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ORIGINAL ARTICLE

A discrete-event simulation model of the kidney transplantation system in Rajasthan, India

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ABSTRACT

We present a discrete-event simulation model of the kidney transplantation system in an Indian state, Rajasthan. Organs are generated across the state based on the organ donation rate among the general population, and are allocated to patients on the kidney transplantation waitlist. The organ allocation algorithm is developed using official guidelines published for kidney transplantation, and model parameters were estimated using publicly available data to the extent possible. Transplantation outcomes generated by the model include: (a) the probabilities of a patient receiving an organ within one to 5 years of registration and (b) the average number of deaths per year due to lack of donated organs. Simulation experiments involving observing the effect of increasing the organ arrival rate and establishing additional transplantation centres on transplantation outcomes are also conducted. We also demonstrate the use of such a model to optimally locate additional transplantation centres using simulation optimisation methods.

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Kidney transplantation India; simulation and logistics; organ transplantation system simulation

1. Introduction and literature review

The exact burden of end-stage renal disease (ESRD) is not known in India due to a lack of reliable patient registries, but recent studies estimate that 220,000–-275,000 new patients require renal replacement therapy, or dialysis (Jha, 2013; Modi & Jha, 2011). Dialysis is an expensive procedure, especially when provided over a patient's lifetime, and also causes substantial impairment of the quality of life of the patient. In comparison with dialysis, renal (kidney) transplantation has proven to be more effective in prolonging the lives of ESRD patients, and when lifetime costs and effectiveness in terms of improvement in quality of life and productivity are also considered, renal transplantation has been proven to be substantially more cost-effective as well (National Kidney Federation (NKF), 2010; Rosselli et al., 2015). However, a massive shortage in donated organs in India has led to a precarious situation for ESRD patients on the waitlist for transplantation. In this paper, we describe the development of a discrete-event simulation model of the kidney transplantation system in Rajasthan, the largest state (province) in India, and demonstrate how the organ shortage in Rajasthan affects transplantation outcomes for waitlisted patients. We also demonstrate the use of the model to analyse new logistical situations for kidney transplantation, such as estimating the effect of locating additional transplantation centres in the state on organ transport times and organ allocation rates within the state. We also demonstrate the use of the model, in conjunction with simulation optimisation methods such as the NSGS procedure (Hong et al., 2015), to optimally locate new transplantation centres in terms of minimising average organ transport times.

The organ donation rate in India, at 0.34 per million population in 2014 (in comparison to 26 and 36 - per million population in the USA and Spain, respectively), is one of the lowest in the world (Organ India and Mohan Foundation, 2014). The southern states of India lead the rest of the country in terms of organ donation and transplantation activity, while the northern states, having traditionally lagged behind, are now working on establishing the required infrastructure. Due to campaigns to increase awareness regarding organ donation by several key stakeholders including the Government of India, the organ donation rate has steadily increased to 0.8 organs per million population in 2017 (New Delhi Television Limited (NDTV), 2017), and is expected to continue to grow. Further, as part of efforts to both improve organ donation rates, avoid organ wastage, and to establish the infrastructure for organ procurement and transplantation in light of increasing organ donation rates, the government has plans to substantially increase the number of organ retrieval (procurement) and transplant centres across the country (New Delhi Television Limited (NDTV), 2017). Therefore, it becomes important to also develop the mathematical and computational infrastructure to model, analyse and optimise organ transplantation systems in the Indian context. We

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develop a simulation model of the kidney transplantation system in Rajasthan as a first step towards addressing this need. We focused on kidney transplantation due to the following reasons: (1) the high estimated prevalence of ESRD in the country, and (2) kidneys are the most donated organs in India (Rajmohan et al., 2017). We chose to model the kidney transplantation system in the state of Rajasthan because (a) it is the largest state in India in terms of area, and the eighth largest state in terms of population (Census Commissioner of India, Ministry of Home Affairs, 2011), and (b) the state recently established its organ transplantation network and had publicly available (anonymised) data regarding waitlisted patients and donors. Further, we focus our analysis on organ transplantation from deceased donors. This is because less than 2% of donated organs come from deceased donors (Rajmohan et al., 2017), and therefore, there is tremendous potential in increasing deceased organ donation among the general public.

Based on Rajasthan's population, we estimate that approximately 11,600 patients require a transplant in Rajasthan every year. However, according to the data published by the Rajasthan Network for Organ Sharing (RNOS), the governmental organisation that oversees organ transplantation in the state, there are only 303 patients on the waitlist as of December 2019 (Rajasthan Network for Organ Sharing (RNOS), 2019a). In Rajasthan, only 43 kidneys were donated in 2017 (Rajasthan Network for Organ Sharing (RNOS), 2019a). Given the increasing awareness among ESRD patients about kidney transplantation as the optimal option, and the increase in kidney donation rates, a critical analysis of the kidney transplantation system in terms of its outcomes on patients, including answering the question of whether the existing capacity in terms of both organ procurement centres and transplant centres will be sufficient to accommodate demand, will become important. We model the kidney transplantation system in Rajasthan as a prototype that can be scaled up for the entire country and in the process identify issues that need to be addressed before doing so.

A substantial amount of work has been conducted in applying the methods of operations research and simulation to improve various aspects of organ transplantation in many countries. A comprehensive review of the operations research literature in organ transplantation in its entirety is beyond the scope of this article, so we focus our survey of the literature on (a) a brief discussion of studies applying operations research methods to optimise decision-making (e.g., optimal timing of transplantations, organ acceptance/rejection policies), (b) simulation studies conducted to analyse and optimise organ transplantation systems, and (b) more specifically, on relevant operations research studies conducted in the Indian context. For a comprehensive account of the literature in organ transplantation network management (i.e., optimally locating transplantation centres or organ procurement centres, reorganising the boundaries of administrative regions to reduce geographical disparities in organ allocation), we refer the reader to a detailed review of the literature on organ transplantation network management by Ahmadvand and Pishvaee (2018).

Several studies applying operations research methods to optimise decision-making in transplantation have also been published (Alagoz et al., 2004, 2007a, 2007b; Batun et al., 2018; Sandıkçı et al., 2008, 2013). To the best of our knowledge, almost all of these studies have involved liver transplantation. These studies range from determining the optimal timing for a living-donor liver transplantation (Alagoz et al., 2004), the effect of the waiting list on cadaveric liver acceptance decisions (Alagoz et al., 2007b), the effect of incomplete information regarding the waiting list on organ accept/reject decisions (Sandıkçı et al., 2013), to incorporating patient preferences in liver acceptance decisions (Batun et al., 2018). Most of these studies utilise a Markov decision process framework to formulate the decision problem in terms of finding the optimal policy under uncertainty, and do not utilise simulation. Simulation models have been developed primarily to address issues around the policies governing the allocation of organs to waitlisted patients. A majority of the models have addressed liver transplantation (Comas et al., 2008; Kreke et al., 2002; Pritsker et al., 1995; Shechter et al., 2005), including one of the earliest simulation models of an organ transplantation system by Pritsker et al. (1995). Kreke et al. (2002) introduced the natural history of end-stage liver disease patients with and without a transplant into their model that operated independently of any allocation scheme. Shechter et al. (2005) and Alagoz et al. (2005) built upon this work and used such a model to test changes in liver allocation policies. Similar simulation models have been developed subsequently to evaluate liver allocation policies, liver transplantation capacity, and other aspects of liver transplantation (Feng et al., 2013; Iyer et al., 2011; Kilambi et al., 2018; Toro-Díaz et al., 2015).

All of the above studies have been conducted for the United States transplantation system. Our search of the literature yielded one study that was not liver or kidney transplantation-related: Comas et al. (2008) developed a simulation model of the Spanish cataract transplantation system to evaluate an alternative waiting list prioritisation scheme in comparison with a first-in first-out system.

Compared to liver transplantation, fewer studies involving kidney transplantation were identified. Zenios et al. (1999) developed a Monte Carlo simulation model to compare different allocation policies, and simulated the operations of a single organ procurement

organisation in the United States. They incorporated changes in recipient and donor characteristics, patient and graft survival rates, and quality of life in their model. Su et al. (2004) developed a simulation model of the kidney allocation system in the United States to evaluate the effect of incorporation of recipient choice to accept or reject a donated kidney based on the projected increase in quality-adjusted life years it would yield. A. Davis et al. (2013) developed a simulation model of the kidney transplantation system in the United States as part of a series of studies describing efforts to reduce geographical disparities in kidney allocation across the United States (Davis et al., 2015, 2014). Most recently, Sandıkçı et al. (2019) develop a new clinically and operationally detailed simulation model of the kidney transplantation system in the United States that reduces computational runtime in comparison to the simulation maintained by the United Network for Organ Sharing (the organisation that maintains the organ procurement and transplantation network in the United States) by taking advantage of parallel computing methods.

Our work represents a first step towards applying the methods of simulation and optimisation to analysing and optimising organ transplantation systems in the Indian context. We develop a discrete-event simulation model of the kidney transplantation system in Rajasthan, India that models both the logistical and allocation aspects of kidney transplantation. From a logistical standpoint, the model incorporates the district-wise generation of kidneys across the state of Rajasthan, and its subsequent transportation to the district where the transplantation to the recipient is to be performed. From an allocation standpoint, the model generates multiple clinical parameters, such as the patient age, blood group, whether the patient has had one or more immunological graft failures from a previous transplant, time on dialysis, and panel reactive antibody (PRA) levels. These parameters are used to calculate the patient's Kidney Allocation Priority (KAP) score, which determines the patient's position on the waitlist. Further, the removal time for a patient is also generated based on the life expectancy of an ESRD patient on dialysis and the time the patient has already spent on dialysis at the time of registration on the waitlist. Therefore, our model can be used in efforts to optimise both the logistical and allocation aspects of kidney transplantation. For example, from a logistical standpoint, our model can be used in conjunction with simulation optimisation methods to identify optimal locations of transplantation centres (demonstrated in Section 4.1), and from an allocation standpoint, our model can evaluate multiple allocation policies to determine the policy that maximises patient outcomes (e.g., maximise probability of receiving a transplant). Our search of the literature did not yield a model for kidney transplantation that incorporated both logistical and clinical parameters to the extent that we have – while Zenios et al. (1999) incorporated multiple clinical characteristics, they conducted their analysis for a single organ procurement organisation. Further, to the best of our knowledge, our study is the first to demonstrate the use of simulation optimisation methods to identify optimal locations for transplantation centres from a discrete set of alternatives. Thus, our study, in addition to being capable of evaluating allocation policies, also demonstrates its use to evaluate and improve logistical aspects of transplantation systems, which have traditionally been the domain of optimisation formulations.

To the best of our knowledge, there is only one relevant study that has been conducted in the Indian context for organ transplantation: the work by Rajmohan et al. (2017) that involved optimally locating organ procurement organisations across the country so that total distance (weighted by demand for organs) between transplant centres and organ procurement organisations is minimised using a deterministic framework. In comparison to this work, our approach represents variability in organ transplantation explicitly, and also has the advantage of being able to address problems in both transplantation logistics and allocation using the same model. Further, given that a simulation model represents variability explicitly, it enables evaluation of the effect of an "optimal" solution on patient outcomes in a more comprehensive manner than a deterministic optimisation model. This can include, for example, evaluation of the location of a new organ transplantation or procurement centre generated by an optimal facility location model in terms of its effect on the distribution of organ transport time; or, as we demonstrate, finding the optimal location using ranking and selection simulation optimisation methods from a discrete set of locations that may be generated, for instance, by a traditional continuous optimal facility location model.

The remainder of the paper is organised as follows: in section 2, we describe the kidney allocation algorithm modelled in this article. In section 3, we describe the development of the simulation model and the estimation of its parameters. In section 4, we describe simulation experiments conducted using the model and their results. We conclude in section 5 with a brief summary of the article, with its limitations, and a discussion of future work.

2. Overview of Kidney Transplantation in India

The principal governmental authority overseeing organ and tissue transplantation in India is the National Organ and Tissue Transplantation Organisation (NOTTO), headquartered in New Delhi, the Indian capital. Five regional authorities,

each called the Regional Organ and Tissue Transplantation Organisation (ROTTO), were set up under the umbrella of NOTTO to oversee organ donation and transplantation in five principal geographical regions of the country. Each ROTTO oversees organ donation and transplantation in several states, and its activities include coordination for organ procurement and distribution, preservation of organs, quality management in organs, records maintenance, data protection and confidentiality, etc. ROTTOs also assist NOTTO in developing guidelines for organ procurement and allocation. The guidelines for kidney procurement and allocation that we use in this model to perform kidney allocation were developed and published by NOTTO (National Organ and Tissue Transplant Organization (NOTTO), 2018).

Kidney allocation is a complex process, influenced by a number of factors including medical urgency and donor-recipient matching. According to the guidelines published by NOTTO, the patient should be less than 75 years of age at the time of registration, should be a case of ESRD on maintenance dialysis for more than 3 months on a regular basis and should be registered only in one approved hospital (a transplantation centre). When a patient is registered in a hospital (a transplantation centre), he/she is added to the corresponding state's waitlist and is assigned a KAP score that determines his/her position on the waitlist. The KAP score is calculated according to a scoring system designed by NOTTO, depicted in the Table 1 below (sourced from the kidney allocation guidelines published by NOTTO, page 2) (National Organ and Tissue Transplant Organization (NOTTO), 2018).

We note here that we do not consider items 6 and 7 in the calculation of KAP scores for patients in the model, as we assumed that the likelihood of the associated scenarios being encountered is very low.

According to the allocation guidelines, a cadaveric kidney retrieved in a government (public) hospital is first considered for allocation only to patients registered in government transplant hospitals in that state; if an appropriate recipient is not found, then a waitlist comprised of patients registered in private transplant hospitals alone in that state is considered. If the retrieving hospital is privately owned/managed, then the same recipient selection process is followed, but in the reverse order. Thus, the type of transplant hospital (public or private) in which a patient is registered can impact their chances of receiving a transplant.

Within the waitlist comprising patients registered in government or private hospitals, the allocation will be done first based on the associated district's waiting list (where the organ was retrieved). If no recipient is eligible in the retrieval district's waiting list, then allocation will be done considering the state's waitlist. If a match is not found in the state's waitlist, then the organ is considered for allocation to other states administered by the associated ROTTO, and then to other ROTTOs nationally. Further, if the kidney is donated by a paediatric donor (less than 18 years), it will first be allocated to a paediatric waitlisted patient. If no paediatric patient is eligible, then the kidney will be allocated to an adult patient. Allocation is then done by matching blood groups of the deceased kidney donor and the patients. A blood group O kidney will be allocated to a recipient with group O, then to the next available patient on the waitlist of other compatible blood groups – that is, first to group A, then to group B, and lastly to group AB in that sequence. If the kidney is of blood group A or B, the organ will be allocated to the same blood group failing which it will be allocated to blood group AB. An AB group kidney will only be allocated to an AB patient. This allocation process is depicted in algorithm below, and is incorporated by the model to the extent that the organ is allocated to a patient within the state (Rajasthan).

Table 1. Scoring system for prioritising waitlisted patients for organ allocation.

Sl No.	Criteria for scoring	Points allotted
1	Time on dialysis	(+1) for each month on dialysis
2	Previous immunological graft failure within 3 months of transplantation	(+3) for each graft failure
3	Age of recipient	(+3) for less than 6 years (+2) for 6 to less than 12 years (+1) for 12 to less than 18 years
4	Patient on temporary vascular access	
a)	With failed all AV Fistula sites	(+2)
b)	With failed AV Graft after all failed AVF sites	(+4)
5	PRA (Panel Reactive Antibody)	(+0.5) for every 10% above 20%
6	Previous living donor now requiring kidney transplant	(+5)
7	Near relative (as per definition of THOTA) of previous deceased donor requiring kidney transplant	(+5)

Kidney allocation process

1. Let the retrieval hospital type be **"G" (government)**, and if there are patients on the state waitlist registered in "G" type hospitals, then the allocation process for patients registered in "G" type hospitals is followed, as described below. Initialise *flag = 0*.
   - 1.1.Set current waitlist = district waitlist
     - 1.1.1. If the current waitlist is not empty:
       - 1.1.1.1. Call *Age Check Subroutine* in **(2)**
       - 1.1.1.2. If no recipient is found, go to **(1.2)**
     - 1.1.2. If the current waitlist is empty:
       - 1.1.2.1. Go to **(1.2)**
   - 1.2. Set current waitlist = state waitlist
     - 1.2.1. If the current waitlist is not empty:
       - 1.2.1.1. Call *Age Check Subroutine* **(2)**
       - 1.2.1.2. If suitable recipient is not found, set *flag = flag + 1* and go to **(1.3)**

1.2.2. If the current waitlist is empty:
1.2.2.1. Go to **(1.3)**
1.3. If *flag* < *2*, change hospital type from "G" to "P" (or vice versa) in the district waitlist
1.3.1. Repeat allocation procedure in **(1.1)**
1.3.2. If suitable recipient is not found:
1.3.2.1. Organ unallocated, terminate allocation for this organ, reset *flag* = *0*
2. *Age Check Subroutine*: Check for the age of donor
2.1. If donor age <18 years:
2.1.1. Check whether the current waitlist contains patients with age <18 years. If yes:
2.1.1.1. Filter waitlist to keep only patients with age <18 years
2.1.1.2. Call *Blood Group Matching Subroutine* **(3)**
2.1.1.2.1. If a suitable recipient is not found, go to 2.2.1
2.2. If donor age >18 years:
2.2.1. Set current waitlist to contain patients of all ages
2.2.2. Call *Blood Group Matching Subroutine* **(3)**
2.2.2.1. If a suitable recipient is not found, return
3. *Blood Group Matching Subroutine*: Check for the blood group of donor and match against the patients in the current waitlist
3.1. If one or more matches are found, allocate the organ to the match with the highest KAP score
3.1.1. Update patient list and organ donated list, stop allocation process

3.2.If no match is found, return

Finally, the allocation guidelines published by NOTTO consider two additional aspects that we do not incorporate into the model: (a) the consideration of an "urgent" patient waitlist, which can accommodate a very small number of patients in immediate need of a kidney, and (b) consideration of patients requiring multiple organs (e.g., a heart and a kidney transplant). Given that the size of these waitlists is typically small, and hence are likely to not affect average behaviour of the model to a great extent, we do not incorporate these into the model at this stage.

3. Model development and parameter estimation

3.1. Model structure

We now describe the structure of the discrete-event simulation developed to model kidney transplantation in Rajasthan, India. The structure of the simulation model is depicted in Figure 1.

The model is initialised with patients randomly chosen from the waitlist of all patients registered for kidney transplants in the state of Rajasthan that is maintained by the RNOS, downloaded from the RNOS website in December 2019 (Rajasthan Network for Organ Sharing (RNOS), 2019a). Waitlists of patients registered for kidney transplants in each district of Rajasthan are generated from the overall state waitlist. We provide more details regarding initialisation of the simulation in Section 4. In the meanwhile, a snapshot of the information contained in the state waitlist is depicted in Figure 2 below. The information in the waitlist – in particular, the date of registration with RNOS, date of dialysis, registered hospital, blood group – is used to estimate multiple model parameters, as we discuss in Section 3.2. Advancement of the simulation is dependent on three principal events: patient arrival, patient removal due to death, and organ arrival. The next patient arrival time and the next organ arrival times are generated using appropriate interarrival time distributions (see Section 3.2). Removal of a patient from the waitlist occurs in one of two ways: the patient receives a transplant, or the patient dies (i.e., we do not consider patients baulking or reneging from the waitlist). Patient removal due to transplantation is governed by whether the patient is allocated an organ and undergoes a subsequent successful transplant, and patient removal due to death is determined using the literature-based removal time assigned to the patient when they are added to the waitlists in the model. The patient removal time due to death assigned to the patient is calculated taking into account the time the patient has already spent on dialysis at the time of entry into the waitlist. More details regarding input parameter estimation are provided in Section 3.2. The distances, and therefore the average travel times, between the districts of Rajasthan are acquired from Google Maps, and the travel time matrix generated in this manner is also part of the initialisation of the simulation. In our model, the districts are assumed to be at point locations (at their respective district headquarters).

When a patient arrives, his/her KAP score is calculated, a removal time due to death is assigned, and the district and the transplant centre (hospital) where the patient is registered is also assigned. The values of the clinical parameters required to calculate the patient's KAP score are generated by distributions that are primarily estimated from clinical literature (see Section 3.2). The patient is then added to both the state waitlist and his/her district waitlist for kidney transplantation.

The position of each patient in both waitlists are determined by his/her KAP score. After the patient is added to the state and district waitlists, the time of the next patient removal due to death is updated (which may change depending on the removal time due to death assigned to the newly arrived patient), the time of arrival of the next patient is generated and the overall simulation time is updated accordingly.

If patient removal due to death is the next event to occur (i.e., the patient has not received a transplant), then the patient is removed from both the state and

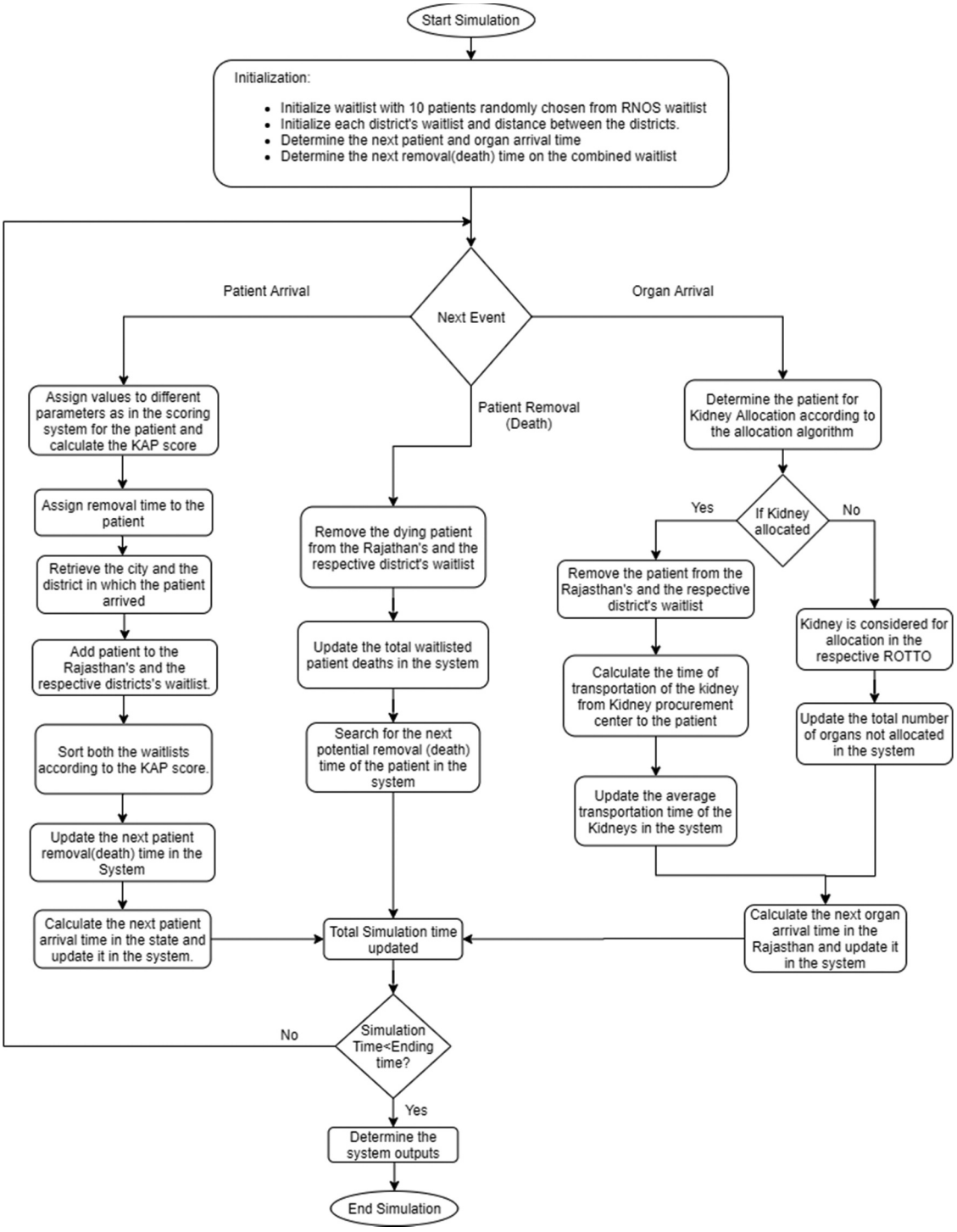

Figure 1. Simulation model structure.

BLOOD GROUP	HOSPITAL NAME	CITY	DATE OF DIALYSIS	REGISTERED IN RNOS
O+	NARAYANA MULTISPECIALITY HOSPITAL	Karauli	5/5/2006	19/05/2015
O+	Mahatma Gandhi Hospital	Jaipur	12/6/2007	5/1/2015

Figure 2. RNOS kidney transplant waitlist: a snapshot.

district waitlists. The total number of patients who have died without receiving a transplant is then updated. The time of the next patient removal due to death is then identified from the state waitlist and is updated in the system. The overall simulation time is then updated.

If the next event to occur is an organ arrival, then the district where the kidney is donated is determined using the population-based probability of donation assigned to each district of Rajasthan. Values of associated parameters such as donor age, donor blood group, and type of hospital (government/private or

retrieval/transplant centre) where the kidney is retrieved are also generated (see Section 3.2). The organ is then allocated according to the allocation algorithms developed by NOTTO (Section 2). If a suitable recipient is identified, then the patient is removed from the state waitlist and also from the corresponding district waitlist. The total transportation time from the kidney procurement centre to the transplantation hospital where the patient has been registered is calculated and the average transportation time of kidneys in Rajasthan is updated. On the other hand, if no suitable patient is found according to NOTTO's state-level allocation algorithm, then the kidney is considered for allocation in Rajasthan's associated ROTTO. The number of organs not allocated within the state is then updated in the system, the time of the next organ arrival is scheduled, and the overall simulation time is updated.

3.2. Estimation of model parameters

We identify two primary types of model parameters: those related to patients, and those related to organs. We now describe how these parameters are estimated and their associated data sources.

3.2.1. Patient-related parameters

Patient-related parameters are estimated using data published on the RNOS website (including the patient waitlist), and also using information obtained from the literature.

We estimate multiple parameters from the waitlist published on the RNOS website (Rajasthan Network for Organ Sharing (RNOS), 2019a), downloaded in December 2019. The waitlist consisted of patient entries from January 2015 onwards; however, the data available for 2015 were of poor quality (relatively fewer patients were registered in 2015 than in subsequent years and arrived in batches, indicating that patients may have been registered in batches into the waitlist even if they had arrived according to a regular pattern), and hence data from patients registering in the waitlist from 2016 to the end of 2018 was used to estimate model parameters. Data for patients registering in the waitlist in 2019 were set aside for validating model outcomes.

The distribution of the interarrival times of patients was estimated using the dates of registration of patients in the RNOS state waitlist. However, because the dates of registration of many patients in the waitlist in a month were the same (i.e., they appeared to have registered on the same day), it was not possible to use the interarrival times directly (as this would yield many zero values for interarrival times, more than would be realistic) in determining a distribution for the interarrival times or the arrival rate of patients into the waitlist. Hence, the number of patients arriving in a month was used to determine the distribution of patient arrival rate. A chi-squared goodness of fit test was performed to determine the fit of various distributions to the monthly arrival rates, and the Poisson distribution, with a p-value of 0.7 (with the following null hypothesis: monthly arrival rate follows the Poisson distribution, and the alternate hypothesis: the monthly arrival rate does not follow the Poisson distribution). Thus, the interarrival times of patients are estimated from the monthly arrival rate estimated using the RNOS waitlist, and it follows an exponential distribution with a mean of 5.83 days. We anticipate using a more comprehensive data modelling approach to estimate the distribution of patient interarrival times as appropriately detailed data also becomes available from RNOS; for example, a time-series forecasting approach used to estimate the time-dependent means of a non-stationary arrival process (Poisson or otherwise), as described in (Angelo et al., 2017).

The model was initialised by selecting 10 patients randomly from the RNOS state waitlist. Only 10 patients were used for initialisation as selecting a larger number of patients from the waitlist would require longer warm-up periods for the simulation, as the simulation does not reach steady state until all patients chosen to initialise the waitlist are removed from the waitlists. Separate district waitlists are created based on the city of origin of patients as recorded in the state waitlist, and are created because NOTTO mandates that organs should first be allocated to patients in the same city/district before considering waitlisted patients in other districts/cities.

Patients may be removed from the waitlist if they die before receiving a transplant, and are therefore assigned a removal time due to death when they arrive in the waitlist. The removal time due to death of a patient is estimated from a recently published retrospective study that investigated haemodialysis practice patterns and outcomes in Indian ESRD patients (Lakshminarayana et al., 2017). The study enrolled patients who had spent a minimum of 3 months on maintenance haemodialysis, similar to the NOTTO eligibility criteria for registering on the transplant waitlist, and found that the mean survival time of patients on haemodialysis was 40.31 months (standard deviation of 26.69 months). In the absence of further information (e.g., raw data that could be used for distribution fitting), we assumed that a beta distribution for the removal time, and calculated its alpha and beta parameters from the mean and standard deviation. We chose the beta distribution as it enables imposing a lower limit of zero on the removal time. We reiterate here that the actual removal time assigned to a patient is computed by the subtracting the time on dialysis at registration from the survival time estimated from the beta distribution discussed above. If the overall simulation time becomes equal to

the removal time due to death of a patient, then he/she is removed from the waitlist.

The time on dialysis at registration was estimated using the date of dialysis and date of registration fields in the RNOS waitlist (i.e., by subtracting the latter date from the former). Outliers were identified using a box and whisker plot and removed from the data, and Anderson-Darling goodness of fit tests were performed to identify the best-fitting distribution to the time on dialysis at registration data. The exponential distribution was found to be the best-fitting distribution to the time on dialysis at registration, with a p-value of 0.581 (test hypotheses the same as that for patient arrival rates). Per the NOTTO allocation algorithm, the KAP score of a patient is updated as the amount of time the patient spends on dialysis in the simulation increases.

In Rajasthan, transplant centres are present only in the state capital Jaipur (10 centres) and Ganganagar (1 centre) districts, and hence the probabilities of patients registering with a transplant centre in a given district are calculated accordingly. Patient blood group and age, which are essential to determine organ allocation, are calculated using data obtained from on the state waitlist and other reports published on the RNOS website (RNOS, 2019c, 2019d). The data for patient age are obtained from a histogram of patient ages published on the RNOS website (Rajasthan Network for Organ Sharing (RNOS), 2019a). The data from the frequency distribution depicted in the histogram were recreated by bootstrapping from the histogram bins, and the best-fitting distribution for this data was determined by conducting the Anderson-Darling goodness of fit tests. The Gaussian distribution was found to the best-fitting distribution with a p-value of 0.389 (null and alternate hypotheses the same as those specified for the patient arrival rates). The estimated Gaussian distribution was truncated by a lower limit of 1 year and an upper limit of 75 years (limits were estimated based on NOTTO guidelines). Patient blood group is generated from a discrete distribution parameterised by data from the state waitlist (see Figure 2).

Estimation of other clinical parameters such as PRA levels for a patient, probability of a patient with all failed arteriovenous (AV) fistula sites, and the probability of a patient with failed AV graft after all failed AV fistula sites were estimated using data from the clinical literature (Cecka et al., 2011; Chandrashekar et al., 2014). Our search of the literature did not yield studies that reported PRA levels among Indian patients registered on kidney transplantation waitlists, and hence PRA levels were estimated from an American study that reported calculated PRA levels among patients registered on the American kidney transplant waitlist (Cecka et al., 2011). The study reported proportions of patients with PRA levels within various ranges (see Table 2), and these proportions and ranges were used to generate PRA levels for a patient. For example, approximately 5.6% of patients reported PRA levels between 1% and 20%, and with a probability of 0.056, a patient is assigned a PRA level sampled from a uniform distribution from the interval [1, 20]. The proportions of patients with all failed AV fistula sites and with a failed AV graft after all failed AV fistula sites was estimated from an Indian study reporting survival characteristics of patients on maintenance haemodialysis (Chandrashekar et al., 2014).

The probability of registering a patient with a previous immunological graft failure within the first 3 months of a previous transplant is also estimated from a clinical report describing the progress in renal transplantation in India (Abraham et al., 2009). The study reported the probability of immunological graft failure within a year of transplant and this was converted into the corresponding three-month probability.

Table 2 below lists all patient-related parameters, their distributions/estimates and corresponding sources. The KAP score of a patient was calculated as a function of the above clinical parameters using the scoring algorithm published by NOTTO, as described

Table 2. Patient-related model parameters.

Parameter	Distribution	Estimate	Source
Patient arrival	Poisson	5.828 patients/month	RNOS (2019a)
Time on dialysis	Exponential	260.3 days (IAT)	RNOS (2019a)
Patient removal time	Beta	Mean = 40.31 (SD = 26.69)	Lakshminarayana et al. (2017)
District in which patient is registered	Discrete	P(Jaipur) = 0.92; P(Ganganagar) = 0.08; P(others) = 0.00	RNOS (2019a)
Age (years)	Normal	Mean = 40.78 (SD = 12.18)	RNOS (2019d)
Blood Group	Discrete	O = 0.448; A = 0.144; B = 0.339; AB = 0.0689	RNOS (2019c)
PRA level	Discrete	P(PRA level = 0) = 0.650; P(1–20) = 0.056; P(21–79) = 0.136;P (80–100) = 0.158	Cecka et al. (2011)
Probability of a previous immunological graft failure within 3 months of transplantation	Discrete	P(yes) = 0.020; P(no) = 0.980	Abraham et al. (2009)
With Failed all AV Fistula sites	Discrete	P(yes) = 0.052; P(no) = 0.948	Chandrashekar et al. (2014)
With Failed AV Graft after all failed AVF sites	Discrete	P(yes) = 0.03125; P(no) = 0.96875	Chandrashekar et al. (2014)

in Section 2 (National Organ and Tissue Transplant Organization (NOTTO), 2018).

3.2.2. Organ-related parameters

Precise data regarding the dates of arrival of organs (for instance, similar to that available for patient arrival) was not available on the RNOS website. Therefore, the distribution of interarrival times for kidneys from deceased donors was assumed to be exponential, and its parameters were estimated using aggregate organ donation data published by RNOS. According to the most recent data published on the RNOS website (RNOS, 2019b), the number of organs donated in the years 2015, 2016 and 2017 were 12, 4, and 16, respectively. Assuming a mean of 14 kidneys being donated every year (we assumed that 2016 was an outlier), the interarrival times of donated kidneys in Rajasthan was assumed to be exponentially distributed with a mean of 7 donors/year (since two kidneys are retrieved from a deceased donor).

We assume that kidneys are donated in each district of Rajasthan according to a district-specific probability. These probabilities have been assigned based on the proportion of Rajasthan's population in each of its districts, with the population of Rajasthan and its districts obtained from the most recent Official Census of India (Census Commissioner of India, Ministry of Home Affairs, 2011). Other parameters of the donor such as the blood group and age, which are required to determine allocation of the kidney, are also calculated according to the proportions of various blood groups and age ranges in the population of the entire state of Rajasthan. We have assumed that in a district, kidneys can be retrieved from a deceased donor in a private or a government hospital with equal probability. We have made the further assumption that if the district where the kidney is retrieved has a transplantation centre (for Rajasthan, only Jaipur and Ganganagar districts have transplantation centres) then the retrieval is performed in a transplantation centre, else the retrieval is performed in a hospital not capable of performing kidney transplantations (i.e., a retrieval centre).

After the kidney is retrieved from either a retrieval or a transplant centre, it will be allocated to a patient (recipient) in the system (Rajasthan) according to the allocation algorithm. Table 3 below lists all organ-related parameters, their distributions/estimates and corresponding sources. Due to space limitations, we do not list all of the district-specific probabilities of an organ originating from a district; we provide the probabilities associated with a few sample districts.

Table 3. Organ-related parameters.

Parameter	Distribution	Estimate	Source
Organ interarrival Time	Exponential	Mean = 52.36 days	RNOS (2019b)
Donor age	Empirical	$3.298\exp(3.176x)$; $x \sim U(0, 1)$	Census Commissioner of India, Ministry of Home Affairs (2011)
Donor blood group	Discrete	P(A) = 0.229; P(B) = 0.323; P(AB) = 0.077; P(O) = 0.371	Agrawal et al. (2014)
Probability of kidney originating in a district	Discrete	Ajmer = 0.038; Jaipur = 0.026; Sirohi = 0.039	Census Commissioner of India, Ministry of Home Affairs (2011)

4. Simulation experiments and analyses

The simulation was programmed on the Matlab computing platform. A warm-up period of 12 years was used before results were collected over a period of 12 years. 100 replications were performed for collecting and reporting results. The output parameters collected from the simulation include year-wise probabilities of receiving a transplant while on the waitlist, average organ transport time, average time to transplant for a waitlisted patient, total number of patient deaths, number of unallocated organs and the total number of transplants in the simulation period. The probabilities of transplant are calculated as follows: patients arriving in each year (e.g., the first year after the warm-up period) are tracked separately and the proportion of these patients receiving a transplant at the end of each subsequent year is updated. For example, the two-year probability of transplant for patients arriving in the 16^{th} year is estimated by calculating the proportion of the same set of patients who have received a transplant within 2 years of their arrival. The same calculation process is followed for patients arriving in every year post the warm-up period.

Average organ transport time is defined as the average time required to transport an organ from the retrieval location to its destination (a transplant centre). Average time to transplant is calculated only for patients who received a transplant during the steady-state simulation period. Both the probabilities of receiving a transplant and the average time to transplant are calculated separately for different blood groups and the type of transplant hospital in which patients are registered in order to quantify disparities in transplantation outcomes on the basis of these characteristics. The number of deaths is calculated by counting those who are removed from the waitlist without receiving a transplant during the simulation period. A list of outputs (not limited to those described above) is provided in Table 4 and the

Table 4. Key simulation outcomes.

Simulation Outcome	Estimate (95% CI)
Average number of organs transplanted per year	13.36 (12.98, 13.75)
Average transportation time (hours)	5.81 (5.73, 5.88)
Average time to transplant on the waitlist (days)	1148.85 (1137.54, 1160.15)
Average time to transplant by type of hospital (days)	Public = 1112.73 (1082.95, 1142.52) Private = 1183.23 (1163.29, 1203.16)
Average time to transplant by blood group (days)	A = 859.16 (826.63, 891.68) AB = 844.54 (805, 884) B = 1216.14 (1193.19, 1239.10) O = 1342.62 (1322.90, 1362.34)
Average number of unallocated organs per year	0.46 (0.38, 0.54)
Average number of deaths per year	48.63 (48.25, 49.01)
Probability of receiving a transplant within 5 years	0.138 (0.137, 0.139)
Probability of receiving a transplant within 5 years by blood group	P(A) = 0.273 (0.271, 0.275) P(AB) = 0.194 (0.192, 0.197) P(B) = 0.129 (0.128, 0.131) P(O) = 0.096 (0.095, 0.097)
Probability of receiving a transplant within 5 years by type of hospital	P(Public) = 0.153(0.152, 0.154) P(Private) = 0.128 (0.127, 0.129)

changes in probabilities of receiving a transplant with respect to time are depicted in Figure 3. The simulation outcome estimates provided in Table 4 are averages and their 95% confidence intervals calculated using their standard errors. We have also provided the distributions of the outcome random variables (e.g., organ transport time) themselves in the Appendix A (Table A1), because it may be of interest to estimate, for example, the probability that the organ transport time exceeds 8 hours.

It is clear from the above results that cold ischaemia time, the maximum time permissible between organ retrieval from the deceased donor and transplantation into the recipient, is likely not to be of significant concern in Rajasthan as far as the kidney transplantation time is concerned. This is because the cold ischaemia time for a kidney is between 24 and 36 hours (Ponticelli, 2015), well above the average organ transport time (5.8 hours) estimated by the model. That said, each additional hour of cold ischaemia time for a kidney increases both risk of graft failure and mortality (Debout et al., 2015), and hence we consider the problem of locating additional transplant centres within Rajasthan to determine the extent to which they reduce average transport time. Also, locating additional transplant centres may prove to have a much more substantial effect on transplantation outcomes for other organs (such as the heart, liver, lungs, etc.) which have much shorter cold ischaemia times when compared to the kidney, and hence is a question worth considering for organ transplantation in general.

In comparison to average kidney transport time, the average time to transplant and the probabilities of receiving a transplant while on the waitlist are causes for significant concern. The mean survival time on haemodialysis is approximately 40 months, with a high standard deviation of approximately 27 months; therefore, given that the average time to transplant is approximately 38 months, there is a significant likelihood that a waitlisted patient might die before receiving a transplant. This is supported by the substantial number of deaths observed per year. There are some disparities in transplant outcomes by blood group and type of hospital: patients with the O blood group are significantly less likely to receive a transplant than those with other blood groups, and patients registered in a private hospital are approximately 16% less likely to receive a transplant than those registered in a government hospital. The results observed for patients with the O blood group are supported by a study conducted in Kerala, a southern Indian state (Tom & Kumar, 2016). The observed disparities are occurring likely because while the rate at which the O blood group patients enter the

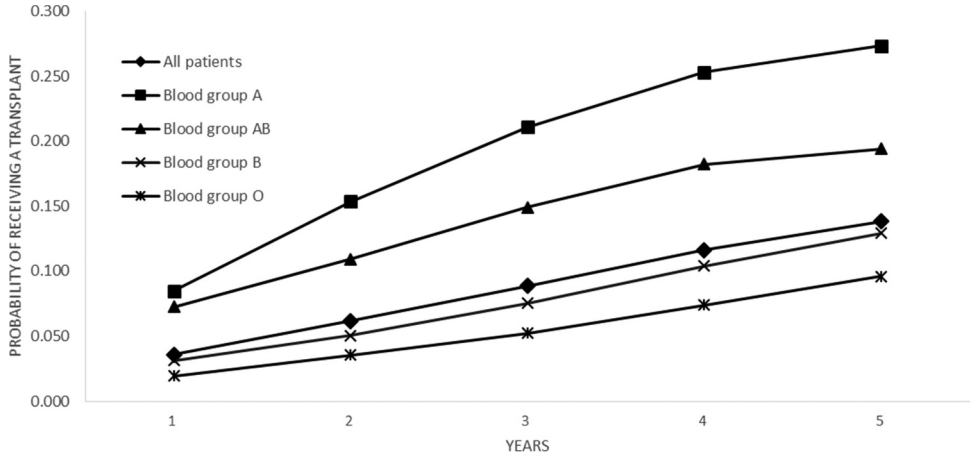

Figure 3. Probabilities of receiving a transplant with respect to time for different blood groups.

waitlist is approximately 3.1 times that of the A group and 6.5 times that of the AB group, the rate at which the O blood group organs arrive is only 1.6 times that of the A group and 4.8 times that of the AB group. These disparities between the relative rates of arrival of the patients and organs between blood groups, combined with having to wait significantly longer than in a first-come first-served system because of the complex allocation algorithm, is reflected in the disparities between probabilities of transplant as well. For instance, the probabilities of transplant for the O group are less than half that of the A group (≈ 1.6/3.1) and less than 0.75 times (≈ 4.8/6.5) that of the AB group.

Validation of the simulation model is a challenge given the limited data available regarding kidney transplantation outcomes in the Indian context. We performed a preliminary round of validation by comparing patient arrival numbers for approximately 330 days from the simulation with patient arrival numbers in 2019 as published on the RNOS website. As mentioned earlier, the RNOS waitlist data for 2019 was set aside for validating the outcomes of the model. Since only the waitlist data were available to validate the outcomes of the model, we were only able to validate the rates at which patients register in the waitlist. The results of this validation exercise are provided in Table 5 below.

It is clear from the above table that the model outcomes are reasonable when compared to the data recorded by RNOS. The numbers of patients with the AB and A blood groups registered in the waitlist in 2019 lies outside the 95% confidence intervals for the corresponding model estimates; however, this is likely because we are comparing only a single validation data point to the simulation outcomes. The overall number of patients registering on the waitlist in 2019, however, is within 1% of the simulation estimate, and hence lends credence to the validity of the simulated patient arrival process.

We also attempted another simple approach towards validating a key outcome of the model – the five-year probability of transplant – that illustrates how simple theoretical queueing frameworks may provide limited insight in analysing the complex queueing discipline represented by the organ allocation process operating in the kidney transplantation system. This involved attempting to compare the five-year probability of transplant to the ratio of the overall organ arrival rate to the overall patient arrival rate. This latter quantity can be considered as an approximate equivalent of the concept of utilisation from queueing theory – that is, the long-run probability of the system being "busy" would correspond to the long-run probability of receiving a transplant. The estimate of the ratio of these quantities from the model is 0.212 (95% CI: [0.194, 0.240]), and the estimate from RNOS data is 0.222, indicating the patient arrival and organ arrival processes are being simulated accurately. However, the five-year probability of receiving a transplant while on the waitlist is approximately 0.138 (95% CI: [0.137, 0.139]). This significant difference is likely because the patients arriving into the transplantation system are not served on a first-come first-served basis, and are instead allocated organs based on the complex allocation algorithm. Thus, patients wait longer than they would if they were allocated organs on a first-come first-served basis. While this indicates that a simple queueing framework may provide limited insight for such systems, a heavy-traffic queueing framework with probabilistic reneging times and job priorities approximating the priority systems represented by the allocation processes based on blood group matching may be capable of offering more insight. For example, the distributions of KAP scores of incoming patients can be estimated (from a simulation of arriving patients alone) for each blood group and used to determine priorities. We reserve this analysis for future research.

More comprehensive validation of model would ideally be performed; however, the lack of availability of public data has hampered our efforts in this direction. Other potential avenues of validating the model include working with transplantation authorities (such as NOTTO) to validate the model structure, and obtain additional data from these bodies to refine model parameter estimates.

Table 5. Validation outcomes.

Parameter	Actual (RNOS, 2019a)	Simulation Estimate (95% CI)
Number of patients registered in 2019 (up till December 4 2019)	63	62.47 (54.18, 70.76)
Waitlisted patients with blood group A	15	8.77 (5.83, 11.7)
Waitlisted patients with blood group AB	8	4.44 (2.66, 6.23)
Waitlisted patients with blood group B	17	21.42 (17.16, 25.67)
Waitlisted patients with blood group O	23	27.84 (22.41, 33.27)

4.1. Simulation experiments

In addition to generating the above model outcomes, we also performed the following simulation experiments: a) increasing the organ arrival rate from current rate of 14 per year to approximately 120 organs per year (in increments of 7 organs/year), and b) increasing the number of districts with transplantation centres from an initial level of 2 districts to 22 districts, by adding one transplantation centre in each district considered (with a different district considered in each iteration). We first present the outcomes from increasing the organ arrival rate (Figures 4(a)–(c) below).

In Figure 4(a), we present the effect of increasing the organ arrival rates on two-year probabilities of transplant (and not, for instance, the five-year probabilities of transplant) as this measure might be of more immediate interest to patients and healthcare providers alike. Once again, we see that the rate of increase for the O blood group is the smallest among all the blood groups. Further, it is clear from Figure 4(a) that the probability of receiving a transplant increases with the organ arrival (donation) rate up to a certain point (around 85%, corresponding to an organ arrival rate of around 80 organs per year) and then the rate of increase becomes much slower and the two-year probability of transplant stabilises around 91%. Such behaviour likely occurs because as the organ arrival rate increases to a point where a significant majority of patients (approximately 91%) receive an organ, when an organ of a particular blood group arrives (e.g., A), a corresponding patient may not be present in the waitlist, and the organ thus goes unallocated within the state. Further, for some patients (particularly those with randomly assigned small removal times due to death), an organ with the appropriate

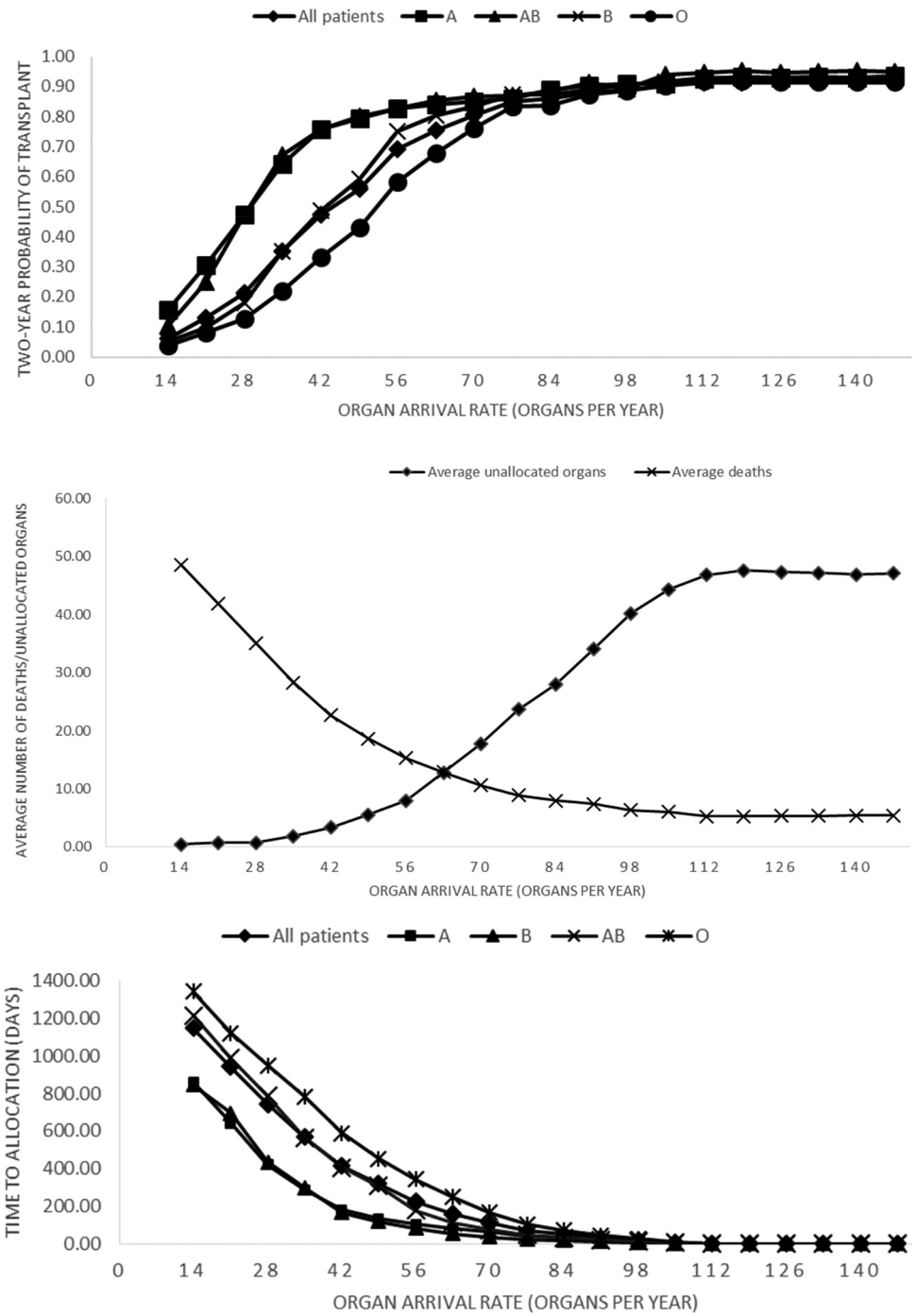

Figure 4. (a) Effect of increasing the organ arrival rates on two-year probabilities of transplant by blood group. (b). Effect of increasing the organ arrival rates on the average number of deaths and the average number of unallocated organs. (c) Effect of increasing the organ arrival rates on average time to a transplant for all the patients and by blood groups.

blood group may not arrive before their removal time due to death. Note that we see that the probabilities of transplant do not increase exponentially with organ donation rates. Under relatively simple queueing theory frameworks – for example, with first-come first-served queuing disciplines – it would be expected that the probabilities of transplant (which can, as discussed earlier, be considered an approximation of the "utilisation" of the system) would increase at approximately exponential rate with increase in organ arrival rates until a certain threshold organ arrival rate. However, because the queueing discipline in this case is the organ allocation process, which is based on various patient characteristics and not purely on a first-come first-served basis, we see a slower rate of increase of the probability of transplant. In fact, second degree polynomials appear to best describe how probability of transplant changes with organ arrival rates (assuming that after a certain threshold organ arrival rate, the probabilities of transplant will approach 1 at much slower rates).

Figure 4(b) depicts how the average number of deaths and the average number of unallocated organs change when the organ arrival rate increases. Figure 4(c) depicts the change (decrease) in average time to a transplant for all patients and by blood group. We see that approximately the same behaviour as in Figure 4(a) is observed for the average time to transplant as well. Significant improvements in average waiting time for a transplant are also evident – the average waiting time for a transplant (for all patients) reduces significantly from an initial wait time of nearly 1150 days at an organ arrival rate of 14 per year to less than a day days at arrival rates exceeding 105 organs per year. However, these results must be interpreted cautiously as it is likely that as the awareness regarding organ donation increases, the awareness regarding organ transplantation in general may also increase, and the number of patients on the waitlist may also increase.

Also of interest, as mentioned previously, is that the average number of kidneys that go unallocated within Rajasthan also increases with organ arrival rate. This implies that if a state has a high donation rate of a particular organ relative to the number of patients on the waitlist, then it is likely that these organs will be available to neighbouring states. This underscores the need for establishing more organ procurement and transplantation centres across the country, as this will decrease interstate organ transport times, thus increasing organ viability for transplantation. However, as mentioned earlier, it is likely that increasing awareness regarding organ donation and transplantation will lead to donation rates lagging behind the rate at which patients will register on the waitlist (as observed in developed countries), and therefore it is unlikely that a significant proportion of organs will remain unallocated within the state in such a situation.

To observe the effect of having more transplantation centres across the state of Rajasthan we increased the number of transplant centres in increments of one per district until there are 22 (two-thirds of the total number of districts in Rajasthan) districts with transplantation centres. The number of transplantation centres was increased from 12 initially in two districts to a total of 32 transplantation centres in 22 districts. These districts were selected randomly and the type of the transplantation centres added in each district was randomly (with equal probability) assigned to be a government or private hospital. Figure 5(a) shows the behaviour of logistical transplantation outcomes – average transportation time, and the number of instances where transportation time is greater than 8 hours when the number of transplantation centres are increased. From Figure 5(a), we see that as expected, with more transplantation centres the average transportation time decreases from 5.8 hours to 4.9 hours with 18 districts and further decreases to 4.5 hours with 22 districts. We do not include maximum transportation time in the figure. This is because, as expected, the maximum transportation time remains largely unchanged as more transplantation centres are added, since patients and organ donors are generated randomly from across the state, and the maximum transportation time is unlikely to change as extreme cases are still likely to be generated unless both the number of patients registering as well as organ donation rates increase substantially. However, the number of instances where organ transport time was more than 8 hours reduced from almost 14.8 initially to 13.3 at 32 transplantation centres in 22 districts. This reduction may seem smaller than expected, but this is likely due to the large geographical area of the state, and the fact that organ donation rates are low. Therefore, given that districts with the highest populations have the highest probability of generating organs as well, patients registered in transplantation centres in districts with lower populations are likely to receive organs from districts with higher populations, which may be located at a relatively large distance. However, if organ donation rates increase, then more organs are likely to be generated from low-population districts, thereby decreasing the average transportation times. We test this notion by adding transplantation centres in three districts (chosen randomly), yielding a total of 15 transplantation centres in 5 districts, and increase the organ arrival rate to 49 organs per year. We see that at the current organ arrival rate of 14 organs per year, the average transportation time reduces to 5.6 hours from 5.8 hours, whereas at the organ arrival rate of 49 organs per year, the average transportation time

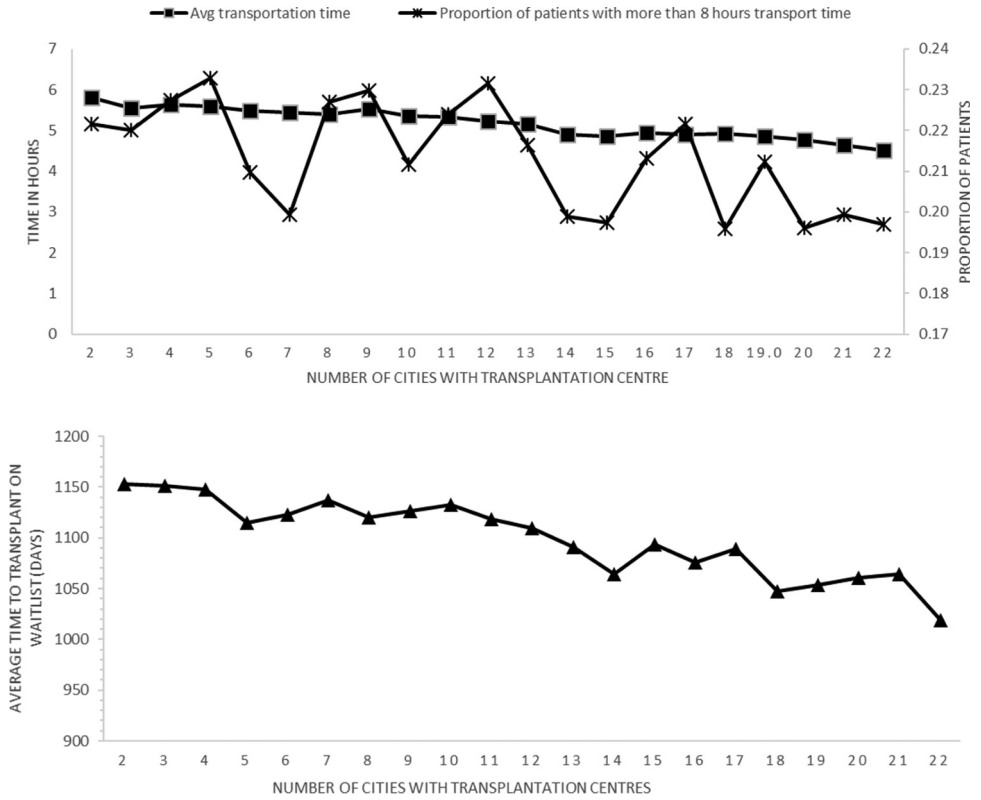

Figure 5. (a). Effect of increasing the number of transplantation centres on logistical outcomes related to transplantation. (b). Effect of increasing the number of transplantation centres on time to allocation.

reduces to 5.4 hours, and if three optimally located districts are chosen (as will be seen in the simulation optimisation section), the average transportation time reduces further to 5.25 hours.

Nonetheless, even this seemingly small reduction can be significant for other organ transplantation systems such as liver, heart, etc. wherein the cold ischaemia time is substantially lower than that for the kidney. Even in the case of the kidney transplantation system, as discussed before, reducing cold ischaemia time by every hour improves both graft and patient survival.

As expected, most clinical transplantation outcomes (average number of deaths, average number of transplants, etc.) are not affected by adding transplantation centres, as these are dictated largely by organ donation rates. However, the average time to receiving a transplant is observed to decrease with an increase in the number of transplantation centres, and this is likely due to the fact that an organ is first considered for allocation within its district of origin. Therefore, given that a patient originating in a district is likely to register in that district, he/she will be more likely to be allocated a kidney if it also originates from that district. This is depicted in Figure 5(b) below.

We now demonstrate the use of a ranking and selection simulation optimisation method to optimally select the location of transplantation centres in terms of minimising the average transportation time for an organ. We consider the problem of selecting the optimal locations for three transplantation centres from among 10 alternative location sets. We consider only 10 alternatives for each problem in our analysis as a proof-of-concept of this approach; however, ranking and selection methods such as the NSGS (Nelson et al., 2001) and KN procedures (Kim & Nelson, 2001) can be used for relatively larger numbers of decision alternatives – for example, the NSGS procedure has been demonstrated to work with reasonable computational expense for more than 1000 systems (Hong et al., 2015).

We apply the NSGS procedure to select the best alternative in terms of minimisation of average transportation time. Each alternative for the 3-centre problem is a set of three districts, which we refer to hereafter as a thruple. We now provide a brief description of the NSGS procedure. The NSGS procedure requires that the replications associated with each feasible solution – in this case, a transplantation centre location thruple – are *iid* and are normally distributed, and that the replications associated with each alternative are independent of those from other alternatives, implying that common random numbers cannot be used in generating these replications. The NSGS algorithm is based upon the indifference zone approach; that is, it provides the statistical guarantee that, given m alternatives, the best alternative will be selected with a probability $1 - \alpha$, provided that the best alternative is at least δ better than the next best alternative. In other words, the analyst

is "indifferent" to alternatives within δ units of the best alternative. The NSGS method involves first generating a prespecified number of replications (n_0) for each alternative, and then using α and δ (set by the analyst), identifies a subset I of the original m alternatives guaranteed to contain the best alternative with $1 - \alpha$ probability. This is the screening stage. Note that the NSGS procedure utilises Rinott's constant (Wilcox, 1984) and the estimated variances for each system during the screening stage.

After the first-stage subset I is formed, the ranking and selection stage commences, wherein for each alternative in I, the number of additional replications to be generated is calculated. The mean for each alternative is updated after these additional replications are generated using the simulation, and the alternative with the lowest average transportation time is selected as the best alternative.

For the 3-centre problem, we used an α of 0.05 and a δ of 0.20 hours of transportation time. The number of initial replications n_0 generated from each alternative was set to 30. We constructed the set of 10 feasible solutions as follows: one consisted of a thruple of centrally located districts (with respect to the geography of the state), three thruples covered the northern, southern, eastern and western corners of the state, and one thruple was located close to the district (the state capital) that contained 11 out of 12 existing transplantation centres. The remainder (5 thruples) were randomly chosen. Intuitively, central locations or locations equally distributed across the geographical extent of the state would be expected to yield lower average transportation times. The results of the simulation optimisation exercise reflect this intuition, as the optimal solution is one of the randomly chosen thruples that, along with the two districts already contain transplantation centres, are located such that they are approximately equally distributed across the geographical extent of Rajasthan. This optimal thruple yields a reduction of approximately 0.60 hours in mean transportation time, whereas the next best solution, well within the indifference zone ($\delta = 0.2$), yields a reduction of approximately 0.58 hours in mean transportation time. This next best thruple corresponds to locations that are approximately central. Therefore, this provides statistical validation to the insight that if sufficient resources to establish a limited number of new transplantation centres are available, choosing locations that are spread equally across the region of interest or are centrally located is most beneficial from the standpoint of minimising organ transportation time.

5. Conclusions and discussion

The work presented in this article is a first step towards modelling, analysing and optimising the organ transplantation system in India. Therefore, there are several avenues of research that we plan to pursue in the immediate future, including the following: (a) extend and adapt the model of the kidney transplantation system of Rajasthan to other states and for the entire country; (b) utilise the simulation in conjunction with machine learning methods to quantify the influence of each patient characteristic on the probability of receiving a transplant, based on the methodology in Baldwa et al. (2020); (c) determine the effect of organ donation awareness campaigns on transplantation outcomes. A model such as this can be adapted for other organ transplantation systems (e.g., liver, heart) in India.

The lack of reliable data required to build and validate such models in the Indian context remains a challenge. The southern Indian states of Tamil Nadu and Kerala have a more well-established transplant system (Tom & Kumar, 2016), and hence have better organised data as well. However, we chose the state of Rajasthan for this study because, while the above states have more established transplant systems and better organised data, the RNOS website provides more granular information regarding the patients on the waitlist (e.g., patient age and blood group data, time on dialysis before registration). Therefore, a natural choice for next modelling steps would be to adapt the model to these states. We hope that the model presented in this paper will provide a roadmap for modelling and parameterising simulation models of organ transplantation systems in developing nations where the availability of public transplantation data is also a challenge.

The utility of a simulation model of an organ transplantation system is evident from previous work done in this field, and also from the simulation experiments conducted using our model and presented in this paper. However, the majority of previous simulation models developed to model kidney and liver transplantation systems address allocation policies, and hence our work provides a proof of concept for the utilisation of such models to address logistical issues related to transplantation as well. For example, while A. Davis et al. (2013) utilise simulation to suggest organ redirection policies to alleviate geographical inequities in kidney transplantation outcomes, they do not evaluate the logistics itself associated with such policies or with the kidney transplantation system they model as a whole. Further, to the best of our knowledge, our study is the first to demonstrate the use of simulation optimisation methods to determine optimal locations of transplant facilities. Our simulation model can similarly also be used, in conjunction with simulation optimisation methods, to optimise organ allocation policies as well. A model such as this can generate insights that are not necessarily intuitive, such as the fact that patients with AB group not having the highest probability of receiving a transplant despite being universal recipients, the

increase in the number of unallocated organs with an increase in organ arrival rate, and the reduction in average time spent on the waitlist before receiving a transplant when the number of districts with transplantation centres are increased. As the transplantation infrastructure in India develops further, the need for such a model to analyse and optimise allocation as well as logistical aspects of the transplantation system will be felt more acutely. However, it is also evident from the outcomes generated by the model that it is imperative to consolidate and expand public awareness programmes to increase the organ donation rate in the country so that the average time to transplant is reduced and the number of deaths while on the waitlist are reduced.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix A

Table A1. Distribution of key model outcomes.

S. No.	Simulation outcome	Distribution	p-value
1	Time to allocation	Logistic (1151.9, 135.6)	0.250
2	Organ transport time	Normal (5.78, 1.41)	0.326
3	Time to allocation: blood group A	Normal (873.9, 434.6) with Box-Cox transformation ($\lambda = 0.674$)	0.096
4	Time to allocation: blood group AB	Gaussian kernel density (160.299)	Not applicable
5	Time to allocation: blood group B	Logistic (1208, 244)	0.179
6	Time to allocation: blood group O	Logistic (1352.1, 288.7)	0.250
7	Time to allocation: public hospital	Logistic (1112.6, 207.96)	0.230
8	Time to allocation: private hospital	Logistic (1181.1, 200.3)	0.250