Timing of the pre-transplant workup for renal transplantation: Is there room for improvement?

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Abbreviations

ADPKD, autosomal dominant polycystic kidney disease

BMI, body mass index

CKD, chronic kidney disease

CKD5, chronic kidney disease stage 5 (eGFR < 15 ml/min/1.73m²)

eGFR, estimated glomerular filtration rate

ERBP, European Renal Best Practice

RRT, renal replacement therapy

USRDS, United States Renal Data System
ABSTRACT

Background. Since patient survival after kidney transplantation is significantly improved with a shorter time on dialysis, it is recommended to start the transplant workup in a timely fashion.

Methods. This retrospective study analyses the chronology of actions taken during the care for patients with CKD stage 5 who were waitlisted for a first kidney transplant at the Antwerp University Hospital between 2016 and 2019. We aimed to identify risk factors for a delayed start of the transplant workup (i.e. after dialysis initiation) and factors that prolong its duration.

Results. Of the 161 patients included, only 43% started the transplant workup before starting dialysis. We identified the number of hospitalization days (OR 0.79, 95%CI: 0.69-0.89, p < 0.001), language barriers (OR 0.20, 95%CI: 0.06-0.61, p=0.005) and a shorter nephrology follow-up before CKD stage 5 (OR 0.99, 95%CI: 1.0-0.98, p=0.034) as factors having a significant negative impact on the probability of starting the transplant screening before dialysis. The workup took a median of 8.6 months (IQR 5-14) to complete. The number of hospitalization days significantly prolonged its duration.

Conclusion. The transplant workup was often started too late and the time needed to complete it was surprisingly long. By starting the transplant workup in a timely fashion and reducing the time spent on the screening examinations, we should be able to register patients on the waiting list before or at least at the start of dialysis. We believe that such an internal audit could be of value for every transplant center.

Keywords: chronic renal failure, CKD, dialysis, ESRD, kidney transplantation, predialysis.
INTRODUCTION

Renal transplantation is the preferred treatment for patients with renal failure as it increases survival\(^1\)-\(^3\) and improves quality of life.\(^4\) The time spent on dialysis before transplantation appears to have a directly proportional negative effect on patient survival and possibly also graft survival.\(^5\)-\(^12\) Therefore it is increasingly recommended to aim for pre-emptive transplantation, either with a living donor or by timely registration on the waiting list for deceased donor transplantation.\(^13\),\(^14\)

Although pre-emptive registration on the transplant waiting list occurs more often in recent years, it is still only performed in a minority of patients.\(^15\)-\(^17\) Furthermore, a variability in the timing of referral to a transplant center persists with some patients spending months to years on dialysis before starting their pre-transplant evaluation.\(^16\),\(^18\),\(^19\) The recently updated KDIGO guidelines specifically recommend referral of potential kidney transplant candidates for evaluation at least 6 to 12 months before anticipated dialysis initiation in order to facilitate the identification and workup of living donors and to plan for possible pre-emptive transplantation.\(^13\) Data about the timing of the transplant workup and the time required to complete it, are scarce however.

MATERIALS AND METHODS

Study design

This study is a multi-centric retrospective analysis evaluating the chronology of actions taken during the care for patients waitlisted for a first kidney transplantation at the Antwerp University Hospital in Belgium. (Pre-)dialysis care of these patients was either performed at the Antwerp University Hospital or one of its referring centers in the province of Antwerp (16 hospitals in total). The transplant workup was
performed in the referring center, and the patient was referred to the transplant center after finalizing the workup to proceed to registration on the waiting list. All physicians (both in the academic center as in the referring hospitals) used a guidance document for the pre-transplant workup that was developed by the academic center and is largely based on the ERBP guidelines.20

Population
Two hundred and one patients were registered on the Antwerp renal transplant deceased donor waiting list between 1/1/2016 and 12/11/2019. Patients were excluded if they were younger than 18 years old (n=9), if they had received a previous renal allograft (n=24), if they were transferred from a different transplant center (n=4), or if there were no data available on the pre-transplant care period (n=3). This led to a total number of 161 patients included for analysis (for exclusion process, see Figure 1). Although this study only includes patients originally waitlisted for a deceased donor transplant, five patients who went through the standard workup for deceased donor renal transplant were eventually transplanted with a living donor later on. Patients were followed up until 31/01/2020.

Data collected
Based on the available literature, we collected a set of patient-derived variables that might influence the timing of pre-transplant care (for details of the definitions used, see table S1 of the supplementary appendix). We examined whether supplementary medical examinations were performed on top of the recommended screening examinations (ERBP guidelines).20 We specifically recorded invasive urologic examinations, colonoscopy, gastroscopy and ultrasound of the carotid arteries and
assessed whether there was a medical indication for these procedures, or as recommended by the aforementioned ERBP guideline or the national cancer screening guidelines.

We recorded the following key moments during pre-transplant nephrology care:

- The date of the first nephrology visit;
- The date of the nephrology visit when the eGFR was < 15 ml/min/1.73m² for the first time (i.e. the start of CKD stage 5);
- The date of the first medical examination performed to screen patients for eligibility for transplantation (i.e. the start of workup);
- The date of the first access procedure for dialysis;
- The date of the first dialysis session;
- The date of registration on the renal transplant waiting list;
- The date of renal transplantation for those who were transplanted during the study period.

Statistical analysis

All statistical analyses were performed with the use of SPSS statistics software. Differences between groups were analyzed using Mann-Whitney U test for continuous variables and Chi square test for categorical variables with Yates’ Correction for Continuity. When the examined numbers were too small, Fisher’s exact test was used. Multiple logistic regression analysis was performed to explore the influence of patient-derived factors on the probability of starting transplant workup before the start of dialysis. To this end, we initially included all clinically relevant parameters. To avoid over-fitting of the model, we selected a final model...
based on clinical relevance and statistical significance in univariable analysis. We ultimately included seven variables in our model.

We subsequently calculated the workup time for every patient as the number of days between the first transplant screening examination and the ultimate registration on the waiting list. For the multiple linear regression analysis we selected the variables based on clinical relevance and statistical significance in the simple linear regression analysis. We calculated $R^2$ to assess to what extent the combination of independent variables could explain the variance in workup time. In order to fulfil the assumption of normal distribution, we used a logarithmic transformation ($\log_{10}$) of the workup time in both the simple and multiple regression models. All listed p-values are two-tailed. Our study was exempt from institutional review board approval.

RESULTS

Patients

Baseline characteristics at the time of waitlisting are shown in table 1. The median age was 53 years and 62% were male. Patients with autosomal dominant polycystic kidney disease (ADPKD) or glomerular disease comprised almost half of the population. Fifty seven per cent of patients (57%) were treated with hemodialysis and 29% with peritoneal dialysis at the time of registration on the waiting list. The remaining 14% of patients were pre-emptively registered. Nearly one fourth of patients had cardiovascular disease and one in three patients experienced one or more infectious episodes between the start of CKD stage 5 and the moment of registration on the waiting list. One third of patients mentioned some degree of financial difficulties and more than 20% were late referrals. The median time
between the first nephrology contact and the start of CKD stage 5 was 41 months (3.4 years).

Timing of the pre-transplant workup

Only 43% (69/161) of patients started their transplant evaluation before the start of dialysis, and 32% (51/161) started the evaluation before they had their first dialysis access created. Of the 69 patients who started the transplant workup before the start of dialysis, 23 (33%) were waitlisted before the start of dialysis. This corresponds to 14.2% of the total population. Five of them (5/69 or 7%) were preemptively transplanted, amongst whom 3 received a kidney from a living donor (Figure 2). Compared to patients who started the transplant workup before the start of dialysis, those who started the transplant workup after dialysis were more often male (71 vs. 51%, p=0.01), were more likely to have hypertensive nephropathy and less likely to have ADPKD as primary renal disease (18 vs. 4%, p=0.0075 and 10 vs. 32%, p<0.001, respectively) (Table 1). They had significantly more cardiovascular disease (32 vs. 13%, p=0.008) and were more often hospitalized between the start of CKD stage 5 and the start of the workup (9 vs. 0 days, p<0.001). As for dialysis modality, they were more often treated with hemodialysis than peritoneal dialysis (82 vs. 18%). As for non-medical factors, having some degree of language barrier or financial struggle was more frequent in the group of patients who started the workup after dialysis (39 vs.12%, p<0.001 and 40 vs. 23%, p=0.023, respectively). They also had a significantly shorter time in nephrology care prior to CKD stage 5 (21 vs. 62 months, p<0.001) and were more often late referrals (33 vs. 7%, p<0.001). The time interval between the start of CKD stage 5 and the start of dialysis was significantly
shorter (3 vs. 10 months, \( p<0.001 \)) but this difference lost statistical significance after exclusion of late referrals (data not shown). Furthermore, patients were less likely to start their transplant workup before starting dialysis when they were cared for in one of the referring centers instead of the transplant center (14 vs. 33%, \( p=0.007 \)).

Multiple logistic regression analysis was performed to assess the relative impact of different patient-derived factors on the likelihood of starting the transplant workup before the start of dialysis (Table 2). Three variables appear to make a statistically significant contribution to the model. The most important predictor was the number of hospitalization days with an odds ratio of 0.79 (95%CI: 0.69-0.89). Patients with language difficulties were also less likely to pre-emptively start their pre-transplant workup (OR 0.20; 95%CI: 0.06-0.61). The amount of time in nephrology care before the start of CKD stage 5 was the third contributor with an odds ratio of 1.01 (95%CI: 1.00-1.02).

**Duration of the transplant workup**

After starting the transplant workup, it took a median of 8.6 months (IQR 5-14) to finalize the workup and be registered on the waiting list. There was no significant difference between the patients that started the transplant evaluation before or after starting dialysis with a median duration of 10 versus 8 months (\( p=0.46 \)) (Table 3).

For the patients who started the workup after they started dialysis (n=91), there was a median delay of 4.2 months (IQR 1.6-12) between the start of dialysis and the start of the transplant evaluation. This additional delay led to a median of 11.2 months (IQR 5.7-19.8) spent on dialysis before being registered on the transplant waiting list (n=138, after exclusion of the 23 patients who were registered prior to the start of dialysis) with a significant difference between the patients that started the transplant
evaluation before versus after dialysis: 4.6 months (IQR 2.3-10.9) vs. 15.4 months (IQR 8.7-25.2), p<0.001.

Because the workup time might have been artificially prolonged in the patients that were pre-emptively wait-listed (because the physician had more time), a separate analysis was performed after exclusion of these patients but this failed to show any improvement (Table 3). Furthermore, when selecting the ‘healthiest’ subgroup of patients (i.e. without cardiovascular disease, diabetes or infections and with a maximum of 5 hospitalization days during the workup period), the median workup time was only marginally shorter. There was no significant difference in time spent on the transplant evaluation between patients cared for in the transplant center compared to the referring centers.

Thirty-one per cent of patients had at least one extra medical examination beyond the recommended workup that had no clear medical indication traceable in the patient file. This was predominantly the case for gastroscopy and ultrasound of the carotid arteries (Table 4).

After multiple linear regression analysis, only the number of hospitalization days appeared significantly related with the time needed to complete the transplant workup (Table 5). However, this model explained only 16% of the total variance in the time spent on the transplant workup, indicating that other unknown factors probably play a major role in its delay.
DISCUSSION

We performed an in-depth retrospective analysis of the chronology of actions taken during the care for transplant-eligible patients with renal failure in our center and our network of referring hospitals in Antwerp, Belgium. Our key conclusion is that less than half (43%) of patients started the transplant evaluation before dialysis initiation and only 14% were pre-emptively waitlisted. These findings are comparable to reports from the United States and Europe. In a single-center analysis from the United States analyzing data from 2004 to 2007 (n=695), Waterman et al observed that between 83% and 60% of patients had been on dialysis for 2 years or more at the time of presentation for transplant evaluation\textsuperscript{19}. In a multi-center analysis of all transplant centers in Georgia, USA (n=1580), Gander et al observed that only 20% of referrals for transplant evaluation were pre-emptive referrals.\textsuperscript{15} Data from Europe concerning the rate of pre-emptive registration are also in line with our findings, ranging from 6% in the 2018 French REIN registry report\textsuperscript{21}, 7.3% in the 2016 Eurotransplant annual report\textsuperscript{22} to 26% in the French North-West network from 2008 to 2012.\textsuperscript{17}

Multivariable analysis identified three variables that were significantly associated with a delayed start of the transplant workup (i.e. after dialysis initiation), which could be addressed to some extent (Table 6). The most important risk factor was the number of hospitalization days from CKD stage 5 to the start of screening, probably representing poorer general health. Medical complications are frequent and not always preventable in patients with kidney failure. Nevertheless, prompt initiation of the workup should be encouraged even in more vulnerable patients because complications tend to accumulate with time spent on dialysis. The second risk factor was the presence of a language barrier. Informing and preparing patients for dialysis...
and transplantation requires extensive patient-tailored communication and is obviously more challenging in case of a language difference. Particularly in this setting, early information on transplantation, preferably before or together with dialysis preparation, could promote timely waitlisting. The third risk factor for a delayed start of the transplant workup was a shorter duration of pre-CKD 5 nephrology care. This was mainly driven by late referrals. Although this subgroup is difficult to target with preventive measures, extra efforts should aim at minimizing the time between dialysis initiation and the start of the transplant workup.\textsuperscript{16, 23, 24}

Studies addressing the timing of the transplant evaluation are scarce. A French study on 1725 patients that started RRT between 1997 and 2003 in the region of Lorraine identified only older age and treatment in a center that does not perform renal transplantation as significant factors reducing the likelihood of being waitlisted before the start of dialysis.\textsuperscript{25} The difference in identified risk factors illustrates the between-center variability in pre-transplant care and highlights the importance for every center to audit its own performance.

We observed a median duration of 8.6 months between the start of the transplant workup and registration on the waiting list, which is similar compared to the limited data available. Single-center data from France (n=50) from 2013-2014 reported a median of $8.1 \pm 4.7$ months to complete the transplant evaluation\textsuperscript{26} and in a 2015 study from the USA, Monson et al observed that 23.4\% of patients did not complete the transplant workup within 1 year after their first pre-transplant visit.\textsuperscript{27}

In our study the time spent on the transplant workup did not differ between patients that started the transplant evaluation before vs. after the start of dialysis. However, we observed an additional median delay of 4.2 months between the start of dialysis and the start of the transplant workup in the last group. This had a dramatic impact
on the total waiting time spent on dialysis before being waitlisted (15.4 vs. 4.6 months). The delay between the start of dialysis and the start of the transplant workup could have had many potential explanations such as access-related complications, late referrals and hope of recovery of renal function among many others. It is however significantly shorter than the time observed in the Southeastern USA by Patzer et al who observed a median delay of 245 days or 8 months between the start of dialysis and referral for transplant evaluation in 11,862 incident dialysis patients between 2016 and 2018.\textsuperscript{16} Despite our elaborate collection of medical and socioeconomic variables, multivariable analysis could only identify the number of hospitalization days as a significantly prolonging factor of the time needed to finalize the transplant workup. Monson et al performed a similar analysis in 256 patients referred for transplant evaluation between 2009 and 2010 in the university hospital of Chicago and observed that needing >1 hospitalization was associated with slower rates of transplant evaluation completion. Contrary to our findings, they observed that needing a greater number of medical tests was associated with longer completion times.\textsuperscript{27} Our model could only explain 16% of the total variance in the time spent on the transplant workup. We therefore presume that significant time is lost during the workup period without a clear explanation and that there is room for improvement. Furthermore, the observation that excellent transplant candidates without comorbidities still need a median of seven months to perform a minimal workup, suggests that the physician’s role is considerable. It is likely that physicians’ and patient’s inertia, and administrative, practical and logistic hurdles all combine to prolong the duration of the transplant workup beyond reasonable limits for many patients.
Our study provides a detailed analysis of the timing and duration of the transplant workup. Nevertheless, it has several limitations. Firstly, due to the limited sample size our analysis is prone to overestimation of the differences between groups and our regression models risk over-fitting of the data. It is possible that other variables which are known to be associated with a lower access to renal transplantation, notably comorbidities such as lung disease²⁸, ²⁹, cardiovascular disease¹⁶, ²⁸ or diabetes¹⁶, ²⁸, might gain significance in a larger sample. Secondly, despite our elaborate collection of variables, we lacked several items that could also have influenced the delay in the transplant workup (e.g. the time lost on prerequisites such as smoking cessation, or the waiting times for different screening examinations in the various hospitals, amongst many others). Thirdly, despite the fact that our population was similar to other large transplant registries with regards to comorbidities such as cardiovascular disease, diabetes and intercurrent infections³⁰, it only lends a very detailed insight into Belgium nephrology care, and might not be generalizable. In fact, the workup time probably even varied between the 16 centers involved in this study, as illustrated by the observation that the workup was more often started before dialysis in the academic center than in the referring centers. However, our cohort was too small to perform an inter-center comparative statistical analysis. Nevertheless, all centers used a guidance document provided by the academic center in order to harmonize the workup between centers and avoid unnecessary examinations as much as possible.

We conclude that, despite international recommendations, patients often start the transplant evaluation too late and the workup takes a relatively long time to finish. We presume that room for improvement exists on all different levels in pre-transplant renal care (Table 6). Education about transplantation, prior or simultaneously with
preparation for dialysis should be a top priority to promote pre-emptive (living-donor) kidney transplantation and to minimize the time spent on dialysis waiting for deceased-donor kidney transplantation. Innovative research has been done regarding more engaging and effective ways of patient education.\textsuperscript{31} Technological tools providing accessible multilingual education and the organization of a specific CKD5-clinic could also be of interest.\textsuperscript{26} Implementation of an external quality control measure assessing center-specific transplant education\textsuperscript{32} and referral rates\textsuperscript{33} have also been proposed together with modifications of payment strategies of dialysis facilities.\textsuperscript{34, 35}

The transplant workup should also be limited to the recommended guidelines and extra examinations should only be performed if there is a clear clinical indication. A recent ERA-EDTA expert opinion paper suggests restricting the transplant workup even further for younger patients (<40 years old) without comorbidities.\textsuperscript{36}

We would also like to stress that the objective to register patients pre-emptively or at the latest at the start of dialysis is not a futile action. Although it is true that time on dialysis is an important factor affecting an individual’s ranking on the waiting list for deceased donor transplantation and hence his or her chance to be transplanted, there is still a significant chance of being pre-emptively transplanted. Indeed, data from the 2016 Eurotransplant annual report show that 7% of patients were pre-emptively registered and 4.3% were pre-emptively transplanted with a deceased donor.\textsuperscript{22} These statistics are consistent across the years, which means that about 30-50\% of the pre-emptively registered patients also received a deceased-donor kidney pre-emptively. In other words, striving for pre-emptive registration has clear advantages for our patients and is not outweighed by the impact of waiting time on a patient’s ranking on the waiting list.
In summary, we feel that analyzing the timing of the start and the duration of the transplant workup could be of value for every transplant center and that these data should be collected in national or international registries in order to further improve the care we give to our patients with renal failure.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Table 1. Descriptive statistics

|                                      | Total population (n=161) | Start of transplant workup Before start of dialysis (n=69) | After start of dialysis (n=92) | P-value |
|--------------------------------------|--------------------------|----------------------------------------------------------|---------------------------------|---------|
| Median age – years (IQR)             | 53 (43-64)               | 52 (39-61)                                               | 53.5 (45-65)                    | p = 0.16|
| Male - no. (%)                       | 100 (62.1)               | 35 (50.7)                                                | 65 (70.7)                       | p = 0.01|
| BMI - kg/m2 (IQR)                    | 26.3 (23.4-29.5)         | 25.7 (23-29)                                             | 27 (24.5-30)                    | p = 0.065|
| Smoking - no. (%)                    | 14 (8.7)                 | 5 (7.2)                                                  | 9 (9.8)                         | p = 0.78|
| **Primary renal disease**            |                          |                                                          |                                 |         |
| ADPKD - no. (%)                      | 31 (19.2)                | 22 (32.0)                                                | 9 (9.8)                         | p = 0.001|
| Diabetic nephropathy - no. (%)       | 26 (16.15)               | 8 (11.6)                                                 | 18 (19.6)                       | p = 0.17|
| Glomerular disease - no. (%)         | 35 (21.7)                | 14 (20.3)                                                | 21 (22.8)                       | p = 0.7  |
| Hypertensive nephropathy - no. (%)   | 20 (12.4)                | 3 (4.35)                                                 | 17 (18.5)                       | p = 0.0075|
| Tubulointerstitial disease - no. (%) | 17 (10.6)                | 8 (11.6)                                                 | 9 (9.8)                         | p = 0.80 |
| CAKUT - no. (%)                      | 12 (7.4)                 | 7 (10.1)                                                 | 5 (5.4)                         | p = 0.36 |
| Other - no. (%)                      | 6 (3.7)                  | 2 (2.9)                                                  | 4 (4.3)                         | p = 0.70 |
| Unknown - no. (%)                    | 14 (8.7)                 | 5 (7.25)                                                 | 9 (9.8)                         | p = 0.78 |
| **Dialysis modality at waitlisting** |                          |                                                          |                                 |         |
| Hemodialysis - no. (%)               | 92 (57.1)                | 17 (24.6)                                                | 75 (81.5)                       | p = 0.001|
| Peritoneal dialysis - no. (%)        | 46 (28.6)                | 29 (42.0)                                                | 17 (18.5)                       | p = 0.001|
| Not yet treated with dialysis - no.  | 23 (14.2)                | 23 (33.3)                                                | NA                              |         |
| **Comorbidities**                    |                          |                                                          |                                 |         |
| Diabetes mellitus - no. (%)          | 38 (23.6)                | 11 (15.9)                                                | 27 (29.3)                       | p = 0.05 |
| Cardiovascular disease - no. (%)     | 38 (23.6)                | 9 (13.0)                                                 | 29 (31.5)                       | p = 0.006|
| Lung disease - no. (%)               | 36 (22.4)                | 12 (17.4)                                                | 24 (26.1)                       | p = 0.19 |
| Liver disease - no. (%)              | 8 (5.0)                  | 2 (2.9)                                                  | 6 (6.5)                         | p = 0.47 |
| Psychiatric disease - no. (%)        | 25 (15.5)                | 8 (11.6)                                                 | 17 (18.5)                       | p = 0.23 |
| Infection - no. (%)                  | 54 (33.5)                | 17 (24.6)                                                | 37 (40.2)                       | p = 0.057|
| History of malignancy - no. (%)      | 9 (5.6)                  | 2 (2.9)                                                  | 7 (7.6)                         | p = 0.30 |
| **Hospitalization days between start of CKD stage 5 and start of transplant workup - days (IQR)** | 2 (0-11)                | 0.00 (0-0)                                               | 9.00 (2-20)                     | p = 0.001|
| **Psychosocial**                     |                          |                                                          |                                 |         |
| Financial issues - no. (%)           | 33 (20.9)                | 16 (23.2)                                                | 37 (40.2)                       | p = 0.023|
| Insufficient health insurance - no.  | 12 (7.4)                 | 2 (2.9)                                                  | 10 (10.9)                       | p = 0.07 |
| Language difficulties - no. (%)      | 44 (27.3)                | 8 (11.6)                                                 | 36 (39.1)                       | p = 0.001|
| Complete language barrier - no. (%)  | 24 (14.9)                | 5 (7.2)                                                  | 19 (20.6)                       | p = 0.024|
| Non-adherence - no. (%)              | 29 (18.0)                | 9 (13.0)                                                 | 20 (21.7)                       | p = 0.15 |
| **Timing of nephrology care**        |                          |                                                          |                                 |         |
| Median time between first nephrology contact and start of CKD stage 5 - months (IQR) | 41.2 (4.3-87)           | 61.9 (26.8-133.6)                                        | 20.9 (0-65.2)                   | p = 0.001|
| Late referral - no. (%)              | 35 (21.7)                | 5 (7.3)                                                  | 30 (32.6)                       | p = 0.001|
| Start of workup before first access procedure - no. (%) | 51 (31.7)                | 51 (74.0)                                                | NA                              | p = 0.001|
| Median time between start of CKD stage 5 and start of dialysis - months (IQR) | 4.8 (0.6-12)            | 9.6 (3.4-13)                                             | 2.7 (0.1-10.4)                  | p = 0.001|
| **Treating center is renal transplant center - no. (%)** | 36 (22.4)                | 23 (33.3)                                                | 13 (14.1)                       | p = 0.007|

Descriptive statistics of the total population and the two subgroups (those who started the transplant workup before the start of dialysis and those who started after the start of dialysis). All percentages are column percentages. Univariate analysis p-values are presented.

NA = Not applicable.
**Table 2. Multiple logistic regression model**

|                                | Odds ratio | 95% CI for odds ratio | P-value |
|--------------------------------|------------|-----------------------|---------|
| Age at registration on waiting list | 1.0        | 0.97 - 1.04           | 0.979   |
| Sex (1 = male)                  | 0.42       | 0.16 - 1.05           | 0.063   |
| Cardiovascular disease          | 0.44       | 0.13 - 1.46           | 0.179   |
| Diabetes mellitus               | 0.53       | 0.17 - 1.68           | 0.277   |
| Language difficulties           | 0.20       | 0.06 - 0.61           | 0.005   |
| Months between first nephrology contact and CKD 5 | 1.01 | 1.00 - 1.02 | 0.034 |
| Hospitalisation days between CKD 5 and start workup | 0.79 | 0.69 - 0.89 | <0.001 |

Multiple logistic regression model predicting the likelihood of starting the transplant workup before the start of dialysis (dependent variable = starting the transplant workup before starting dialysis). The model classified 81% of cases correctly. The Nagelkerke pseudo R squared was 59%.
Table 3. Descriptive statistics of the workup time in the total population and certain subpopulations

| Description                                                                 | Screening time (months) | P-value |
|----------------------------------------------------------------------------|-------------------------|---------|
| **Total population (n=160)** - months (IQR)                               | 8.6 (5-14)              |         |
| **Excluding pre-emptive waitlisting (n = 137)** - months (IQR)             | 8.7 (5-14)              |         |
| **Excluding cardiovascular disease, diabetes, infections and more than 5**|                         |         |
| hospitalization days during the workup period (n=58) - months (IQR)       | 7.2 (4-11.6)            |         |
| **Timing of the transplant workup**                                        |                         |         |
| • Before start of dialysis (n= 69) - months (IQR)                          | 10 (5-15)               | p = 0.46|
| • After start of dialysis (n=91) - months (IQR)                           | 8 (5-14)                |         |
| **Transplant centre**                                                      |                         |         |
| • Transplant centre (n=36) - months (IQR)                                 | 10 (6 - 19)             | p = 0.211|
| • Non-transplant centre (n = 124) - months (IQR)                          | 8.3 (5-13.4)            |         |

Workup time is calculated as the time between the start of workup and the ultimate registration on the waiting list.
Table 4. Supplementary medical examinations included in the pre-transplant workup

| Examination                                      | Total (n=161) | Clear indication | No clear indication |
|--------------------------------------------------|---------------|------------------|---------------------|
| Invasive urologic examination - no. (%)          | 45 (28)       | 30 (67)          | 15 (33)             |
| Gastroscopy - no. (%)                            | 88 (55)       | 55 (63)          | 33 (38)             |
| Colonoscopy - no. (%)                            | 109 (68)      | 105 (96)         | 4 (4)               |
| Ultrasound of the carotid arteries - no. (%)     | 14 (9)        | 5 (36)           | 9 (64)              |
| At least one examination without clear indication - no. (%) | 50 (31) |                  |                     |

Frequency of certain pre-transplant examinations and whether or not a clear indication was found (medical or based on screening guidelines 20). First column: percentages of total. Second and third column: percentages of value in first column (horizontal percentage).
Simple and multiple regression analysis for a variety of patient-derived independent variables and the logarithmically transformed workup time. Our multiple regression model included sex, age, infections, hospitalisation days and lung disease and explained 16.5% of the total variance in workup time, $F (5,151)=5.962$, $p<0.001$. After conversion of the logarithmic scale to the original time value, we can conclude that for every extra hospitalisation day, the workup time increased with 3% or 0.9 days.

$B =$ unstandardized regression coefficient. $SE =$ Standard error. $Exp(B)$ indicates the exponentiation of $B$ ($10^B$) to reverse the logarithmic scale into the original time measured in months.

| Comorbidities | Simple linear regression | Multiple linear regression |
|---------------|-------------------------|---------------------------|
|               | B          | SE       | p-value | Exp(B) | B       | SE   | Beta  | p-value | Exp(B) |
| Age           | 0.001     | 0.002    | 0.436   | 1.0    | 0.001   | 0.002| 0.058 | 0.467   | 1.0    |
| Sex (1=male)  | 0.063     | 0.050    | 0.204   | 1.16   | 0.062   | 0.050| 0.099 | 0.219   | 1.15   |
| Body Mass Index | 0.010   | 0.006    | 0.092   | 1.02   |         |      |       |         |        |
| Comorbidities |           |          |         |        |         |      |       |         |        |
| Cardiovascular disease | 0.040  | 0.057    | 0.480   | 1.1    |         |      |       |         |        |
| Diabetes mellitus | -0.011 | 0.057    | 0.845   | 0.97   |         |      |       |         |        |
| Lung disease   | 0.119     | 0.057    | 0.041   | 1.32   | 0.087   | 0.055| 0.119 | 0.120   | 1.22   |
| Liver disease  | 0.180     | 0.110    | 0.105   | 1.51   |         |      |       |         |        |
| History of malignancy | -0.170 | 0.104    | 0.105   | 0.68   |         |      |       |         |        |
| Psychiatric disease | 0.014  | 0.067    | 0.840   | 1.03   |         |      |       |         |        |
| Infection between start of CKD 5 and registration on the waiting list | 0.153  | 0.050    | 0.003   | 1.42   | 0.087   | 0.051| 0.134 | 0.090   | 1.22   |
| Non-adherence  | 0.073     | 0.063    | 0.247   | 1.18   |         |      |       |         |        |
| Language difficulties | 0.057  | 0.054    | 0.295   | 1.14   |         |      |       |         |        |
| Financial issues | 0.095  | 0.051    | 0.066   | 1.24   |         |      |       |         |        |
| Number of extra exams | 0.034  | 0.024    | 0.157   | 1.08   |         |      |       |         |        |
| Hospitalisation days between start of workup and registration | 0.015  | 0.003    | <0.001  | 1.04   | 0.013   | 0.004| 0.390 | <0.001  | 1.03   |
| Haemodialysis (vs. PD or not yet on dialysis) | 0.037  | 0.050    | 0.465   | 1.09   |         |      |       |         |        |

Simple and multiple regression analysis for a variety of patient-derived independent variables and the logarithmically transformed workup time. Our multiple regression model included sex, age, infections, hospitalisation days and lung disease and explained 16.5% of the total variance in workup time, $F (5,151)=5.962$, $p<0.001$. After conversion of the logarithmic scale to the original time value, we can conclude that for every extra hospitalisation day, the workup time increased with 3% or 0.9 days. $B =$ unstandardized regression coefficient. $SE =$ Standard error. $Exp(B)$ indicates the exponentiation of $B$ ($10^B$) to reverse the logarithmic scale into the original time measured in months.
Table 6. Summary of the variables that were independently associated with a delayed start of the workup or a prolonged workup

| Variables delaying the start of the workup | Modifiable? | Suggested actions |
|------------------------------------------|-------------|-------------------|
| Language difficulties                     | Yes         | Stimulate patients to learn the local language
|                                          |             | Have interpreters readily available during the pre-transplant process. |
|                                          |             | Use technological tools providing accessible multilingual education |
| Months between first nephrology contact and start of CKD stage 5 | No          | Timely referral of CKD patients to the nephrologist as according to published guidelines |
| Hospitalization days between start of CKD stage 5 and start of the workup | No          | Timely start of the transplant workup (minimum of 6 months before estimated start of dialysis) to avoid delay of workup initiation due to kidney failure-related complications. |

| Variables prolonging the workup |
|--------------------------------|
| Hospitalization days between start of workup and registration | No | Timely start of the transplant workup to avoid prolonging the workup duration due to kidney failure-related complications. |
201 patients registered on the renal transplant waiting list between 1 Jan 2016 and 12 Nov 2019

- Patients with a previous renal allograft (n=24)
- Younger than 18 years old (n=9)
- Patients transferred from a different transplant centre (n=4)
- Insufficient data (n=3)

161 patients were included for analysis

Figure 1. Exclusion process
Figure 2. Proportion of patients that started the transplant workup and were registered on the waiting list before the start of dialysis.