Facteurs associés aux disparités régionales d’inscription en liste d’attente de greffe hépatique en France

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Summary
Aim. — This study compared the gap between supply and need for liver transplantation among the geographic regions of France.
Methods. — Supply was estimated by registration rates on the national waiting list and need by cirrhosis-related death rates. Hierarchical ascendant classification and principal component analysis were applied to identify regional patterns in the gap between supply and need. Associations between socio-ecodemographics and regional healthcare factors were investigated.
Results. — We have found regional disparities between supply and need, mainly in regions with high rates of cirrhosis-related death. Among the 22 regions studied, six regional patterns were identified. The biggest gap between supply and need was found in regions characterized by the lack of a regional transplantation center or a low density of general and specialized practitioners. These regions were mainly rural or without a city with more than 200,000 inhabitants, and had high proportions of young people and lower social classes. The smallest gap between supply and need was found in regions presenting the opposite patterns.
Conclusion. — These results might be considered by health authorities when planning resource allocation for liver transplantation. Transplantation teams and their networks should strive for better geographical access before registration on the waiting list.

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Introduction

Liver transplantation can be an effective treatment for selected patients with end-stage liver disease caused by alcoholic or viral cirrhosis or certain types of liver cancer. Supply of donor organs is however limited [1—3]. In France, these causes of liver failure were observed in approximately 27, 16 and 20% of patients on the national liver transplantation waiting list in 2006 [3]. The number of liver transplantations performed in France has increased steadily from 806 in 2000 to 1037 in 2006, but needs continue to grow with 1028 new patients registered on the waiting list in 2000 and 1302 in 2006. This has led to a shortage with 122 waiting list deaths in 2006.

The lack of an exhaustive registry of all deaths caused by end-stage cirrhosis or hepatocellular carcinoma makes it difficult to estimate needs for organ donor in France. The registration rate on the waiting list is an indicator of graft supply, but also corresponds to the clearly expressed demand for liver transplantation. In this context, waiting list registration depends on management and referral practices to transplantation centers and medicosurgical teams’ registration practices in application of published guidelines. It also reflects access to the waiting list [4—10]. In France, 11 out of the 24 administrative regions do not have a liver transplantation center, which implies that patients residing in these regions depend on an interregional referral scheme. In 2006, and considering all reasons for registration, registration rates varied by region from 4.8 registrations per million inhabitants in French West Indies and Guyana to 29.9 per million inhabitants in Corsica [11]. These differences could be related to regional differences in liver disease and risk factors, management practices, density of healthcare facilities, demographic and socioeconomic factors, and also the overall health status of the population and the prevalence of comorbid conditions incompatible with registration on the waiting list. The overall impact of these factors is rarely studied. There has been only one report on this topic, an American study that demonstrated deficient registration of elderly persons of African ethnic background with alcoholic cirrhosis [12]. Using indicators of demand, healthcare availability as well as demographic and socioeconomic factors in French regions and their population, the purpose of this study was to identify and explain regional disparities in access to liver transplantation, defined as registration on the national waiting list.

Patients and methods

Construction of the database

The following domains were screened to search for indicators with data available on the regional level: organ procurement and transplantation activity, socioeconomic and demographic factors, healthcare supply and demand. To be included in the database, data for a given variable had to be available from 1999 to 2002. If the variable exhibited a particularly wide data spread, an annual mean was calculated for this period. After eliminating redundant variables, data were available for 137 variables for 22 regions. The French West Indies and Guyana and Reunion Island regions were excluded from the analysis because data were missing for several variables.

Data on registration and transplantation were collected from the CRISTAL information system operated by ‘’Agence de la biomédecine’’. Data were recorded by the transplantation center since registration was mandatory for transplantation. The region of each individual patient was identified, mostly in the region of residence. Official databases were also consulted to obtain indicators, including those maintained by the following organisms: Institut national de la statistique et des études économiques (Insee), Direction de la recherche, des études, de l’évaluation et des statistiques (Drees), Caisse nationale d’assurance maladie des travailleurs salariés (CNAVTS), CépiDC of the Institut national de la santé et de la recherche médicale (Inserm) and Fédération nationale des observatoires régionaux de santé (FNORS).
Factors associated with regional disparities for registration on the French national liver transplantation waiting list

Statistical analysis

After description (position and dispersion), the normality of the data distributions was checked graphically for each variable. Using centered and reduced variables, correlation matrices were constructed between variables in each category then with the average rate of new registrations; this procedure eliminated collinear variables and variables not correlated with the registration rate ($p > 0.2$). This left 24 variables for each region: number of cities with more than 200,000 inhabitants, gross domestic product (GDP) expressed in nominal value, disposable household income, percentage of occupationally active persons by sector of activity and by socio-occupational category, distribution of the population by nationality, percentage of population by age group. For healthcare supply, the variables retained for analysis were density of general practitioners and specialists (including radiologists and gastroenterologists) working in private practice per million inhabitants, number of intensive care beds in hospitals with organ procurement activity and number of liver transplantation centers. For mortality, the variables retained for analysis were: comparative rate of death by alcoholism and alcoholic psychosis per 100,000 inhabitants, and the comparative rate of cirrhosis-related death. For organ procurement and liver transplantation activity, the variables were: annual rate (average 1992–2002) of new registrations on the waiting list, number of patients on the waiting list on January 1, number of organs harvested and grafts implanted per million inhabitants.

Ward’s hierarchic ascendant classification analysis was used to group the regions into a small number of homogeneous clusters. Graft supply was described solely by registration rate on the waiting list and graft demand by the comparative rate of cirrhosis-related death in 2000. Principal component analysis, which produces a spatial representation of correlations between different variables, was applied to identify the main variables enabling distinction between regions according to their registration rate. Projection of the individual observations (the regions) on this spatial construction revealed groups of observations with similar characteristics (regional patterns). For this analysis, the Île-de-France region which includes Paris and surrounding suburbs was considered as a supplementary observation because it would have had too much weight in the general analysis and would have masked potential differences between other regions. The spatial position of Île-de-France was thus established by simply applying the value of its variables; data from this region were not considered when constructing the graphic space.

Results

Regional differences in registration rates are illustrated in Fig. 1. Higher rates were observed in southern and central-eastern regions. Bretagne, Île-de-France and Alsace were the only regions in the north with a high registration rate. Conversely, the comparative rate of cirrhosis-related death was lower in the southern regions, increasing towards the western, northern and northeastern regions. Six clusters of regions (five groups plus Île-de-France) could be selected on the hierarchical dendrogram linking registration rate to cirrhosis-related death (Fig. 2). Principal component analysis (Fig. 3) was performed with variables selected by two-way analysis. Three axes explained 83.3% of the model’s inertia in two-way analysis. The first axis (axis 1, 37.9% of the inertia) linked healthcare supply and urbanization with mortality. The second axis (axis 2, 30.4% of the inertia) included the population distribution by age and socio-occupational category and the third (axis 3, 15% of the inertia) combined regional income with nationality. Using these three axes, principal component analysis yielded the loading plot (Fig. 3 left panel) correlating the selected variables and the score.
Figure 2  Ascending hierarchic analysis of the 21 regions of France included in the general analysis dendrogram linking registration rate on the liver transplantation waiting list of region residents to cirrhosis-related mortality.

Dendrogram de classification ascendante hiérarchique représentant la partition des régions selon le taux d’inscription en liste d’attente de greffe hépatique des malades domiciliés et celui de mortalité par cirrhose.

plot (Fig. 3 right panel) positioning the regions in space. For example, the region Languedoc-Roussillon was positioned to the very right on axis 1. Since axis 1 is explained by variables related to urbanization, practitioner density and mortality, this region had a higher urbanization rate, practitioner density and lower mortality than the other regions selected.

The first cluster identified was composed of regions in eastern and southern France namely: Alsace, Franche-Comté, Rhône-Alpes and Languedoc-Roussillon. Each of these regions has at least one liver transplantation center. These regions were characterized by a registration rate of patients residing in the region which was much higher than the national average (75th to 100th percentile) and a comparative rate of cirrhosis-related death lower than the national average (25th to 50th percentile). Registration rate was high compared with mortality in these regions. The principal component analysis characterized these regions as high-income urban areas, or with at least one city with more than 200,000 inhabitants. The population was young and the healthcare supply was higher than the national average.

The second cluster included Corsica, Midi-Pyrénées and Provence-Alpes-Côte-d’Azur. The latter two regions have liver transplantation centers. These regions had registration rates around the 50th percentile and comparative rates of cirrhosis-related death very much below the national average (<25th percentile). These southern regions are rural areas except for Provence-Alpes-Côte-d’Azur but with at least one city with more than 200,000 inhabitants (except for Corsica). Most of these regions had a high income level with an older population and a density of private practitioners above the national average.

The third cluster was composed of Auvergne, Bourgogne, Lorraine, Bretagne, Haute-Normandie, Pays-de-la-Loire and Picardie. The registration rates in these regions varied between the 50th and 75th percentile. However, cirrhosis-related mortality was higher than the national average, around the 75th percentile. Only three of these seven regions had a liver transplantation center. These were rural areas and for the majority did not have a city with more than 200,000 inhabitants. The breakdown by socio-occupational categories showed that these regions had a high proportion of manual laborers, farmers and young subjects. Income level and practitioner density were below the national average.

The fourth cluster was composed of Aquitaine, Limousin, Basse-Normandie, Centre, Champagne-Ardenne and Poitou-Charentes. Registration rates in these regions were much lower than the national average, around the 25th percentile. The comparative cirrhosis-related death rates were slightly higher than the national average, around the 75th percentile. In this cluster, three of the six regions had a liver transplantation center. The proportion of manual laborers was high in those rural regions without a city with more than 200,000 inhabitants (except for Aquitaine and Limousin). The regional income level and the density of private practitioners were lower than the national average.

The fifth cluster had only one region, Nord-Pas-de-Calais, where the registration rate was lower than the national average (below the 25th percentile) and the comparative rate
of cirrhosis-related death was the highest of all regions. This urban area with a very dense suburban zone has a liver transplantation center. The population was young but with a low income level. Excepting general practitioners, the density of private practitioners was low.

Île-de-France (Paris and surrounding suburbs) was not included in the cluster analysis. There are several liver transplantation centers in this region which had a registration rate much higher than the national average (75th to 100th percentile) and a comparative cirrhosis-related death rate much lower than the national average (25th percentile). This region had to be distinguished separately because it has one third of all liver transplantation centers in France and a density of private practitioners which is much higher than the national average. This is a very dense urban area with a high income level and a high proportion of young inhabitants (< 20 years of age).

Variables describing supply and need for liver transplantation were thus linked with other variables retained in this study (Fig. 3).

The comparative cirrhosis-related mortality was positively correlated with the percentage of the population with French nationality and with the percentage of subjects aged less than 20 years. It was negatively correlated with the density of general practitioners and specialists, including gastroenterologists, and with the proportion of craftsmen among the occupationally active population, the percentage of residents with a non-EEC nationality and the number of cities with more than 200,000 inhabitants.

The number of liver transplantation centers was positively correlated with the region’s GDP expressed in nominal value, the percentage of occupationally active with an intermediary profession, the number of cities with more than 200,000 inhabitants, the density of general practitioners...
and specialists, and the number of intensive care beds in hospitals with organ procurement activity.

The rate of registration on the liver transplantation waiting list, positioned as a supplementary variable, was positively linked with the following active variables: density of specialist practitioners and radiologists, number of liver transplantation centers, higher percentage of persons aged less than 20 years and between 20–60 years, percentage of occupationally active with an intermediary profession, percentage of occupationally active working in the primary sector, percentage of farmers and craftsmen among the occupationally active, and percentage of residents with a foreign nationality. The registration rate was not correlated with the mean liver procurement per million inhabitants.

Discussion

Access to liver transplantation can be divided into three phases:

- identification of patients who might benefit from transplantation and their referral to transplantation centers;
- confirmation of the indication for transplantation and registration on the waiting list performed by the transplantation team;
- waiting time from registration to transplantation.

For this first study in France there was only one variable available describing the first two phases: registration rate by region of residence. The results demonstrated a disparity in the distribution by region of patient residence which was not explained by need expressed by hepatic or gastrointestinal disease. This difference would suggest a gap between potential need and supply of liver grafts as expressed by registration. Furthermore, the regional rate of registration was linked with healthcare supply and with the socio-ecodemographics of the region and its population.

Concerning access to care before registration, logically residing within the vicinity of healthcare services would be one of the prerequisites to access such care, as would the level of social protection and the socio-ecodemographics. For liver grafts, the rate of registration on the waiting list was correlated with variables describing the regional healthcare network: from the general practitioner to the presence of a transplantation center. Regions with low registration rates did not have a transplantation center or if they had one, it was within a context of lower practitioner density than the national average. Additionally, these regions were more often rural with no city with more than 200,000 inhabitants, zones known to have the lowest density of general practitioners and specialists in France. Lower probability of registration on the waiting list with increasing geographic distance from the patient’s home to the healthcare center has already been reported for certain treatments such as kidney grafts where the split is between residence in urban versus rural areas [12–14]. One French study has reported better access to kidney graft waiting list for on-dialysis patients followed in a hospital center performing transplantations [15]. It has also been reported that for diseases which can require liver transplantation, the frequency of screening for hepatitis C infection decreases with distance from residence to the general practitioner’s office, with screening occurring more often at the stage of hepatocellular carcinoma for patients living the farthest away from the practitioner’s office [16]. Defects in management practices after diagnosis of hepatitis C have also been linked with gender [17]. Among the other socio-ecodemographic factors having a negative impact, the rate of registration was lower for regions with higher percentage of the population working as farmers, in the primary sector of the economy, young subjects, and a low GDP. If access to care is more difficult in rural areas, it is even more the case among the socioeconomically disfavored population of these rural areas where several unfavorable factors can be associated, particularly access to specialist care [18,19]. These populations are more frequently composed of patients who could benefit from a graft, but also who have comorbid conditions which could contraindicate liver transplantation. In France socio-ecodemographic data, excluding region of residence, is not recorded at the time of registration on the waiting list, ruling out any valid investigation at an individual level. North American studies have reported other factors having a negative impact on access to the waiting list, including lower social class, lower level of social protection, minority ethnic background and presence of alcoholic cirrhosis [4–6,9,18]. We did not differentiate the different types of cirrhosis. The distinction between alcoholic and non-alcoholic cirrhosis is not recorded in the available databases (similar to other less frequent indications).

Regarding registration, practices might also have varied between centers or regions, as might have indications for transplantation and comorbidities or contraindications. Efforts have been made in several countries, including France, to standardize practices and guidelines for registration, but certain points remain difficult to explain. The highest rates of registration for cirrhosis were found in the regions of Southern France where the rate of cirrhosis-related death is low. While alcoholic cirrhosis is frequently associated with other factors having an unfavorable impact on registration, it would be reasonable to assume that contraindications for such reasons would be similar between regions. Nevertheless, different studies have reported that access to care is more difficult for patients with alcoholic cirrhosis; guidelines for good clinical practices for specific registration of these patients on the waiting list have been published [9,10,20]. Moreover, unlike the regions in Southern France, the rate of cirrhosis-related death was very high in the Northern regions where there are few transplantation centers and registration rates are low [21]. Experience of pretransplantation healthcare networks and their impact have been studied and could serve as a way of alleviating this type of regional disparity [22]. The lack of correlation between regional rates of liver procurement and registration might be an expression of insufficient intraregional balance.

The main limitation of this study was the statistical methodology which does not allow quantification of the causal effects between variables. This methodology is however widely used to identify “regional patterns”. For example, and even though the indicators used as variables for this and other studies were not perfectly identical, the regional patterns obtained were very similar to those reported...
by the National Federation of Regional Health Observatories [23]. It was decided to use an overall registration rate (instead of considering only patients with cirrhosis) because this method increased the sample size and because there is a very strong correlation between the cirrhosis-related and non-cirrhosis-related registration rates.

The data sets may appear rather old; registration practices may have evolved. It was noted however that the full data sets required for this analysis were not available for regular periods, or if they were, with considerable delay. Moreover, data concerning social, demographic and economic variables do not change rapidly. It was thus decided that these data sets could be considered as valid for the present study.

This study could serve as a starting point for further reflection regarding the allocation of liver transplantation resources in order to achieve a more homogeneous supply within the framework of interregional health organization schemes for transplantation. These findings may also be helpful in closing the gap between need and supply for liver transplantation by the development of specific networks to improve healthcare and referral practices from diagnosis to transplantation.

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References