whereas the proposed first-come, first served model treats all blood types the same. To analyse the impact of blood type precisely would require not only knowledge of the arrival patterns of the specific blood types (which is available), but also the other aspects affecting physicians as they decide when to transplant across blood group lines. It has until now been generally held that such transplants are rare; however, the evidence in Fig. 1 would seem to suggest it is less rare in the Canadian context at least than previously thought. Clearly, a detailed simulation model is needed to assess the impact of blood type accurately.

Nonetheless, on a qualitative level, the impact of blood type on waiting times of the various blood groups is known in our view, according to the experience reported in Section 4. Blood group O patients will wait the longest, and longer than a single-class queuing model would suggest, as they require a type O organ. Type AB patients are universal recipient, and as such, can be expected to have waits markedly shorter than other blood types and shorter than what a queuing model would suggest. Blood type A candidates who have access to about 88% of the livers (based on the Canadian numbers) can be expected to do better than O and not as well as AB. Blood type B, having access to about 55% of the livers should experience delays somewhere between that seen by type O and type A patients.

The other aspect in which the actual waitlist deviates from the proposed queuing model is the queue discipline. The GI/M/1 model assumed a first-come, first-served (FCFS) discipline; the reality is that sicker patients get transplanted sooner. Qualitatively, this means that the actual delay distribution would be more variable than a FCFS model would suggest. We would anticipate that both the fractions of patients experiencing short delays and those experiencing long delays would be greater than our model predicts. However, if the previous observation that 90% of liver transplants in Canada are allocated on the basis of waiting time alone [2] is still applicable, then the delays suggested by our queuing model should still be fairly accurate. Once again, a detailed simulation study is needed to answer this question, and can address the related question of the impact of changes to other service disciplines such as giving priority on the basis of MELD scores.

Notwithstanding the foregoing limitations, a GI/M/1 queuing model can still provide informative answers to the waiting-time aspects of key questions that decision

makers associated with improving the situation of liver transplant waitlists in Canada must consider. The current discussion is focussed on where one should place additional effort: towards encouraging more donor cards to be signed, or to finding suitable living donors? In order to address this question fully, one needs to consider the distributional aspects of the waiting time. Just how much of a target increase is needed for each of these types of remedies in order to obtain a waitlist system which is not only stable, but produces acceptable waiting times? These are system-wide considerations that a GI/M/1-type model can provide answers to.

Comparison of the previous formulas for the M/M/1 and GI/M/1 queues reveals that the unique root r_0 equals ρ in the case of Poisson arrivals. In general, when the inter-arrival time (IAT) distribution is more variable than an exponential distribution, r_0 is larger than ρ. This leads to predictions of longer delays from the resulting GI/M/1 model. The converse situation occurs when the IAT distribution is less variable. Such conclusions are consistent with the general principle that greater variability in the arrival and/or service processes leads to greater congestion, and hence longer delays.

For the transplant waitlists, the inter-arrival time is more variable than an exponential model. A simple model for such inter-arrival times that relies only on the mean and variance is a hyper-exponential distribution with balanced means [15]. (The resulting queue is denoted H2/M/1.) This distribution is formulated as a mixture of two exponential distributions at rates λ_1 and λ_2 respectively, with a weight of $0<p_1<1$ for the former and $p_2=1-p_1$ for the latter. The resulting inter-arrival time Laplace–Stieltjes transform is

$$A^*(s) = p_1\lambda_1/(s+\lambda_1) + p_2\lambda_2/(s+\lambda_2)$$
$$= (\lambda_1\lambda_2 + (p_1\lambda_1 + p_2\lambda_2)s)/[(s+\lambda_1)(s+\lambda_2)].$$

The unique root $0<r_0<1$ we seek satisfies $r_0=\mathrm{A}(\mu(1-r_0))$. When we substitute for $A^*(s)$ above, a cubic equation is obtained which has one root at unity. When this is removed, the resulting quadratic equation has two positive roots, and the smaller of these is the root we seek. Defining $\rho_i=\lambda_i/\mu$ for $i=1,2$, one obtains

$$r_0 = \left[(1+\rho_1+\rho_2) - \sqrt{\left\{(1+\rho_1+\rho_2)^2 - 4(\rho_1\,\rho_2 + p_1\,\rho_1 + p_2\,\rho_2)\right\}}\right]\Big/2$$

The parameters of this hyper-exponential distribution with balanced means are given by [15]

$$\lambda_i = 2p_i/\mathrm{E}\{\mathrm{T}\};\ \mathrm{i}=1,2;\ \mathrm{p}_1 = 0.5(1+\sqrt{\{(\mathrm{c}_{\mathrm{T}^2}-1)/\mathrm{c}_{\mathrm{T}^2}+1\}});\ \mathrm{p}_2 = 1-\mathrm{p}_1$$

where $C_T{}^2 = \mathrm{Var}\{T\}\Big/E\{T\}^2$ is the squared coefficient of variation of the inter-arrival time,and where $E\{T\}$ and Var $\{T\}$ denote the mean and variance of the IAT respectively. A number of examples based on this model are presented in the next section.

One final cautionary note is that the queuing formulas we use are based on the assumption that the queue is, and always has been, stable at the specified value of ρ. Since in fact a substantial backlog of patients has accumulated, substantial time will be needed to clear it.

9 Sensitivity analysis: assumptions and results

In this section we perform three sets of sensitivity analyses which illustrate the degree of the problem, and the order of magnitude of the response that is needed in order to provide sufficient capacity to meet the need that was present at the end of the study period. Preliminary results along this line suggest that placements in the past few years appear to have stabilized close to the 2004 levels [11].

We have replaced the regional queues by single queues, for both the Ontario (Toronto and London waitlists combined) and national analyses (all six waitlists combined). The national waitlist provides a benchmark of the best that could be achieved if the geographical aspect could be ignored. The national waitlist model assumes that available organs would be controlled and allocated centrally. The limiting factor being the availability of organs, rather than physician or operating room availability, a single server model is appropriate, in that livers would be allocated successively as they became available. Furthermore, if one were in a stable transplant environment, no organ would be wasted if there were no need for it regionally—it would cross the country if there were a patient that could benefit from it. Quantitatively however, the actual mean waiting times and the probabilities of waits in excess of 1 month will be typically greater in the regional waitlists than those forecast by the national model. Of course, the sheer distances involved in Canada argue against a central allocation policy, which would see large numbers of livers travelling great distances prior to transplant, during which the quality of the organ would deteriorate.

Our primary goal here is to provide a reasonable estimate of the numbers of additional livers needed to establish a stable organ transplant system. Both M/M/1 and H2/M/1 models were used for the Ontario data. Only M/M/1 models were used for the national data as we did not have access to individual placement records for the whole country. Such records are necessary in order to estimate the variability in inter-arrival times. Due to the fact that actual inter-placement times are more variable than the assumption of exponential inter-arrival times allows, the waiting times suggested by the M/M/1 model are likely to be optimistic. Where given, we expect the H2/M/1 predictions to be a more accurate barometer of waitlist performance.

Table 5 Lottery System (2004 effective arrival rate, 5-year average service rate)

Ontario, M/M/1			Ontario, H2/M/1		
Effective Arrival Rate (λ)=308·p/year Organ Availability Rate (μ)=141.2/year			λ=308·p/year, μ=141.2/year C_T^2=3.771		
P	Av. Wait (days)	*P* (Wait>1 month)	*P*	Av. Wait (days)	*P* (Wait>1 month)
0.41	25	29%	0.41	55	57%
0.435	51	55%	0.435	117	77%
0.455	344	92%	0.455	818	96%

9.1 Other assumptions

In addition to the question of inter-arrival time variability, there is reason to believe that successive placements of patients on the waitlist might not occur independently in the statistical sense. As we have not studied this phenomenon, we cannot predict if the impact of this is beneficial or detrimental to the degree of the delay incurred.

We note once again that we have ignored the impact of blood type in the sensitivity analyses. To include blood type in the analysis would require a much more complicated queuing model, and the simulation model we will be developing in coming work will be better able to reflect this matter. At the same time, the qualitative impacts on delay when blood type is consider have been discussed at some length in the previous section, as was the matter than sicker patients get transplanted first.

9.1.1 Results for the lottery system

Table 5 presents the average waiting times in days, and the probability that a patient would wait in excess of 1 month for those patients in Ontario who gain access to a lottery system for three different chances of success. We chose a 1-month benchmark arbitrarily to provide some reference point for the likelihood of longer delays. In Table 5, we have used the effective patient placement rates observed in 2004 (the actual rate, discounted by the number of living-related donations), due to the increasing trend observed over the study period. As there was no evidence of a trend in cadaveric organ availability rates, we have used the average of the five yearly rates as our point estimate for the service rate. Three values of the lottery success probability *p* were selected, chosen to produce queue utilizations of close to 90%, 95%, and 99% respectively. Under these assumptions, we can see that a fraction *p* on the order of 43% of patients could have been handled in Ontario. We also observe that the mean delays are substantially longer based on the H2/M/1 model than would be forecast using an M/M/1 model.

The first three columns of Table 6 provide similar results for a single national waitlist as based on the M/M/1 model. About 55% of patients could be treated under a lottery system if there were a single national waitlist. A smaller fraction can be admitted in Ontario, because the effective patient placement rate in 2004 was more than twice the rate at which cadaveric organs became available. (Nationally, the ratio was closer to 1.7.) Of course, this would penalize the other waitlists and patients of their regions to Ontario's benefit.

9.1.2 Results for increased numbers of living donations

We also considered the number of living donors required to bring stability to the transplant systems in Ontario as well as nationally. Again, three values of the necessary number LD of additional living donors would be needed, this time so that the waitlist for the remaining patients

Table 6 National Lottery and LD Results (2004 effective arrival rate, 5-year average service rate)

Lottery, Canada, M/M/1			Living Donor, Canada, M/M/1		
Effective Arrival Rate (λ)=623·p/year Organ Availability Rate (μ)=362.4/year			Effective Arrival Rate (λ)=623–LD/year Organ Availability Rate (μ)=362.4/year		
P	Av. Wait (days)	*P* (Wait>1 month)	LD	Av. Wait (days)	*P* (Wait>1 month)
0.52	10	4.1%	265	83	69%
0.55	19	19%	280	19	20%
0.58	344	92%	300	9	3.8%

Table 7 Increased living donations (2004 effective arrival rate, 5-year average service rate)

Ontario, M/M/1			Ontario, H2/M/1		
Effective Arrival Rate (λ)=308–LD/year Organ Availability Rate (μ)=141.2/year			λ=308–LD/year, μ=141.2/year C_T^2=3.771		
LD	Av. Wait (days)	*P* (Wait>1 month)	LD	Av. Wait (days)	*P* (Wait>1 month)
170	114	77%	170	269	89%
175	45	50%	175	103	74%
180	28	33%	180	62	61%

would operate at utilisations ρ close to 99%, 95%, and 90% respectively.

Table 7 shows that a figure on the order of 175 patients in Ontario would be needed to bring stability to the liver transplant waitlists there, assuming that the patient placement rates have not increased since 2004. Again, we see that the projected waiting times using the H2/M/1 model are substantially longer than those forecast by the M/M/1 model.

The latter three columns of Table 6 above provide the corresponding living-donor results for a single national waitlist, based on the M/M/1 model. Nationally, something on the order of 280 donors would be needed if this were the only source of additional organs.

Using the B.C. figure of $5,500 in expenses paid per living donor, this would represent an anticipated $962,500 expense for Ontario, or $1,540,000 nationally, assuming the respective numbers of donors could indeed be found.

9.1.3 Results for increased cadaveric organ availability

Table 8 below indicates the degree by which the number of cadaveric organs would have to increase, in the absence of any further increase in the living donor rate beyond 2004 levels, in order to achieve stability in the hypothesised Ontario waitlist. Once again, we have sought three values of the degree of increase needed, to come close to utilisations ρ of 99%, 95% and 90% respectively.

Roughly speaking, the cadaveric donation rate would have to almost double nationally in order to achieve stability; the comparable figures for Ontario shown below are even larger. Nationally, an increase in deceased donor livers in the range of 175% to 190% would result in average waiting times of 33 days to 6 days, as forecast by an M/M/1 model. The fraction of patients waiting in excess of 1 month to be transplanted would be about 40% assuming a 175% increase in cadaveric livers, whereas it would be about half a percent assuming a 190% increase.

If one were to assume arbitrarily that this would have to be achieved by a comparable increase the rate of signed donor cards, it could only be achieved if the current rate is notably less than 50%. Otherwise, some amount of increase in the number of living donors would be essential in addition to an increase in the cadaveric rate, to bring about a stable system.

10 Discussion

Even if one were to assume that the national demand for livers has not increased from the rate evident near the end of the study period, it is nonetheless approaching twice the rate of availability from cadaveric sources. Without actions that increase organ availability, a steady or increasing number of patients who could benefit from transplant will never see that stage, and the delays for those that do will increase. In turn, this will mean an increasing number of patients will die while waiting for transplant.

The latter part of this study attempted to quantify the impact of no change in policy via a lottery system. It also

Table 8 Increased cadaveric donations (2004 effective arrival rate, 5-year average service rate)

Ontario, M/M/1			Ontario, H2/M/1		
Effective Arrival Rate (λ)=308/year Organ Availability Rate (μ)=141.2·q/year			Effective Arrival Rate (λ)=308/year Organ Availability Rate (μ)=141.2q/year C_T^2=3.771		
q	Av. Wait (days)	*P* (Wait>1 month)	*q*	Av. Wait (days)	*P* (Wait>1 month)
220%	138	80%	220%	328	91%
230%	22	25%	230%	50	55%
240%	12	7.6%	240%	27	32%

suggests likely increases in cadaveric and/or living donor sources that would be needed to bring stability to the system. We found that, without efforts to increase the supply of organs, only 43% of listed patients in Ontario can reasonably hope to receive an organ, assuming no further increase in the patient placement rate. Nationally, about 55% of patients could be handled, under the same assumption. If living donations are used to ensure all patients have manageable waiting times in the queuing sense, around 175 living donors per year would be needed in Ontario, and 280 nationally. If these living donors were each reimbursed the $5,500 maximum to defray costs that is being paid currently in B.C. and which is being considered by the government of Ontario, the anticipated cost would be about $960,000 in Ontario, and $1.5 million nationally. Without any increase in the number of living donations, the number of donors from cadaveric sources would have to nearly double nationally to ensure a sufficient number of organs. The number in Ontario would have to more than double: a 130% increase would have to be observed. If the cadaveric rate cannot be increased to this degree, living donations would be needed to compensate. In all likelihood, major efforts along both avenues are needed in order to bring stability to the ever-growing waitlists.

11 Future work

We anticipate extensions to the present work in several directions. First, we are embarking on a detailed simulation of the waitlists to determine detailed waiting time answers that reflect the many interacting factors at play, such as selection based on health status and the impact of blood type on patient selection rules under the current regime. This simulation model will compare various patient selection strategies, and their impact on overall patient health. Among the protocols we wish to study are: (1) random allocation; (2) allocation according to time spent in queue; and (3) allocation according to the probability of dying without transplantation, with the sickest being transplanted first. Once tested, we would like to refine the models to analyse the clinical models, comparing CAN-WAIT and the MELD system employed in the USA, in order to identify the set or type of patients whose clinical course would have been changed under MELD.

On the theoretical side, a priority queuing model in which a customer's priority level can increase suddenly (to reflect changed health status) will be considered. It is hoped that such a model would be tractable in the exponential-service case that is justified in our setting.

An area of possible statistical study would be to estimate the actual level of donor card signing, in Ontario as well as the rest of Canada. Currently, not much seems to be known in this regard.

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