



Evaluation on the Use of Italian High-Speed Rail to Support Transportation Network for Transplantation Activities

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ABSTRACT

Background. One of the main activities connected with transplantation is the rapid and timely transportation of patients, medical teams, and human organs from donation to transplantation centers under the compliance of national guidelines and principles of quality, performance, and safety. High-speed transportation on a railway network is becoming relevant both in terms of performance and extensiveness of the service.

Methods and Objectives. Our study explores the feasibility of adopting a high-speed rail network for the transportation of those organs with large cold ischemia time and those less influenced by transportation-related perturbations (ie, temperature, speed, vibrations), assessing savings and relative performance improvement. In this study, only kidneys have been considered; the transplantation database has been integrated with the national high-speed railway network and timetables. A function is implemented that allocates to air transportations those records with 1 of the 2 ends situated on islands, remote regions, and abroad, while rail transportation is preferred where constraints on capacity and compliance with cold ischemia time are met. Road transportation is still feasible for those records involving 2 adjacent regions and for intraregional transportation.

Results. The opportunity of integrated road-rail transportation in place of air or all-road transportation allows users to lower generalized costs and reduce driven distance for personnel and vehicles allocated to a regional transplantation center's fleet and staff. Savings in fleet and staff usage can serve to improve the performances at the local level.

Conclusions. The knowledge and analysis of transportation alternatives for human organs with less stringent safety and preservation criteria allow a more efficient allocation of resources both at the local and national level—without compromising quality and reliability of the system.

TRANSPLANT logistics involves both medical and transportation engineering topics. When the former field is concerned, issues such as compatibility, consensus, and cold ischemia time (CIT) are involved. Operation research has been used to reduce/optimize the costs or to design the optimal location of nodes (ie, transplant centers [TC]) based on demand and supply. A literature review on this last topic can be found in Cacchiani et al [1]. The transportation phase, finally, requires decision on which alternative to use based on performances, equipment, evaluation of costs/impacts, and %CIT (percentage of the

cold ischemia time spent during transportation phases, as defined by Mantecchini et al [2]).

Donation and transplant networks are influenced by logistics as well as technology and surgery innovations; to this purpose, the positive follow-up of the transplant is

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correlated with low values of CIT on varying donor characteristics and organ typology. Organ donation involves uncertainty on the location of both donor and patient; therefore, reliability, timeliness, and effectiveness of the procedures are of the highest importance. The topic of transportation logistics for health care purposes is present in Fuzzati [3], Siqueira et al [4], and Carrara et al [5] as well as in guidelines issued by national departments for health care.

In this article, pros and cons of organ transportation by high-speed rail (HSR) are analyzed to investigate the scope for cost optimization compared to current transportation alternatives, while keeping high quality and efficiency levels and, at the same time, reducing impacts (both ground and air transportation have higher polluting emission ratio per km). Air transportation is the preferred option in case of urgencies or long displacements involving geographic obstacles, but costs are relevant when on-call services are needed [6]; on the other hand, road transportation has no competitors for short displacement and, unlike rail and air transportation—which both have intermediate stops—grants an end-to-end trip. Only a high-speed rail network has been considered in this study due to performances and expected reliability. To ensure compatibility between travel time and the CIT, only kidneys have been considered at this stage; although the scope of the study might appear limited in extension due to the presence of a single organ type, kidneys account for more than 50% of 2017 transplant events in Italy, are handled at the majority of Italian TCs, and account for as much as 75% of patients on waiting list according to Italian National Transplant Center (CNT) data.

THE ITALIAN CONTEXT AND AIMS OF THE RESEARCH

Regions and the CNT cooperate in the organization of the transplant logistic chain. When a match donor-organ is found within the same region, the displacement is usually within driving distance, and hence road transport is used; in case of national emergency protocol and an extraregional match, the modal alternative varies according to the total distance, presence of multiorgans, and CIT. A monitoring campaign at the national level [7] pointed out road and air transportation as preferred options for organ displacement. According to the authors' data, 58% of transportation events between 2 regions take place by air, of which 66% are accompanied by a medical team. In those cases, helicopters, military forces, and, preferably, on-call air service providers or scheduled airlines are involved. Operation and performance standards have been set for providers of on-call air transportation services. In the case of road transportation, organs, tissues, and blood samples travel onboard vehicles issued by military forces, nonprofit organizations, or regional centers' fleets. To this scope, Paganelli et al [8] highlighted that the optimum number of aircraft needed to operate organ transportation in Italy over an average year is 6, but aircraft utilization rate is as much as 30%. Both air and rail transportation options entail a short-to-medium road displacement between transportation nodes (either

stations and aerodromes) and donor centers (DCs) or TCs, which can be performed by a regional center's fleet. As far as costs are concerned, a distinction is made between accompanied organ—costs charged to the TC—and non-accompanied organs—costs charged to the regional center that performs the transportation. With HSR transportation, each regional center pays its road displacement, while the cost of HSR—a public utility service—shall be 0, as it already happens with scheduled transportation services by air (ie, Alitalia, Ryanair, or whichever commercial airline). In parallel, rail linkages are usually shorter than the corresponding ones by road, and the risk of congestion and delays is reduced. Indeed, a consistent delay due to transportation phases can impact the TC's daily surgery schedule and, even worse, lead to the violation of the CIT rule.

Kidneys have the longest CIT; therefore, the violation of the CIT rule is unlikely at this stage of the analysis. For this reason, while many transportation events take place during the nighttime (in particular, thoracic organs and multiple transplants) to reach TCs close to the scheduled time of transplant start, HSR travels on daily times. Therefore, a rescheduling of surgery planning foreseeing thoracic transplants at nights, routine surgeries in mornings and early afternoons, and nonthoracic transplants in the late afternoon-evening times would be enough to make the HSR option feasible.

UPDATED DATA ON TRANSPLANTS PERFORMED IN ITALY UP TO 2017

The Italian territory, from the point of view of health care logistics, is divided into regions and agglomerations of multiple regions; around 65% of transplant events take place within the same region. According to CNT data, the Italian transplant network is made of 43 TCs (each specialized in 1 or more organ surgery types, with a minimum amount of surgeries/year to keep the transplant team efficient). The top 3 TCs—Torino, Padua, and Milan Niguarda—total 930 transplants, which is 25% of the national total, which is in turn accounted for by the figures of the 25 minor TCs. Kidney transplants are performed in 39 out of 43 TCs, while, respectively, only 15 and 10 TCs perform heart and lung transplants. This figure influences the modal alternative necessary to displace organs from DCs to TCs. Kidneys are both the organ most frequently involved in transplant and have the longest waiting list (75% out of 8713 patients, with an average permanence on the list greater than 3 years). In 2018, there were 1763 donors in Italy (of which 326 were living donors; 800 out of the 1437 were deceased donors lived in the north of Italy) for a total of 3950 organs transplanted (2234 kidneys, of which 310 were from living donors, 1312 livers of which 16 were from living donors, 265 were hearts, and 144 were lungs) (source: CNT data). Donations from deceased and living donors have grown notably with reference to year 2000 (+25% from deceased donors and +50% from living donors), despite a relevant share of opposition to organ

donation that is still present in central and southern regions (up to 40% to 50%). To reduce opposition in Italy, a project linking consent to organ donation to the emission of updated identity cards started in 2016; up to March 2019, as many as 5 million people took part, with consent rates at around 80%, mainly among 30- to 45-year-old people.

HIGH-SPEED RAIL SERVICES IN ITALY

Italian HSR lines have been built to be integrated within the European Union (EU) network in terms of technology, separation, power supply, and vehicles. A 300 km/h peak speed is allowed, thus greatly reducing travel times and influencing demand and modal share [9]. In addition, more attractive linkage opportunities between cities have emerged with positive effects on tourism, commuting, local economy, and reduced pollution [10]. Therefore, HSR has become a substitute for air transportation on medium-range displacement (between 300 and 600 km), allowing higher frequency and supply and reduced waste of time and diversion nodes. Compared to road transportation, HSR grants the traveler less stress and an adequate frequency. In Italy, the earliest projects date back to 1970s, but services started only in 2005. Flaws usually connected with HSR in Europe have been overestimation of demand and underestimation of costs [11]. The Italian HSR network has principal and secondary branches, with the former linking all the principal cities in the north (Turin, Milan, Bergamo, Venice) and along the western coast of the country (Milano, Bologna, Florence, Rome, Naples) up to Salerno. Secondary branches link Trento, Verona, and Brescia with the main branches and Rome with Foggia and Bari. At the end of 2017, there were as much as 24,500 km of tracks in Italy, of which 1500 were HSR. Reduced slopes, wider curves, and long tunnels had a relevant impact on the total cost. EU directives on liberalization of rail services allow for the presence of 2 providers of HSR services in Italy: Trenitalia (Frecciarossa and Frecciargento) and Italo, which compete for slots, tariffs, and capacity. Italo trains are even more powerful than Trenitalia's ones, but Trenitalia—former incumbent of the national service—has bargaining power and infrastructure control.

To fulfill the scope of the research, a database with information on frequency, schedule of the service, stops, and timetables has been built with reference to year 2017. Stops and timetables are the joining link with the transplant database: DCs and TCs location, organ picking, and transplant's start times cordon off the HSR supply to perform the transportation of the organ.

GUIDELINES ON KIDNEY TRANSPLANT

First of all, it is possible to distinguish between the “centralized” allocation system (ie. Eurotransplant, with a single waiting list for the group of member countries) and “hierarchical” (multiple waiting lists within a country, each of which is associated with a structural entity such as a

hospital, a city, or a region, as it is in the United States, Turkey, and Italy). Although the former method is fairer, as the organ is transferred to the most suitable patient, the latter ensures the allocation to the closest suitable recipient, increasing the chances of success [12]. The standard allocation of kidneys is based on a point score system based on waitlist time, HLA, and donor location; specific procedures for pediatric recipients and for candidates ≥ 65 years exist.

End-stage renal diseases—which entail a relevant decrease of life quality and risk of premature death—are increasing with a year-on-year worldwide trend of 7%. Evidence shows that both graft and patient survival rates have been increasing over time and that transplants from living donors to younger patients have higher chances of good follow-up [13,14].

Clinical guidelines have been published by many countries, dealing with topics such as ethics, typology of donation (brain death, circulatory death, living donors, cross or Samaritan donation), policy to support donation protocols, surgery techniques, storage, allocation criteria, and follow-up. Eligibility should be determined based on medical and surgical grounds; be transparent; and not be based on social status, sex, race, or personal/public appeal. The EU guidelines on renal transplant suggest shortening as much as possible the duration of cold ischemia for elderly (> 55 years) and marginal donors. Contrast exists on the criteria to enter the waitlist, with some countries referring to the deterioration of an organ's performance and others to the first treatment of dialysis [15,16].

The patient's follow-up is divided into an early post-operative phase when prevention of acute rejection and opportunistic infection are paramount and a later phase when the aims switch toward preserving good functionality and being compliant to drugs prescriptions [17].

Despite the long CIT, many authors are concerned on the negative effects of a prolonged ischemia. After the clamping, the organ is stored with scales of ice in a box at 4°C and perfused in a chemical solution that is similar to human blood. Tennankore et al [18] focus their analysis on the warm ischemia period, which can cause delayed function, longer hospitalization, and reduced patient/organ survival rates when prolonged after 30 to 35 minutes. Debout et al [19] report that the increased age of both patient and donor, as well as the increased frequency of expanded criteria to cope with endemic organ shortage, has affected performance and patient survival rate. According to their findings, CIT < 30 hours has no relevant negative effect on organs' functionality. Ponticelli [20] lists inflammatory and immune response, delayed graft function, enhanced reactivity, and development of progressive pathologic changes as possible effects of late organ reperfusion, despite immunosuppression.

Organization and costs involved in health care logistics for transplant purposes have been investigated for national case studies (see [12] for a robust review). In this work, a first step to introduce optimization criteria for ground transportation is proposed to help the decider in matching

the right transportation solution to each event, granting high performance and reliability while optimizing costs (for example, multistep or multiorgan trip chain under the strict respect of the CIT rule). Public security forces' vehicles and personnel shall remain to complement the service under specific conditions, as it is for military flights supporting on-call air transportation services for emergency and overlapping events.

Matesanz et al [21] and Tokalak et al [22] highlight the role of national, regional, and local coordination for organ procurement and for enhancing awareness and cooperation. In addition, Genc [23] lists unfair allocation, flaws along the information flow, inadequate logistic, transplant tourism, inhomogeneous consent law, and trafficking as issues to be addressed to increase donation rates. White et al [24] called for immediate actions such as legal framework to protect donors and recipients, as well as the wide training of specialist surgeons, physicians, and nurses. Czerwiński et al [25] presented a tentative framework to deal with nonresident potential donors deceased in Poland. Further, regional cooperation can enhance the development of organ donation and transplant capacity even for small countries.

Finally, Demmons et al [26] support the idea of transporting brain-dead donors to the TCs to perform both procurement and transplantation at the same place, thus drastically reducing risks due to organs' ischemia as well as the fatigue and schedule of medical teams; on the other hand, Scalea et al [27] speculate on the likely use of drones in the future for short range/same city organ displacement, supporting the idea with medical evidences about reduced alteration induced to the organ sample tested.

MATERIALS AND METHODS

The methodology underlying this work is summarized in Fig 1 below. The Italian Transplant Database from June 2015 to December 2017 is used, discarding the records involving displacements from/to islands and abroad, which must rely on air transportation, and the records involving organs other than kidneys unless paired in the same transportation event with a single or double kidney. The notable information to be collected are the time of picking end at the DC and the time of transplant start at the TC, in addition to the original transportation solution and its duration T_0 . Then the timetable of each Italian rail station is analyzed; the target station is discarded if HSR is not present and HSR supply is

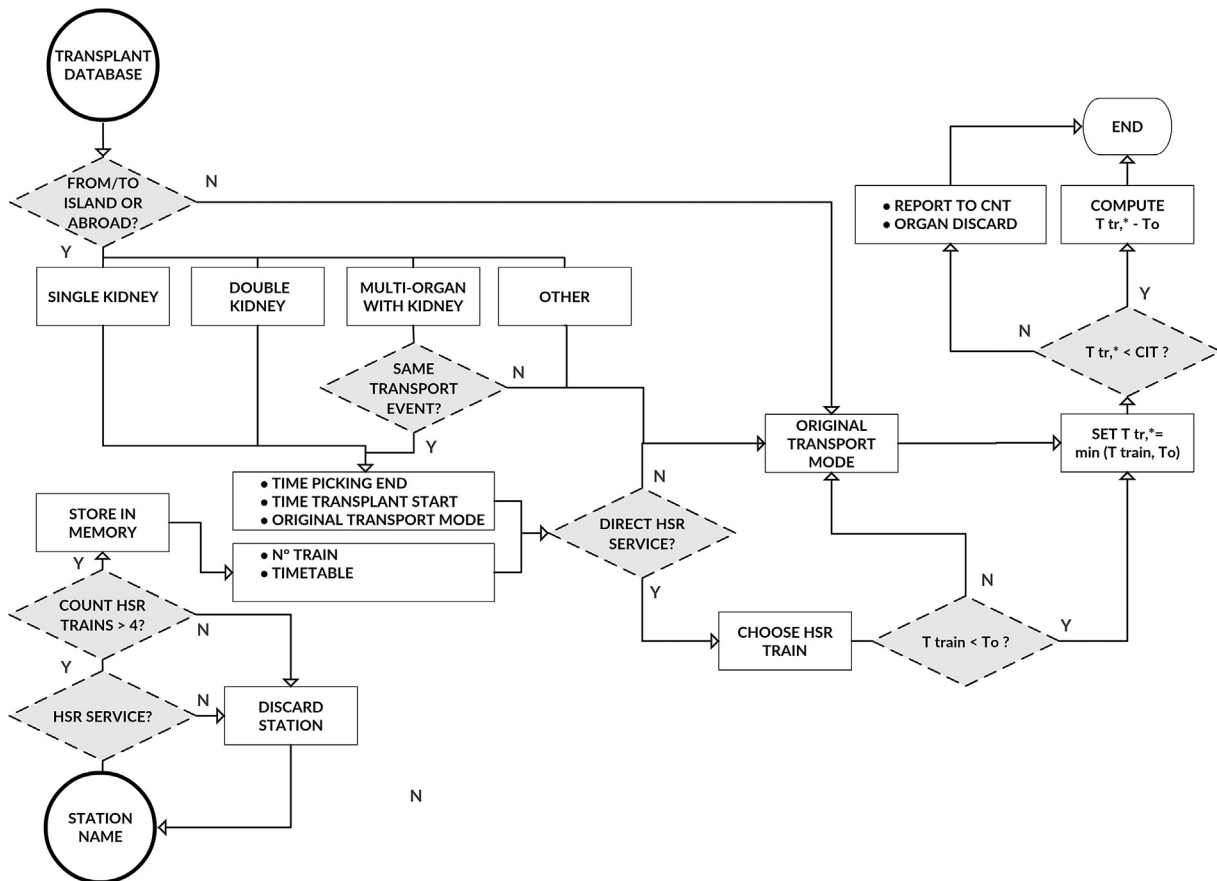


Fig 1. Methodology architecture (source: authors). CIT, cold ischemia time; CNT, Italian National Transplant Centre; T_0 , original transportation time; Transpl., transplantation; HSR, high-speed rail; N° , number; T_{train} , time onboard train; $T_{tr,*}$, transportation time after analysis.

below the threshold of 4 trains/direction/day (as supply is deemed not sufficient to grant a timely connection to ensure CIT rule compliance). In the case of compliance, for each station, a list of trains-stops-timetables is made. Time instants of picking end, transplant start, and HSR schedule are used to determine how many direct connections exist between the railway stations appointed for the DC and TC. If direct connections are not feasible, the record remains assigned to its original transportation mode; otherwise, it is assigned to HSR provided that the displacement time T_{train} is shorter than T_0 . Then, for each record, the minimum value between T_{train} and T_0 is defined as $T_{tr,*}$ and compared to CIT. If this last test is positive, the time saved $T_{tr,*}-T_0$ is computed for each record; otherwise, the violation of the CIT rule is notified to CNT, which will choose another transportation option.

In addition, for each HSR branch compliant to the minimum service requirement, a driving time between DCs and TCs and the appointed station includes as much as 40 minutes on average of urban congestion and speed conditions, and maps have been drawn with the help of the freeware software www.oalley.net. An example can be found in Fig 2, where the shaded areas include places with less than 40 minutes driving distance from each HSR Italian station used in this analysis.

The results obtained are summarized in the next section of the article, in particular a comparison between the modal share prior and after the implementation of HSR solution. For each record, the total time of the original transportation solution and for the rail option (displacement times of the 2 road segments and time on board HSR) are presented and compared. It is also possible to derive the total amount of time and the amount of pollutant emission saved thanks to the implementation of the HSR transportation option.

RESULTS

Table 1 summarizes the structure of the analysis carried out in this article. The collection of the Italian database on extraregional transplantation activities started in 2015 and is

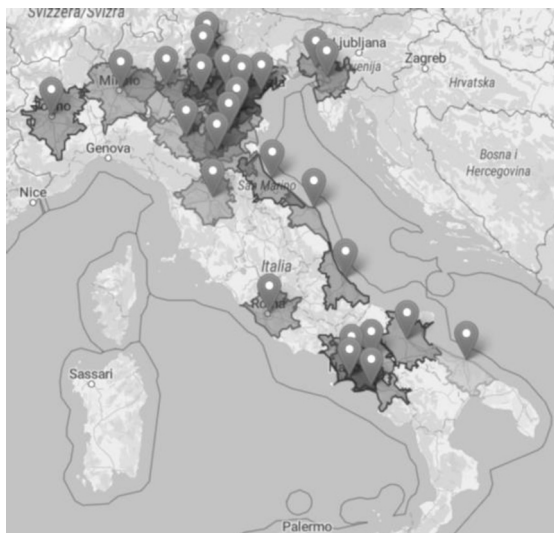


Fig 2. Areas less than 40 minutes driving from each Italian high-speed rail station included in the study (source: authors).

currently ongoing. The principal findings and purposes of the research that have been made possible by this tool have been presented [1,2,7,8]. The time window considered in this analysis spans from June 2015 to December 2017 when a total of 2645 organs (for a total of 1474 transportation events) took place. For the research's purposes, only records involving kidneys transportation within the twelve Italian regions traversed by HSR (see Table 2) and compliant with the methodology in Fig 1 have been considered in this research, for a total of 437 organs and 302 events. Transportation events to islands, abroad, and with 1 of the 2 ends outside the study area have been discarded (the area of analysis concentrated on 1726 organ records during the period inspected, which is 65% of the national total).

Table 2 lists the HSR lines considered and Table 3 the origin-destination matrix of the transportation events involving kidneys (ie, 19 transportation events took place between region A=Piemonte and C=Veneto). According to the methodology, the original transportation solution (93 events by aircraft and 209 by road, making up—respectively—30.8% and 69.2% of the modal split) can be modified by the presence of HSR services. In particular, according to the constraints listed in the methodology (sufficient supply of HSR no-transfer service, shorter travel time, compliance with the CIT rule), the results obtained can be explained as follows:

1. For those records that have kept the original transportation mode, either no direct linkage with HSR exists or the original travel time is very similar to the HSR travel time (difference < 30 minutes) due to the long displacement by road needed to take the organ from the DC to the closest HSR station. This is in particular the case of kidneys originating in regions A and I (Piemonte and Toscana, respectively) as only 1 HSR station exists in a large territory

2. Accompanied organs have been transferred to the HSR transportation solution only when the records' DC and TC were located in cities within the HSR network so as to

Table 1. Summary of the Database Included in the Analysis and Modal Split Associated With Transportation Events Before and After the Analysis (Source: Authors)

Organs displaced (Jun 2015-Dec 2017)	2645
Transportation events (Jun 2015-Dec 2017)	1474
Organs displaced inland (no from/to island/abroad)	1894
Organs displaced in the study area (12 regions)	1726
Kidneys displaced in the study area (12 regions)	437 (25.32% within the study area, 16.52% of the total)
Transportation events in the study area (12 regions)	302 (20.5% of the total)
Transportation events modal split before analysis	93 air (30.8%), 209 road (69.2%)
Transportation events modal split after analysis	17 air (5.6%), 71 road (23.5%), 214 HSR (70.9%)

Table 2. Italian Regions Traversed by High-Speed Rail (HSR) Included in the Analysis

	HSR1	HSR2W	HSR2E	HSR3	HSR4	HSR5
A	X	X	X			
B	X	X	X		X	
C	X				X	X
D					X	
E	X					
F		X	X		X	X
G			X			
H			X			
I		X			X	X
J		X		X	X	X
K		X		X		X
L				X		

HSR1, Turin, Milan, Brescia, Verona, Vicenza, Padua, Venice, Trieste; HSR2W, Turin, Milan, Reggio Emilia, Bologna, Florence, Rome, Naples, Salerno; HSR2E, Turin, Milan, Reggio Emilia, Bologna, Rimini, Ancona, Pescara; HSR3, Rome, Caserta, Benevento, Foggia, Bari; HSR4, Trento-Rovereto, (Brescia), Verona, Bologna, Florence, Rome; HSR5, Venice, Padua, Rovigo, Ferrara, Bologna, Florence, Rome, Naples.

A, Piemonte; B, Lombardia; C, Veneto; D, Trentino AA; E, Friuli VG; F, Emilia Romagna; G, Marche; H, Abruzzo; I, Tuscany; J, Lazio; K, Campania; L, Puglia.

minimize road displacement and transplant teams' fatigue. HSR allows a reduction of total cost since both road and on-call air services require a vehicle and a pilot for the entire duration of the transportation event.

3. The values included in Table 3 are coherent with the HSR network and the methodology constraints (there are actually transportation records between, for example, Puglia and Veneto, but the cell reports 0 because no direct HSR service is in place between the 2 regions). In addition, Marche-Lombardia-Veneto-Friuli VG are part of the same macroregion, and we don't have data referring to organ exchanges between them.

4. The value of the CIT considered in this work is 18 hours, which is highly precautionary with reference to

Table 3. Origin/Destination Matrix for Transportation Events Included in the Analysis—All Transportation Modes (Source: Authors)

	A	B	C	D	E	F	G	H	I	J	K	L	TOT
A	0	16	19	0	0	12	4	0	9	4	3	0	67
B	0	0	0	0	0	9	0	0	2	16	2	0	29
C	0	0	0	0	0	6	0	0	2	7	2	0	17
D	0	0	0	0	0	2	0	0	1	2	0	0	5
E	0	0	0	0	0	0	0	0	1	1	0	0	2
F	0	13	14	0	0	0	1	0	3	5	0	0	36
G	0	0	0	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	2	1	0	0	0	0	0	3
I	0	17	30	0	0	20	0	0	0	7	3	0	77
J	0	12	14	0	0	2	0	0	4	0	1	0	33
K	0	8	8	0	0	0	0	0	2	9	0	0	27
L	0	0	0	0	0	0	0	0	0	6	0	0	6
TOT	0	66	85	0	0	53	6	0	24	57	11	0	302

A, Piemonte; B, Lombardia; C, Veneto; D, Trentino AA; E, Friuli VG; F, Emilia Romagna; G, Marche; H, Abruzzo; I, Tuscany; J, Lazio; K, Campania; L, Puglia; TOT, Total.

literature values. Thus, the CIT rule is never infringed upon in both transportation scenarios.

5. The result of the transportation analysis after the introduction of a high-speed train is that the new transportation solution is potentially feasible for as many as 214 events (70.9% of the total), while, respectively, 17 (5.6%) and 71 (23.5%) events are assigned to air and road transportation. Road transportation is the best solution for displacement below 150 km and when both the DC and TC are more than 50 km away from HSR nodes, while air transportation is attractive when no direct HSR connection linking DC and TC exists or the 2 nodes are distant both between each other in absolute terms and from/to HSR stations.

CONCLUSIONS

This article studies the feasibility of high-speed rail service within the health care logistic chain in Italy. Transplantation figures are growing, and, in addition to quality of service, cost optimization shall be pursued when the scope is present. The long CIT associated to kidneys travelling alone allows us to substitute costly on-call air transportation and long road displacements (over 300 km) with a high-speed train—where the service is present—both saving money and reducing pollution (transportation costs grow with distance, likewise a reduction from 10% to as much as 70% of CO₂ and noxious emission can be scored on enlarging the distance of displacement). As a whole, HSR allows a relevant saving of time in comparison with road-only transportation, while it is notably slower than air transportation for displacements over 500 km; nevertheless, the compliance to the CIT rule is always preserved in this study. The solution proposed might be feasible under 2 conditions:

1. A coherent scheduling of surgeries at the TC (night-time for combined and thoracic transplantations, daytime/afternoon for kidney-only events) reflecting HSR timetables and the end chain trips by road, which are kept in charge of the 2 regional centers involved.

2. The commitment toward quality, timeliness, and reliability of the service from all the actors involved in this service chain to minimize delays, fatigue of medical teams, and waste of time has to be granted in a world where technology and organization of transplantation logistics are fast moving forward.

Studies on shipping brain-dead donors—artificially kept alive—to TCs or on introducing drones for short displacements to reduce sources of damage and organs' discard rates sketch promising results, which nevertheless need cautious and balanced steps between the regulation and the ethical points of view.

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