Outcomes after renal transplantation of obese patients: a French cohort-based study

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Abstract

Background.

Whilst there are numbers of publications comparing the relationship between the body mass index (BMI) of kidney transplant recipients and graft/patient survival, no study was performed in French patients.

Methods.

In this study, cause-specific Cox models were used to study patients and graft survival and several other different times-to-event. Logistic regressions were performed to study surgical complications at 30 days post-transplantation as well as delayed graft function.

Results.

Among the 4691 included patients, 747 patients were considered obese with a BMI level higher than 30 kg/m². We observed a higher mortality of obese recipients (HR = 1.37, p = 0.0086) and higher risks of serious bacterial infections (HR = 1.24, p = 0.0006) and cardiac complications (HR = 1.45, p < 0.0001). We reported a trend with death censored graft survival (HR = 1.22, p = 0.0666) and no significant increased risk of early surgical complications.

Conclusions.

We showed that obesity increased the risk of death and serious bacterial infections and cardiac complications in French kidney transplant recipients. Further epidemiologic studies aiming to compare obese recipients versus obese candidates staying in dialysis are needed for improving the guidelines of access to transplantation of obese patients.

Background

According to the World Health Organization report [1], obesity has tripled worldwide since 1975 and 650 million adults were classified as obese in 2016. It is defined by a body mass index (BMI) greater than or equal to 30. Obesity is associated with an increase in rates of cardiovascular diseases, diabetes, musculoskeletal disorders and cancer [2]. Obesity also increases the risk for chronic kidney disease and its progression to End-Stage Renal Disease (ESRD) [3]. In the north-American patients, the obesity rates have increased by 33% from 1995 to 2002 [4]. In France, the prevalence of obesity is around 21% in patients undergoing hemodialysis, whilst an increase in survival for ESRD patients with a high-level BMI have been reported [5, 6].
In ERSD patients, transplantation is recognized as the best long-term treatment compared to dialysis in terms of both the quality and the quantity of life [7, 8]. Unfortunately, obesity may be an obstacle to access to transplantation, the waiting time in dialysis of obese patients depending on center/country practices and guidelines [9–11]. In France, obese patients have a transplantation likelihood lower than non-obese ones [12]. Several reasons can explain this situation; especially the increased risk of complications after transplantation such as wound healing, delayed graft function, hospital readmissions, or new-onset diabetes [13, 14]. In contrast, the literature remains controversial concerning graft and patient outcomes. Several recent meta-analyses illustrate this debate.

Nicoletto et al. [15] reported that the only consequence of obesity was the higher incidence of Delayed Graft Function (DGF). Lafranca et al. [16] showed no significant difference between obese and non-obese patients in terms of patient and graft survival. In contrast, the authors observed a protective relationship between high-level BMI and 3-year mortality. Hill et al. [17] reported no significant correlation between obesity and patient survival, a weak relationship with death-censored graft survival, and a correlation with DGF. Sood et al. [18] reported that obese patients had an increased risk of DGF, acute rejection, death and death-censored graft failure.

Consequently, even an important literature on this field, results of these previous studies did not allow a good appraisal in term of post-transplantation patients and graft survival in obese kidney transplant recipients. One can identify a weak literature from European countries. Most of the papers concerned north-American patients [15–18]. More specifically, no study based on a large cohort of French patients was performed. The only French study concerned 250 patients [19]. In this context, the aim of our study was to analyze the relationships between obesity and post-transplant outcomes by using a large and multicentric cohort of French kidney transplanted recipients.

**Methods**

**Studied population**

Data were extracted from the French prospective DIVAT cohort (www.divat.fr, French Research Ministry: RC12_0452, last agreement No 13 334, No CNIL for the cohort: 891735) composed of kidney transplant recipients followed in Nantes, Paris (Necker and Saint-Louis), Montpellier, Nancy, Lyon, and Nice University Hospitals. This represents around one third of the kidney transplantations performed in France. The study was performed in accordance with the Declaration of Helsinki and we obtained the agreement of the DIVAT Scientific Council. The quality of the DIVAT data bank is validated by a center audit. The participants gave informed consent. The included patients were older than 18 years with a BMI-level higher than 18.5 kg/m² at the time of their transplantation. Only first kidney transplants from deceased donors were considered. Multiple organ transplant recipients were not included. The study was limited to transplantations performed from January 2005 to December 2016 to respect current practices. Patients were considered in the obese group if their BMI at transplantation was higher than 30 kg/m².

**Available data at transplantation**

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Donor variables extracted from the database were age, sex, last serum creatininemia, donor cause of death and type (living or deceased including heart or non-heart beating donors), and expanded donor criteria (ECD).\(^{20}\) Recipient characteristics at baseline were age, sex, blood group, initial renal disease, comorbidities prior to transplantation (diabetes, hypertension, dyslipidemia, neoplasia, cardiovascular history), duration on waiting list before transplantation, type of dialysis before transplantation (peritoneal, hemodialysis or pre-emptive) and anti-HLA class I or anti-class II immunization before transplantation. Transplantation parameters were cold ischemia time, number of HLA-A-B-DR incompatibilities and induction therapy. For donor and recipients, EBV and CMV serology were also extracted.

**Post-transplantation outcomes**

The long-term outcomes were the patient and graft survival (defined by the time between the transplantation and the first event between return to dialysis, pre-emptive re-transplantation or death), graft survival (death with a functioning graft were right-censored) and patient survival (return to dialysis or pre-emptive re-transplantation were right-censored). The mid-term outcomes were the time to the first biopsy-proven acute rejection episode, cardiac complication, serious bacterial infection and cancer (solid, skin and PTLD). The short-term outcomes were the surgical or renal vascular complications occurring within the first month post-transplantation. Two sub-group analyses were performed to study DGF occurrence (defined by the need for dialysis in the first week post-transplantation) and the time to New Onset Diabetes After transplantation (NODAT). The analysis of the DGF excluded the pre-emptive patients and those on peritoneal dialysis, whereas the analysis of the time to NODAT excluded the diabetic patients prior to transplantation.

**Statistical analyses**

The characteristics between the two groups of interest (obese and non-obese recipients) were compared using Chi-square tests for categorical variables and Student t-tests for continuous variables. Survival curves were obtained by using the Kaplan-Meier estimator. To further compare the outcomes and to consider possible confounders, multivariate logistic regressions were used for binary outcomes and cause-specific Cox models for times-to-event. Variables significantly associated with both the outcome and the obesity status in univariate regressions were retained (p < 0.20) in the multivariable models. The log-linearity assumption was automatically checked: rejection of this assumption occurred when the Bayesian Information Criterion decreased using natural spline transformation compared to the inclusion of the covariate in its natural scale. In cases of violation, variables were categorized. Hazard proportionality was checked by plotting log-minus-log survival curves according to the two groups of interest and studying the Schoenfeld residuals. All the models were also center-adjusted (baseline hazard stratification for the Cox regressions). Statistical analyses were performed using Plug-Stat© (www.labcom-risca.com).

**Results**

**Cohort description**
The characteristics of the 4691 patients included in the study are described in Table 1. 3944 patients were in the non-obese group (NOG, 84.1%) versus 747 in the obese group (OG, 15.9%). 113 patients had a BMI > 35 kg/m². In the NOG, the mean BMI was 24.2 (± 2.9) kg/m² (ranging from 18.6 to 30.0) versus 32.8 (± 2.5) kg/m² in the OG (ranging from 30.1 to 50.3). As expected, several characteristics at transplantation differed between the two groups. The prevalence of recipients older than 55 years was 60.4% in the OG versus 50.3% in the NOG (p < 0.0001). The percentage of male recipients was lower in the OG (55.4% versus 65.0, p < 0.0001), but the prevalence of patients with diabetes and history of dyslipidemia was higher (38.3% versus 16.2%, p < 0.0001; and 56.0% versus 38.4%, p < 0.0001). Obese patients were more likely to receive ECD grafts (52.3% versus 46.1%, p = 0.0021), probably because they were older compared to non-obese recipients.
Table 1
Description of the cohort according to obesity status.

|                                                | Whole sample (n = 4691) | Non-obese (n = 3944) | Obese (n = 747) | p-value |
|------------------------------------------------|-------------------------|-----------------------|-----------------|---------|
| Male recipient                                 | NA                      | 2977 (63.5)           | 0 (2563)        | 414 (55.4) | < 0.0001 |
| Recurrent causal nephropathy                   | 1 (23.8)                | 1114 (23.8)           | 983 (24.9)      | 0 (131)  | 17.5 | < 0.0001 |
| Preemptive transplantation                     | 8 (9.6)                 | 450 (10.0)            | 395 (10.0)      | 0 (55)   | 7.4 | 0.0231 |
| History of diabetes                            | 0 (19.7)                | 923 (19.7)            | 637 (16.2)      | 0 (286)  | 38.3 | < 0.0001 |
| History of hypertension                        | 0 (84.2)                | 3949 (84.2)           | 3301 (83.7)     | 0 (648)  | 86.7 | 0.0362 |
| History of vascular disease                    | 0 (17.8)                | 837 (17.8)            | 696 (17.6)      | 0 (141)  | 18.9 | 0.4214 |
| History of cardiac disease                     | 0 (28.9)                | 1355 (28.9)           | 1095 (27.8)     | 0 (260)  | 34.8 | 0.0001 |
| History of cardiovascular disease              | 0 (38.5)                | 1806 (38.5)           | 1475 (37.4)     | 0 (331)  | 44.3 | 0.0004 |
| History of malignancy                          | 0 (10.1)                | 476 (10.1)            | 406 (10.3)      | 0 (70)   | 9.4 | 0.4435 |
| History of dyslipidemia                        | 0 (41.2)                | 1934 (41.2)           | 1516 (38.4)     | 0 (418)  | 56.0 | < 0.0001 |
| History of B or C hepatitis                    | 0 (5.3)                 | 250 (5.3)             | 224 (5.7)       | 0 (26)   | 3.5 | 0.0142 |
| Positive recipient CMV serology                | 47 (65.2)               | 3028 (65.2)           | 2515 (64.4)     | 7 (513)  | 69.3 | 0.0102 |
| Positive recipient EBV serology                | 62 (97.0)               | 4488 (97.0)           | 3765 (96.8)     | 9 (723)  | 98.0 | 0.0806 |
| Positive anti-class I                          | 378 (31.7)              | 1369 (31.7)           | 1145 (31.6)     | 60 (224) | 32.6 | 0.5956 |
| Positive anti-class II                         | 432 (28.7)              | 1223 (28.7)           | 1033 (28.8)     | 72 (190) | 28.1 | 0.7224 |
| Recipient blood group                          | 3                       | 1                     | 2               |         |     | 0.4660 |
| A                                              | 2018 (43.0)             | 1695 (43.0)           | 323 (43.4)      |         |     |
|                                     | Whole sample (n = 4691) | Non-obeses (n = 3944) | Obeses (n = 747) | p-value |
|-------------------------------------|--------------------------|------------------------|-----------------|---------|
| AB                                  | 221                      | 4.7                    | 178             | 43      | 5.8    |
| B                                   | 533                      | 11.4                   | 448             | 85      | 11.4   |
| O                                   | 1916                     | 40.9                   | 1622            | 294     | 39.5   |
| Male donor                          | 5                        | 2766                   | 2320            | 446     | 59.9   | 0.6117 |
| ECD donor                           | 53                       | 2186                   | 1798            | 388     | 52.3   | 0.0021 |
| Non heart-beating donor             | 0                        | 204                    | 180             | 24      | 3.2    | 0.0969 |
| Vascular cause of donor death       | 12                       | 2533                   | 2105            | 428     | 57.4   | 0.0477 |
| Donor hypertension                  | 192                      | 1409                   | 1174            | 235     | 32.6   | 0.4203 |
| Positive donor CMV serology         | 13                       | 2584                   | 2165            | 419     | 56.2   | 0.5477 |
| Positive donor EBV serology         | 42                       | 4461                   | 3743            | 718     | 97.2   | 0.0704 |
| Donor blood group                   | 3                        | 3                      | 0               | 0.5152  |
| A                                   | 2021                     | 43.1                   | 1696            | 325     | 43.5   |
| AB                                  | 195                      | 4.2                    | 157             | 38      | 5.1    |
| B                                   | 486                      | 10.4                   | 408             | 78      | 10.4   |
| O                                   | 1986                     | 42.4                   | 1680            | 306     | 41.0   |
| HLA A-B-DR incomp. ≥4               | 43                       | 720                    | 610             | 110     | 14.9   | 0.6318 |
| Depleting induction                 | 0                        | 2505                   | 2060            | 445     | 59.6   | 0.0002 |
| Recipient age ≥ 55 years            | 0                        | 2435                   | 1984            | 451     | 60.4   | < 0.0001 |
| Donor age ≥ 55 years                | 15                       | 2509                   | 2062            | 447     | 59.9   | 0.0002 |
| Waiting list (months)               | NA                       | mean 25.9              | sd 22.7         | mean 25.9 | sd 22.8 | NA 25.6 | sd 21.7 | 0.6865 |
| Donor creatininemia (µmol/l)        | 29                       | 92.5                   | 24              | 92.1    | 57.7   | 5       | 94.6    | 64.0    | 0.3093 |
|                        | Whole sample (n = 4691) | Non-obese (n = 3944) | Obese (n = 747) | p-value |
|------------------------|------------------------|----------------------|----------------|---------|
| **Cold ischemia time** |                        |                      |                |         |
| (hours)                | 18                     | 18.1                 | 7.4            | 0.4490  |

During the follow-up, 462 patients died with a functioning graft (including 101 in the OG), 614 returned to dialysis (including 118 in the OG) and 12 were preemptively re-transplantations (including 1 in the OG). Median follow-up time for the cohort was 4.0 years (range from 0.0 to 13.2).

**Graft and/or patient survival**

The patient and graft survival curves are presented in Fig. 1. The survival was 44% (95%CI from 38–52%) at 10 years post-transplantation in the OG versus 58% (95%CI from 55–61%) in the NOG. As illustrated in **Table S1**, the corresponding confounder-adjusted HR of the obese versus non-obese group was 1.28 (95%CI from 1.09 to 1.50, p = 0.0021): an obese patient has a 1.28-fold increased risk of death or return to dialysis compared to a non-obese patient with similar risk factors at transplantation. When deaths were censored, the confounder-adjusted HR of graft failure was 1.22 (**Table S2**, 95%CI from 0.99 to 1.51, p = 0.0666). When graft failures were censored, the confounder-adjusted HR of death with functioning graft was 1.37 (**Table S3**, 95%CI from 1.08 to 1.72, p = 0.0086). These two cause-specific results illustrated that the worst prognosis of obese recipients in terms of patient and graft survival was related to the excess mortality. All the results in terms of confounder-adjusted relative effects are summarized in Fig. 2.

**Bacterial infection, neoplasia, cardiac complications and acute rejection episodes**

The cumulative probability of bacterial infection at 5 years post-transplantation was 0.44 (95%CI from 0.42 to 0.46) in the NOG versus 0.55 (95%CI from 0.50 to 0.58) in the OG. The corresponding confounder-adjusted HR was 1.24 (**Table S4**, 95%CI from 1.10 to 1.40, p = 0.0006), meaning a 1.2-fold increase in the risk of bacterial infection for obese patients. The cumulative probability of cancer at 5 years post-transplantation was 0.16 (95%CI from 0.15 to 0.18) in the NOG versus 0.14 (95%CI from 0.11 to 0.18) in the OG. In contrast to bacterial infections, obese patients had a lower risk of cancer compared with non-obese patients (**Table S5**, confounder-adjuster HR = 0.73, 95%CI from 0.57 to 0.94, p = 0.0160). The cumulative probability of cardiac complication at 5 years post-transplantation was 0.23 (95%CI from 0.22 to 0.25) in the NOG versus 0.32 (95%CI from 0.28 to 0.36) in the OG. The corresponding confounder-adjusted HR was 1.21 (**Table S6**, 95%CI from 1.03 to 1.43, p < 0.0192). Finally, the cumulative probability of acute rejection episode at 5 years post-transplantation was 0.28 (95%CI from 0.26 to 0.29) in the NOG versus 0.31 (95%CI from 0.27 to 0.35) in the OG. The corresponding confounder-adjusted HR for obese versus non-obese recipients was 1.17 (**Table S7**, 95%CI from 0.99 to 1.37, p = 0.0580).

**Early urological surgical and vascular complications**
The overall percentage of urological surgical complications was 8.6% (n = 402): 9.9% in the OG (95%CI from 9.0–10.8%) versus 8.3% in the NOG (95%CI from 7.5–9.2%). When adjusted on possible confounders (Table S8a), no significant difference was established (OR = 1.11, 95%CI from 0.84 to 1.47, p = 0.4443). However, we observed that obese patients presented higher rates of lymphocele that required surgical intervention (48.6%) compared to non-obese patients (36%). In contrast, we observed less ureteral fistula in obese patients (23% versus 35.1% respectively, Table S8b).

Vascular complications were similar in the two groups, with 15.5% in the OG (95%CI from 14.4–16.7%) versus 14.8% in the NOG (95%CI from 13.7–15.9%). Confounder-adjusted results confirmed non-significant differences in vascular complications within the first month after the transplantation (Table S9a, OR = 0.92, 95%CI from 0.72 to 1.16). As illustrated in Table S9b, despite overall vascular complications being quite similar in the two groups, we observed that arterial thrombosis was more frequent in obese (23.3%) compared to non-obese patients (11.6%).

**Subgroup analyses: metabolic complication and DGF**

For NODAT analysis, 930 patients were excluded because they were already diabetic before the transplantation. Characteristics of the 3760 studied patients are described in Table S10. 458 patients were in the OG (12.2%) versus 3302 in the NOG (87.8%). The cumulative probability of developing NODAT at 5 years post-transplantation was 0.17 (95%CI from 0.16 to 0.19) in the NOG compared to 0.42 in the OG (95%CI from 0.36 to 0.47). After considering possible confounders (Table S11), obese patients presented a 1.2-fold increase in the risk of NODAT within 2 years after transplantation (95%CI from 1.74 to 2.57, p < 0.0001). This hazard ratio then increased to 4.24 (95%CI from 2.46 to 7.29, p < 0.0001).

For DGF analysis, 1005 patients were excluded because they were in peritoneal dialysis or not dialyzed before transplantation, the need for dialysis in the first week post-transplantation being not evaluable for these recipients. Characteristics of the 3686 patients are described in Table S12. 615 patients were in the OG (16.7%) versus 3071 in the NOG (83.3%). We found a DGF prevalence of 26.2% (95%CI from 24.8–27.6%) in the NOG compared to 42.1% (95%CI from 40.5–43.7%) in the OG. When adjusted for possible confounders (Table S13), we confirmed that obese patients have a higher DGF susceptibility (OR = 1.89; 95%CI from 1.56 to 2.29; p < 0.0001) compared with non-obese patients.

**Discussion**

Based on a French cohort, we reported that obesity did not significantly increase the risk of urologic or vascular complications or graft loss but seemed to increase the risk of cardiac and infectious complications and the mortality.

Our results are likely to be representative of the entire French transplantation cohort since we studied more than 4500 recipients of a first kidney graft between 2005 and 2016, from a multicenter cohort gathering one third of the national transplantation activity. The proportion of obese patients in our transplantation cohort was 15.9%, in-line with French practices recently described from the national
French Registry. One can note that 20% of dialyzed patients in France are obese, illustrating that obesity may be an obstacle to access to transplantation, as previously reported [20]. This was the main reason of our study, obese patients have a lower access to transplantation in France, while the risk/benefit ratio associated with transplantation remains unknown in French obese patients. The French health authority recommends limiting transplantation to recipients with a BMI below 35 kg/m\(^2\) [21], this cutoff being mainly decided based on north-American studies. In our cohort, only 2.4% (n = 113) of patients presented a BMI above 35 kg/m\(^2\), meaning that the relevance of this threshold cannot be investigated due to the small sample size.

In terms of early complications, and particularly delayed graft function, our results agree with previously published findings [16, 22]. DGF is the most consensual complication observed in obese patients. This could be explained by the greater difficulty in assessing the need for dialysis in these overweight patients, resulting in an over-indication for dialysis post-transplantation. Another explanation could be a longer surgery time required for kidney implantation in obese patients which may predispose to additional complications [23]. This was not the case in our cohort since we reported similar risk of urologic and vascular complications in obese and non-obese patients. However, we only retained early complications requiring surgical intervention, which probably underestimated these events.

The higher DGF rate could be responsible for the higher rate of acute rejection observed in obese patients [24]. Indeed, obesity has been described as the cause of an increase in inflammation and alloimmunity and a decrease in the bioavailability of immunosuppression [25]. DGF and acute rejection are both risk factors of graft failure and patient death, in agreement with the lower patient and graft survival we observed for obese patients. More precisely, we reported that obesity tends to increase the risk of graft failure and significantly increase the risk of death with functioning graft. We additionally reported that obese patients presented more NODAT, more serious bacterial infectious diseases and more cardiac complications, i.e. several short-term events that can explain the worst long-term prognosis of this population.

A North-American studies reported a beneficial effect of transplantation for obese patients with 3.3% deaths per year compared to 6.6% for those who stayed on the waiting list [26, 27]. Therefore, despite we reported worst short- and long-term an increased risk of death after transplantation due to obesity, we could not conclude that it is preferable to maintain patients on dialysis. Nevertheless, considering their risk of comorbidity and death it would be probably useful to help severe obese candidates with BMI above 35 in losing weight, for instance by using bariatric surgery [28]. Dietary intervention for obese patients with a lower BMI before transplantation remains debatable [29].

Other limitations of our study can be underlined. Firstly, obesity is also the consequence of crucial but uncontrollable factors in our cohort, including genetic considerations, social status, eating, physical activity habits and stress, which could obviously limit the interpretation of our results. Secondly, the BMI per se is a rough marker of obesity. Thirdly, additional outcomes would have been interesting to report, as hospital stay or the wound complications.
In conclusion, our study allows to provide updated results related to outcomes of French obese kidney transplant recipients. French obese patients presented a higher risk of death, serious infections and cardiac complications but not of early urologic or vascular complications. For improving a better access to transplantation for obese patients, we need epidemiological studies aiming to compare obese kidney transplant recipients versus obese candidates staying in dialysis, with an attention to the recipient and donor characteristics that can interact with the transplantation effect.

**Abbreviations**

Body Mass Index (BMI), Confidence Interval (CI), Cytomegalovirus (CMV), Delayed Graft Function (DGF), Données Informatisées et Validées en Transplantation (DIVAT), effective (n), End-Stage Renal Disease (ESRD), Epstein-Barr Virus (EBV), Expanded Criteria Donor (ECD), Hazard Ratio (HR), Human Leucocyte Antigen (HLA), mean (m), Number of missing values (NA), New Onset Diabetes After Transplantation (NODAT), Non-Obese Group (NOG), Obese Group (OG), Odds-Ratio (OR), Post-Transplant Lymphoproliferative Disease (PTLD), standard deviation (sd), World Health Organization report (WHO).

**Declarations**

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COMPETING INTEREST

The authors of this manuscript have no conflict of interest to disclose for this study.

AVAILABILITY OF DATA AND MATERIALS

Data from the DIVAT cohort is available free of charge to academic researchers after a request to its scientific council. The procedure is explained at this address: http://www.divat.fr/access-to-data

AUTHORS’ CONTRIBUTIONS

- Yohann Foucher: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing the original draft.
- Marine Lorent: Formal analysis, Writing - original draft
- Solène Roux: Formal analysis
- Laetitia Albano, Valérie Garrigue, Moglie Lequentrec, Christophe Legendre, Fanny Buron, Emmanuel Morelon, Sophie Girerd, Marc Ladrière, Denis Glotz, Carmen Lefaucher, Jacques Dantal, and Julien Branchereau: Writing – original draft
- Clarisse Kerleau: Data curation, Project administration.
- Magali Giral: Supervision, Validation, Visualization, Writing – original draft.

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**Figures**
Figure 1

Patient and graft survival curves according to obesity status.
Figure 2

Summary of confounder-adjusted relative effects of obese versus non-obese recipients.

Supplementary Files

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