Aus der Klinik für Nephrologie und Internistische Intensivmedizin
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Renal Transplantation in Patients with Migration Background and Native-born German Patients: Differences in Setting, Outcome and Compliance

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Malte D. Joswig

aus Berlin

Datum der Promotion: 05.12.2014

Table of Contents

LIST OF ABBREVIATIONS

AUC	area under the receiver operating characteristic curve
BKV	human polyomavirus
BMI	Body mass index
BP	Blood pressure
CAPD	Continuous Ambulatory Peritoneal Dialysis
CI	Confidence interval
CIT	Cold ischemia time
CKD	Chronic kidney disease
CMV	cytomegalovirus
Cox PH-Model	Cox proportional hazard model
CVK	Campus Virchow-Klinikum
DBD	Donation after brain death
DCD	Donation after cardiac death
DGF	Delayed graft function
e.g.	exempli gratia
EBV	Epstein-Barr virus
ECD	Extended criteria donor
ECS	Essener Compliance Score
eGFR	Estimated glomerular filtration rate
ESP	European Senior Program
ESRD	End-stage renal disease
ET	Eurotransplant

GFR	Glomerular filtration rate
HLA	human leukocyte antigen
ISCED	International Standard Classification of Education
OPTN	Organ Procurement and Transplant Network
OR	Odds ratio
PMB	Patients with migration background
PMH	Patienten mit Migrationshintergrund
PTDM	posttransplant diabetes mellitus
RR	Relative risk
SCD	Standard criteria donor
SD	Standard deviation
SRTR	Scientific Registry of Transplant Recipients
TAG	triglyceride
Tx	Transplantation
UK	United Kingdom
UNESCO	United Nations Educational, Scientific and Cultural Organization
US$	US-Dollar
USA	United States of America
UTI	Urinary tract infections
WHO	World Health Organization
yr	years

List of Figures

List of Tables

Abstract

Background: Socioeconomic factors, compliance, and impaired access to the health care system are major factors influencing renal transplantation (RTx) outcome among ethnic minorities. The importance of migration background needs to be clarified in this context. This study investigated, for the first time in Germany, renal transplantation in patients with migration background (PMB; n = 86) and native-born German patients (n = 1180) in a single center study with an observation period from January, 1997 to March, 2011. Numerous determinants of the RTx itself, waiting time and the RTx outcome were analyzed and, as the first study in this context, adherence to the medical regimen was assessed.

Methods: The pre-, peri-, and posttransplant data of patients who underwent renal transplantation were retrieved from an electronic database (TBase 3.0) and analyzed in retrospect. Data about compliance, ancestry and origin, education, employment and language skills were assessed with a questionnaire.

Results: The results show a better outcome for PMB compared to native-born German patients, with significantly better graft function (creatinine, GFR) and fewer graft losses (4.7% vs. 13.2%).

Equal rates of rejection, with first year rejection rates of 39.5% and 35.8% in PMB and native-born German patients, respectively, with shorter rejection-free survival among PMB were demonstrated ($p < 0.01$). Rejections were mostly borderline changes (36.8%) and rejections graded as I (37.2%).

The results show a trend toward longer waiting times among PMB (median of 72 vs. 56 months, after adjustment $p = 0.04$). Overall mismatches, HLA-A and HLA-B mismatches were significantly greater for PMB ($p < 0.05$).

Demographic data demonstrated a younger cohort of PMB (43 yr), compared to the group of native-born German patients (48 yr; $p = 0.001$). Though more PMB have a university degree, in general, education of PMB was inferior.

PMB showed a larger number of patients with a high compliance score and smaller number of patients with a medium or low compliance score, although the data did not reach statistical significance. This observation was confirmed by a significantly larger

number of visits to the outpatient department by PMB as another indicator of compliance.

Discussion: Despite longer waiting time on dialysis and poorer HLA-match associated with a shorter rejection-free survival, PMB population showed a better outcome with regard to the graft function and posttransplant complications. The results were confirmed after age-adjustment. Although not completely clear, the better outcome can be explained by the better therapy adherence found in the PMB group.

Abstrakt

Hintergrund: Sozioökonomische Faktoren, Compliance und erschwerter Zugang zum Gesundheitssystem gelten als Haupteinflussfaktoren auf das Resultat (Outcome) nach Nierentransplantationen (NTx) bei Patienten mit Migrationshintergrund.

Die vorliegende Studie untersuchte erstmals in Deutschland Nierentransplantationen bei Patienten mit Migrationshintergrund (PMH; n = 86) im Vergleich zu deutschstämmigen Patienten (n = 1180) an der Charité, Campus Virchow-Klinikum, über einen Zeitraum von Januar 1997 bis März 2011. Neben Parametern der Transplantation, wurden Wartezeit, Outcome der NTx, sowie, als erste Studie in diesem Kontext, die Compliance analysiert.

Methoden: Daten der Patienten wurden von der elektronischen Datenbank (TBase 3.0) abgefragt. Prä-, Peri-, und Posttransplantationsdaten wurden retrospektiv ausgewertet. Informationen über Compliance, Herkunft und Migrationshintergrund, Ausbildung, Beruf und Sprachfähigkeiten wurden über einen Fragebogen erfasst.

Ergebnisse: Die vorliegenden Ergebnisse zeigen ein besseres Outcome der PMH bezüglich signifikant besserer Transplantatfunktion (Kreatinin, GFR) und geringerem Transplantatversagen bei den PMH (4,7%) im Vergleich zu deutschstämmigen Patienten (13,2%). Ferner unterschieden sich die Abstoßungsraten während des ersten Jahres nach NTx in der PMH-Gruppe (39,5%) und bei deutschstämmige Patienten (35,8%) nicht signifikant ($p > 0,1$), hingegen waren kürzere abstoßungsfreie Zeitintervalle der PMH-Gruppe nachweisbar ($p < 0,01$). Insgesamt fanden wir überwiegend leichte Abstoßungen mit Borderline-Abstoßungen (36,8%) und Grad I (37,2%) ohne signifikante Gruppenunterschiede. Die mediane Anzahl aller Mismatches,

der HLA-A, sowie der HLA-B Mismatches waren signifikant höher bei Transplantationen der PMH ($p < 0,05$).

Weiter zeigen die Ergebnisse eine signifikant jüngere Kohorte der PMH im Vergleich zu den deutschstämmigen Patienten (Mittelwert 43 bzw. 48 Jahre, $p = 0.001$). Obwohl mehr PMH einen Hochschulabschluss erzielten, wiesen insgesamt die PMH ein geringeres Bildungsniveau auf.

Die Ergebnisse zeigen einen Trend zu längeren Wartezeiten der PMH (Median: 72 vs. 56 Monate, $p = 0,07$, nach Alters- und Geschlechtsadjustierung $p = 0,04$). Mehr PMH zeigten einen höheren und weniger einen mittleren und niedrigen Essener Compliance Score, wobei die Ergebnisse keine statistische Signifikanz erreichten. Diese Beobachtung wurde durch höhere Compliance bezüglich einer signifikant höheren Zahl von Besuchen der PMH in unserer Transplantationsambulanz im Vergleich zur Gruppe deutschstämmiger Patienten bestätigt.

Diskussion: Trotz längerer Wartezeit in Dialyse und geringerer HLA-Übereinstimmung, beides bekannterweise assoziiert mit kürzerem abstoßungsfreiem Transplantatüberleben, zeigte die PMH Gruppe ein besseres Outcome hinsichtlich Transplantatfunktion und Komplikationen nach NTx im Vergleich zu deutschstämmigen Patienten. Diese Ergebnisse wurden nach Altersadjustierung bestätigt. Dieses Resultat kann vermutlich durch eine bessere Therapietreue in der PMH Gruppe erklärt werden und sollte mittels weiteren Studien zu Compliance bestätigt werden.

1 Introduction

This single center study presents data on waiting time, outcome and compliance after primary renal transplantation or retransplantation in patients with migration background (PMB) and native-born German patients transplanted between 1997 and 2011 at the Charité Medical Faculty of the Humboldt University of Berlin - Campus Virchow-Clinic.

1.1 Background

1.1.1 Chronic and end-stage renal disease

Chronic kidney disease (CKD) is defined as existing kidney damage commonly discovered by albuminuria described as albumin-to-creatinine ratio of > 30 mg/g in two of three spot urine specimens, or CKD is defined as diminished kidney function with a glomerular filtration rate (GFR) of ≤ 60 mL/min/1.73 m² (Levey et al., 2005). This state of kidney damage or diminished kidney function has to persist over three or more months to be defined as chronic (Levey et al., 2005).

A comprehensive epidemiologic study conducted in the United States shows a prevalence of 1.7 percent among American citizens (4.2 million) in 1990, with at least two elevated creatinine measurements separated by a minimum of 90 days, suggesting chronic kidney disease (Nissenson, Pereira, Collins, & Steinberg, 2001). To our knowledge, there is no representative study or data about the epidemiology of CKD in Germany. However, there is currently an epidemiologic study on the way, investigating CKD in Germany (Schaeffner, personal communication).

Kidney failure is defined as severely reduced kidney function with a GFR of < 15 mL/min per 1.73m², which usually needs treatment with dialysis or transplantation. This state is generally referred to as end-stage renal disease (ESRD) (Levey & Coresh, 2012). The prevalence of end-stage renal disease is 1,738 per million population in the United States, while diabetes and hypertension are responsible for 44 and 27.9 percent of all cases of new onset ESRD, respectively ("U S Renal Data System," 2011).

1.1.2 End-stage renal disease and dialysis

Early detection of chronic kidney disease is essential to prevent serious and uremic complications like bleeding, depression, cognitive impairment, malnutrition, peripheral

neuropathy, increased susceptibility to infections, infertility, serositis and fluid overload ("Clinical practice guidelines for hemodialysis adequacy, update 2006,"). Generally, initiation of dialysis therapy is considered at a GFR less than 15mL/min/1.73², which is defined as chronic kidney disease stage 5 ("Clinical practice guidelines for hemodialysis adequacy, update 2006,"). However, there are many other factors to be considered besides plain kidney function. Certainly, patient preference and quality of life must be discussed, but also accessibility of dialysis, age, compliance and strain on patient, family and society during dialysis have to be considered.

Dialysis is adequate if provided three times per week for 2.5 to 4.5 hours, while more frequent dialysis did not show an increased benefit (Eknoyan et al., 2002). Nevertheless, another study reported a significant decline of left ventricular hypertrophy and hyperphosphatemia in patients averaging 5.2 dialysis sessions per week (Chertow et al., 2010). Among other aspects, the relatively small number of patients in the latter study (Frequent Hemodialysis Trial: n = 125 six times per week vs. n = 120 three times per week) reveals the need for further investigation.

In 2003, in the USA, after a decade of stagnancy in the first-year death rates of patients with ESRD, in the years 2004 through 2008 there has been an improvement of more than 10 percent ("U S Renal Data System," 2011). Nevertheless, lethality after the first three years of ESRD-therapy is still 50 percent with dialysis treatment, while cardiovascular disease is the main cause of death ("U S Renal Data System," 2011). The current adjusted rates of all-cause mortality are thus 6.5 to 7.4 fold higher compared to the general population ("U S Renal Data System," 2011).

In Germany, in 2006, 66,508 patients were under dialysis therapy (prevalence of 808 per million), whilst 25,210 patients were undergoing monitoring after a renal transplantation (Frei & Schober-Halstenberg, 2008). 27 percent of patients under renal replacement therapy received a renal transplant (Frei & Schober-Halstenberg, 2008). In 2006, the mortality rate in Germany amounted to 11,608 patients of 66,508 patients on dialysis (Frei & Schober-Halstenberg, 2008). Currently, there are 90,000 patients receiving dialysis therapy (Schulz & Thaiss, 2012).

High costs of dialysis limit its availability worldwide. Data from the United States Renal Data System show Medicare payments in the USA in 2008 of 77,506 US$ for

haemodialysis and 57,639 US$ for peritoneal dialysis, while payments for renal transplantation were 26,668 US$ per person per year ("U S Renal Data System," 2011).

In Germany, in 2006, mean overall dialysis-related costs were 54,777€ per patient year, while almost 90 percent of patients under dialysis received haemodialysis therapy (Icks et al., 2010).

1.1.3 Renal transplantation

It is widely accepted that renal transplantation is the most effective therapy for end-stage renal disease (ESRD). After successful transplantation, patients' quality of life improves (Dew et al., 1997; Laupacis et al., 1996; Liem, Bosch, Arends, Heijenbrok-Kal, & Hunink, 2007) and the mortality risk diminishes ("U S Renal Data System," 2011; Wolfe et al., 1999). Additionally, the socio-economic burden on society is lighter in terms of costs per patient (Laupacis et al., 1996; "U S Renal Data System," 2011).

1.1.3.1 First steps on the way to a new organ – planning, waiting times and Eurotransplant

Kidney transplantation should be considered as treatment of choice for patients suffering irreversible advanced chronic kidney disease CKD (Bunnapradist & Danovitch, 2007). In addition, patients should be included in a transplant program (e.g., Eurotransplant) if their GFR is less than 30 mL/min/1.73m² (Bunnapradist & Danovitch, 2007) and their medical condition allows them to receive an allograft.

Although transplantation is the best therapy for ESRD, it is limited by the number of donated transplants. In Europe, it is, among others, the Eurotransplant International Foundation (Eurotransplant (ET)) which coordinates distribution of transplants throughout its member countries: Austria, Belgium, Croatia, Germany, Luxembourg, the Netherlands and Slovenia. In 2011, 2,068 kidneys were transplanted in Germany, and 3,630 kidneys in all member countries combined, while 7,573 patients in Germany were still on the waiting list for a renal transplant at the end of the year (Oosterlee & Rahmel, 2012). Median waiting time for a renal transplant in member countries of Eurotransplant was about 42 months in 2011, also illustrated in table 1 (Oosterlee & Rahmel, 2012, p. 44).

Patients who receive a renal transplant from a deceased donor have a worse prognosis compared to recipients who receive an organ from a living donor (Arend, Mallat, Westendorp, van der Woude, & van Es, 1997). In 2011, 1,339 (36.9 percent) and 795 (38.4 percent) of the transplantations were carried out using living donor kidney transplants in the member countries of the ET and Germany, respectively (Oosterlee & Rahmel, 2012, p. 64).

Waiting time (months) based on date start of dialysis	2010 Tx in ET	2011 Tx in ET	2010/2011 Tx in ET	2011 Tx in Germany
Pre-emptive	44	78	77.3%	25
0-5	44	39	-11.4%	13
6-11	101	107	5.9%	47
12-23	401	433	8.0%	192
24-59	1358	1351	-0.5%	598
60+	1474	1293	-12.3%	991
Total	3422	3301	-3.5%	1866

Table 1 Waiting time for kidney-only transplants of all allocation programs of ET, as adopted from Oosterlee and Rahmel (2012).

ET – Eurotransplant; Tx – transplantation

In 2011, mortality of patients in Germany on the ET waiting list was 4.9 percent (370 deaths per 7,573 patients on the waiting list) (Oosterlee & Rahmel, 2012, p. 47).

1.1.3.2 Complications

1.1.3.2.1 Patient survival

Patient survival depends on a variety of factors. A cumulation of mortality during the first year posttransplant could be shown for patients over the age of 40, deceased donor recipients, patients with hypertension or diabetes, men, and smokers (Arend et al., 1997).

In Germany, in 2011, one-year and three-year patient survival was 96.4 percent and 91.1 percent, respectively (AQUA-Institute, 2012).

In the USA, current patient survival in dialysis is as follows: five-year survival is 0.35 for patients on hemodialysis, 0.41 for patients on peritoneal dialysis, and 0.73 for transplanted patients ("U S Renal Data System," 2011).

1.1.3.2.2 Immunologic complications: acute rejections, graft failure and infections

The incidence of acute rejections in the course of the first year after transplantation is 11 percent for deceased, and 10 percent for living-donor recipients, for patients transplanted in the year 2009, according to the United States Renal Data System Annual Data Report of 2012 ("U S Renal Data System," p. 284). The incidence of acute rejections has decreased continuously over recent decades from about 50 percent in 1998 to 20 percent in the year 2001 and 11 percent in 2009, three-fourths of the rejections being confirmed by biopsy ("U S Renal Data System," 2012, p. 289). In 2009, the probability of a graft failure within 10 years posttransplant was 0.39 and 0.56 in patients with a living-donor and a deceased-donor allograft, respectively ("U S Renal Data System," 2012, p. 289).

In Germany, graft survival after the first and third year posttransplantation is currently 94.5 percent and 89.3 percent, respectively. The incidence of acute rejections requiring therapy is to date in Germany 13.5 percent during the first year posttransplant (AQUA-Institute, 2012, p. 29).

A very recent study compared kidney graft survival between Europe, including numerous transplant centers in Germany, and the United States. Gondos and colleagues demonstrate an equal survival for deceased-donor grafts of 91 percent after the first year post transplantation (2012). However, five and ten years after transplantation graft, survival rates were higher for European recipients (77 and 56 percent, respectively) compared to the three populations studied in the United States (whites, 71 and 46 percent, Hispanic, 73 and 48 percent, and African American, 62 and 34 percent (Gondos et al., 2012)).

To improve graft survival and reduce acute and chronic allograft rejections, adequate immunosuppressive therapy is fundamental. Immunosuppressive therapy has seriously

improved the incidence of graft rejection but has increased the risk of opportunistic infections and cancer.

Important infections often transmitted with the graft (Kotton, Fishman, Kotton, & Fishman, 2005), or already present in the recipient, include cytomegalovirus (CMV) and Epstein-Barr virus (Fishman, 2007). Especially CMV disease is a substantial cause of morbidity, mortality and cost after renal transplantation (Schnitzler et al., 2003).
Urinary tract infections (UTI) are the most frequent bacterial infection in renal transplant recipients (de Souza & Olsburgh, 2008). Circumstances that effect accumulation of UTI posttransplant are immunosuppression and manipulation of the urinary tract (e.g., urethral catheters and ureteric stents) (de Souza & Olsburgh, 2008).

1.1.3.2.3 Non-immunological complications: cardiovascular disease, diabetes, and bone metabolism

Cardiovascular disease is the leading cause of death among renal graft recipients (Ojo et al., 2000; "U S Renal Data System," 2011). Hypertension is one of the most important factors provoking cardiovascular disease. Further, hypertension itself is a risk factor for graft failure (Opelz, Wujciak, & Ritz, 1998).

Diabetes is one of the major causes of ESRD. Moreover, new onset diabetes mellitus is a common disease to develop in ESRD and especially after transplantation, then referred to as posttransplant diabetes mellitus (PTDM) (Woodward et al., 2003). Diabetes is a well-known risk factor for cardiovascular disease.
Principal factors to provoke PTDM are the use of steroid-based immunosuppression, but other pathophysiological factors, including calcineurin inhibitors as part of immunosuppressive therapy also provoke PTDM (Woodward et al., 2003).

Impaired bone metabolism is a frequent complication in patients with a renal transplant. Bone disease includes phosphate retention, secondary hyperparathyroidism, aluminum osteomalacia [beta]2-associated amyloidosis and diabetic osteopathy (Heaf, 2003).

1.1.3.3 Adherence or compliance

Adherence to, or compliance with, a medication regimen usually refers to the extent to which patients take the medications as prescribed by the health care provider. Among

patients with chronic diseases, trials suggest adherence rates so not excede 43 to 78 percent to the prescribed medication (Osterberg & Blaschke, 2005).

Noncompliance is an important factor influencing graft function in some patients. A systematic literature review in 2004 (Butler, Roderick, Mullee, Mason, & Peveler) demonstrated a meta-analysis by which a median of 22 percent of transplant recipients were nonadherent and graft loss was seven times more probable in nonadherent compared to adherent subjects. Butler et al. (2004) stated that a median of 36 percent of renal graft losses correlated with prior nonadherence. Another study (Vlaminck 2004) reported a 3.2 fold greater risk of late acute rejections among nonadherent patients compared to adherent patients in a prospective study (n = 146) during a 5-year period.

Adherence to a medication regimen is difficult to assess, be it due to a lack of a universal definition of what is adequate adherence (>80 percent or >95 percent), or to the lack of an omnipresent, gold standard method to measure adherence to a therapy (Osterberg & Blaschke, 2005). Though there are difficulties in evaluating compliance to a therapy, it seems obvious that nonadherence has a significant impact on graft survival.

1.1.4 Health insurance in Germany and the United States

Since 2007, every citizen in Germany it is mandated by law to be covered by health insurance. In 2011, 99.8 percent of the German population was covered by health insurance and 0.2 percent (137.000) was without health insurance (Herter-Eschweiler, 2012). This excellent access to the health care system also assures citizens with a low income equal coverage. In other countries, for example the United States, the situation is considerably different. In the United States, health insurance for transplant patients under 65 of age without disabilities is mostly provided by Medicare (Fan et al., 2010). For these patient groups, however, the Medicare program does not cover immunosuppression medications for more than three years after transplantation which leads to graft failure and a resumption of dialysis for those who cannot afford treatment (Page & Woodward, 2009). Evaluating outcome after renal transplantation in Germany and the United States, one has to consider these differences between the different health care systems.

1.1.5 Migration in Germany

The number of renal transplantations grew dramatically over recent decades, while human mobility and migration have been increasing as well: Especially in countries and cities with a high number of immigrants, sociocultural factors, race, ethnicity, and decreased proficiency in the spoken language are important factors influencing healthcare and are discussed in various studies (Berger, 2012; Einbinder & Schulman, 2000).

Almost 16 million inhabitants of Germany, nearly 20 percent of Germany's population, have a migration background (*Migration Report 2010*, 2011). Residents with migration background are defined persons who immigrated to Germany after 1949, or were born in Germany as foreigners, or at least one of whose parents immigrated to Germany after 1949 (*The Federal Statistical Office*, 2007).

These details illustrate the great importance of investigation on this field and in the field of medical health care and migration. There is a growing body of evidence that the health status of inhabitants with migration background differs on many levels to the one of "native-born German citizens" and correlates in some aspects with an increased risk for health impairment (*The Federal Government*, 2010; Kohls, 2011; Razum et al., 2008). Although residents with migration background have a decreased mortality at the age of 20 to 60 years compared to German citizens, the statistics change at the age above 60, where mortality increases with a migration background (Kohls, 2011).

1.2 Hypotheses

1.2.1 Primary hypothesis

In the first foremost hypothesis, it was supposed that there are differences in outcome, especially with reference to kidney graft function, acute graft rejections, graft survival and transplant age, between patients with migration background (PMB) on the one hand and native-born German patients on the other, in the outpatient department of transplant medicine at the Charité Medical Faculty of Berlin - Campus Virchow-Clinic.

1.2.2 Second hypothesis and sub-hypothesis

The second main hypothesis of this study was a longer waiting time in the cohort of PMB than waiting time in the group of native-born German patients. Circumstances leading to this might be the effect of the following: inhabitants with migration background may have a higher threshold to discuss and address the question of transplantation as a result of difficulties with the German language and greater barriers in dealing with the German health care system. Hence, patients with migration background conceivably are longer in dialysis without being listed at the Eurotransplant waiting list.

The first sub-hypothesis was that human leukocyte antigen (HLA) matching might be lower in the cohort of PMB. It can be explained by slightly different genetic background between the population of residents with migration background and the majority of inhabitants and therefore donors of the member countries of Eurotransplant. Consequently there would be greater difficulties to find a perfect matched graft, or the HLA match would be slightly lower.

1.2.3 Third hypothesis and sub-hypothesis

The third main hypothesis of this study was a possible difference in compliance between our cohort of PMB and native-born German patients. Rationale for this could be found in different life-styles of persons with migration background or native-born Germans. Difficulties to communicate with the health care providers and psychological barriers between the inhabitants with migration background and the German health care system could be further reasons for a difference in compliance.

The second sub-hypothesis was to find different metabolic parameters including their complications. This can be substantiated by a different life-style and diet (e.g., Mediterranean diet).

2 Methodology

2.1 Data Collection

The data of patients who underwent primary renal transplantation or re-transplantation between January 1st, 1997 and March, 2011 at the Charité Medical Faculty of Berlin - Campus Virchow-Clinic were retrieved from an electronic health record database. Data were collected during the episode prior to transplantation, the peri- and the posttransplant phase. During the posttransplant phase, data were assessed at routine controls in the transplant outpatient clinic every week to every 3 months, depending on the time elapsed from transplantation. An observation, retrospective analysis of this data was performed to evaluate, compare and contrast the outcome of patients with migration background (PMB) and German patients after renal transplantation.
The database used in the study, "TBase 3.0", contains all medical data of all patients transplanted and treated at the Charité, Campus Virchow-Clinic, since 1997 and consists of over 4000 patients.

Prospectively, data about patient compliance, ancestry and origin, language skills and education were collected and assessed.

2.1.1 Retrospective Analysis

2.1.1.1 Pre-transplant phase

In retrospect, the following data regarding the pre-transplant period was evaluated: waiting time as time interval between first dialysis and time of transplantation. Further analyzed were the time period between first dialysis and registration at Eurotransplant International Foundation (Eurotransplant) and time period between registration at Eurotransplant and date of transplantation. Moreover, the present study assessed age and gender of donor and recipient, cause of end-stage renal failure and previous transplantations.

2.1.1.2 Peri-transplant phase

Data mentioned below were examined regarding the peri-transplant phase: human leukocyte antigen (HLA) mismatch, panel-reactive antibody levels, percentage of living donations, percentage of kidneys from a deceased donor, cold ischemic, mixed

ischemic and warm ischemic time, days of hospitalization after transplantation and amount of antihypertensive and diabetic medication.

2.1.1.3 Posttransplant phase

The following data concerning the posttransplant course were analyzed: patient and graft survival, biopsy-proven acute rejection episodes, rejection-free survival, type of immunosuppressive treatment and concentration of immunosuppressive drugs, number of visits in the outpatient department per year and body mass index (BMI). Also assessed were biochemical blood data in follow-up that included creatinine, creatinine clearance, proteinuria, hemoglobin, parathormone, calcium, phosphor, uric acid, C reactive protein, hemoglobin A1c (HbA1c - glycohemoglobin), triglyceride (TAG) and cholesterol. The incidence of viral reactivations such as Cytomegalovirus (CMV), human polyomavirus (BKV), Epstein-Barr virus (EBV) and urinary tract infections were also evaluated. Blood pressure was also analyzed.

The incidence and severity of acute rejections were also studied. Episodes of acute rejection were proven by biopsies, histologic evaluation were performed according to the Banff diagnostic categories.

2.1.2 Prospective Analysis

This study prospectively evaluated the patient's compliance using the "Essener Compliance Score" questionnaire (Franke et al., 2009; Joswig et al., *manuscript submitted*). In addition to the 18 items of the ECS, 11 items about ancestry and origin, education, employment and language skills were added. Patients who were easily able to complete the questionnaire by themselves, or were accompanied by their elders who could translate and help where necessary were asked to do so in the outpatient department during their visits. Patients who did not have the opportunity to complete the questionnaire during a visit were interviewed by telephone. Language barriers during the interview, if any, were easily solved by translating into other languages (English or Spanish) or by help of a patients' family member who could translate into the native language.

2.1.2.1 Language skills

The German language skills of PMB were evaluated on the basis of a self-estimation by the patients. In the questionnaire PMB were asked to describe their German language competence on a scale from “no German skills” over “basic knowledge”, “satisfactory German skills”, “good German skills”, “very good German skills” to “native German speaker”.

2.1.2.2 The Essener Compliance Score

The ECS contains 18 items including detailed questions about medication-taking habits and knowledge about the medication (Franke et al., 2009; Joswig et al., *manuscript submitted*). To reply to the multiple choice questions patients could choose between five answers on an ordinal scale to each question. The ECS provides us with a classification of patients with high, medium or low compliance after a cumulative analysis of the scores of each item.

2.1.2.3 Education and Employment

Patients were asked to state whether they completed high school and further education to assess differences in education between the group of patients with migration background (PMB) and native-born German patients. Having a tripartite school system, degrees of school education were as following: “no school-leaving certificated” as the lowest level of education (< 9 years of high school without a school-leaving certificate); school-leaving certificate from the so-called “Hauptschule”, a secondary modern school up to nine or ten years of education providing lower secondary education (Level 2) according to the International Standard Classification of Education (ISCED) by the United Nations Educational, Scientific and Cultural Organization (UNESCO); degree from the so-called “Realschule”, a secondary modern school from fourth, fifth or seventh grade to tenth grade; and the so-called “Abitur”, which is the degree awarded by a “Gymnasium”, after at least 12 or 13 years of education providing advanced secondary education which permits individuals to attend university.

Additionally, further education beyond high school like apprenticeship or vocational training and university degree was assessed. Also evaluated were degrees awarded by

universities of applied sciences, the German “Fachhochschule”, a university with focus on special fields whose degree is comparable to a universities degree.

The current or latest profession of patients was classified in three groups to assess occupational differences. The groups were formed depending on the necessity of an apprenticeship/vocational training or a college degree to be able to perform that occupation, or jobs, in group three, that don’t require an education beyond high school.

2.2 Study Design and Population

The present study is a single-center study comparing retro- and prospective data of patients with migration background in the experimental group to a control group of transplanted patients of German descent.
The retrospective analysis of data regarding the pre-, peri-, and posttransplant period of the 86 patients (7 percent) in the experimental group was compared to the data of 1180 patients (93 percent) of native-born German patients.

The prospective analysis of data about compliance, education, employment and language skills was compared between 57 PMB and a control group of 60 native German patients.

Adapted from the definition of the German census of 2005, patients were classified as immigrants if they were not German citizens, if they were born in a country other than Germany, or if they or at least one of the two parents immigrated to Germany after 1949.

2.3 Statistical Analysis

Parameters which represent directly the kidney function (creatinine, creatinine clearance), metabolism (HbA1C, cholesterol, PTH) and blood pressure were frequently checked during visits in the transplant outpatient clinic. Experience in the outpatient department showed that these parameters are normally distributed in each patient when comparing the measurements throughout a year. To impede the influence of outliers of a patient on data of the whole group, the median measurement of these checks were documented.
Continuous variables are demonstrated as mean ± standard deviation (±SD; normal

distribution) or median plus 25 and 75% percentile (not normally distributed). Categorical variables are shown as percentage of the patient population. The Student's t-test (t-test) were used to analyze continuous variables with normal distribution and the Wilcoxon test (Mann-Whitney U test) for not normally distributed variables. Fisher's exact test was applied to test for statistical differences within categorical variables.

Variables were adjusted for age and for gender, where necessary, to exclude bias. These p-values are in the following called p.adjust.

Statistically significant was considered any *p*-value ≤ 0.05. *P*-values of 0.05 – 0.1 were considered as a statistical trend. All analyses were performed using SPSS version 20. Box plots are demonstrated with median and interquartile range.

3 Results

3.1 Patient Population

There were 1266 patients available for analysis. 1180 (93 percent) of these were native-born German patients and 86 (7 percent) were patients with migration background (PMB).

Characteristics of both cohorts are listed in table 2. Most aspects of the two groups were similar. Interestingly, patients with migration background were significantly younger at date of transplantation than native-born German patients (mean ± SD: 43.16 ± 12 and 47.82 ± 13 years, respectively, p = 0.001, t-test) as shown in table 2. In addition, transplant age of patients with PMB was significantly shorter than the transplant age of German patients.

Patient group Patient characteristics	**Patients with migration background (PMB) n = 86**	**Native-born German patients n = 1180**
Age at tx (mean; range; years)	43 (18-70) **	48 (8-78)
Gender (female)	39.5%	41.4%
Dialyses (CAPD)	2.3%	4.8%
Waiting time pre-transplant (months)	64.0 (0-146)	56.77 (0-251)
Type of graft (living donation)	20.9%	17.9%
Second-/Third transplant	10.5%/1.2%	12%/ 1.8%
Transplant age (months)	56 (1-154) *	76 (1-168)

Table 2 Clinical characteristics of patients enrolled in the study.

* Significant differences between PMB and native-born German patients ($p < 0.05$)

** Highly significant differences between PMB and native German patients ($p < 0.01$; t-test)

CAPD – Continuous Ambulatory Peritoneal Dialysis, tx – transplantation

3.1.1 Origin and language skills

Analysis of origin revealed that patients with Turkish background formed by far the major population group in the PMB cohort with 18 patients (32 percent (of return of questionnaire)) as demonstrated in figure 1. The second largest group of PMB were born in Poland (4 patients (7 percent)) followed by the group of patients born in countries of the former Soviet Union.

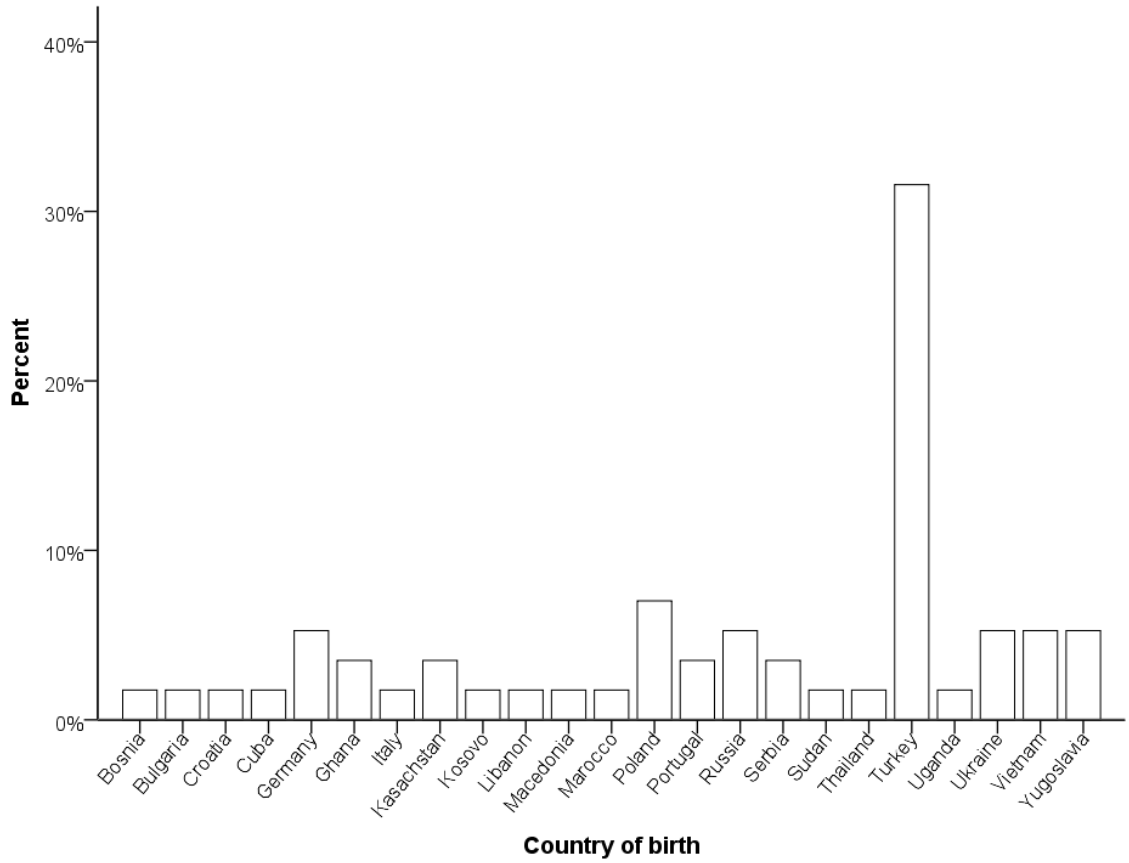

Figure 1 Origin of patients with migration background.

Regarding the time of migration, nearly all patients immigrated to Germany before 2001 (91 percent), hence, they have been living in Germany for already more than 10 years. Still, the majority of patients with migration background (59 percent) immigrated to Germany before 1991 and therefore reside in Germany even longer than 20 years as illustrated in figure 2.

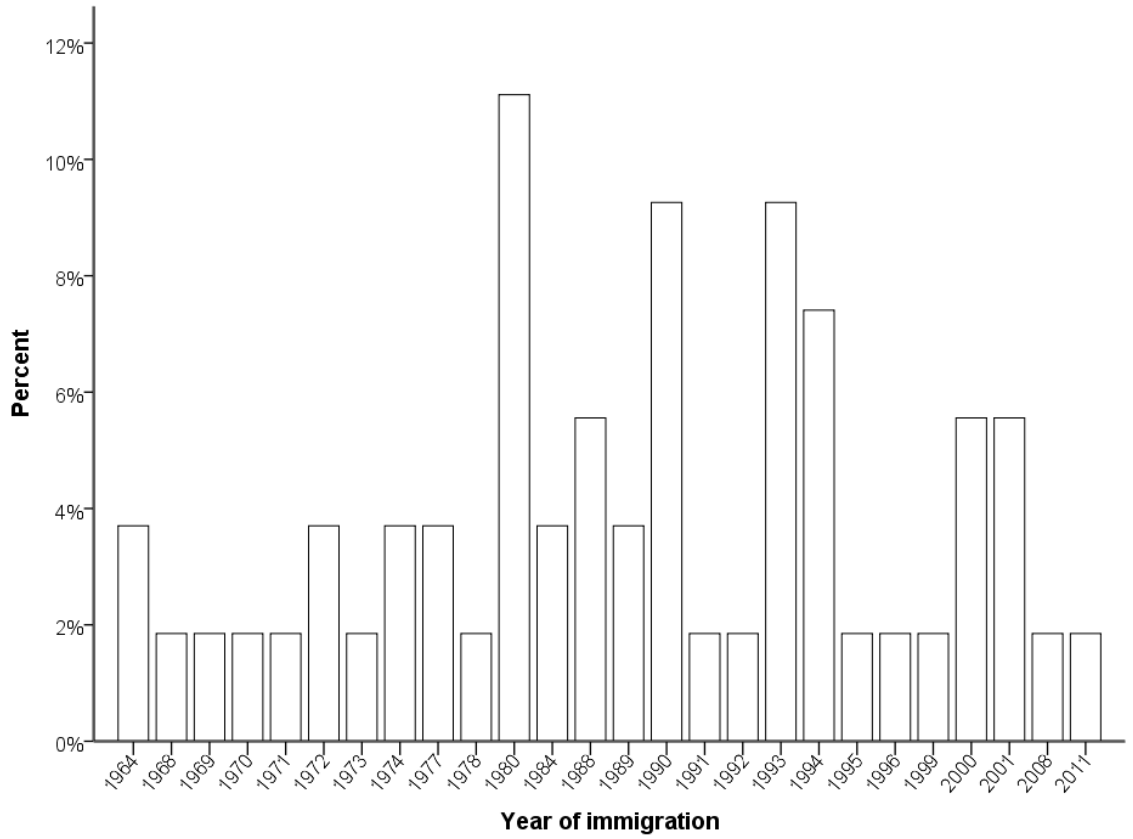

Figure 2 **Year of immigration of patients with migration background.**

Language is one of the most important elements of adequate communication between health care staff and patients. German language skills were evaluated as shown in figure 3. The vast majority (77 percent) of PMB had satisfactory or better German language skills. Still the majority (54 percent) of PMB believe their German to be good, very good or consider themselves as native speakers.

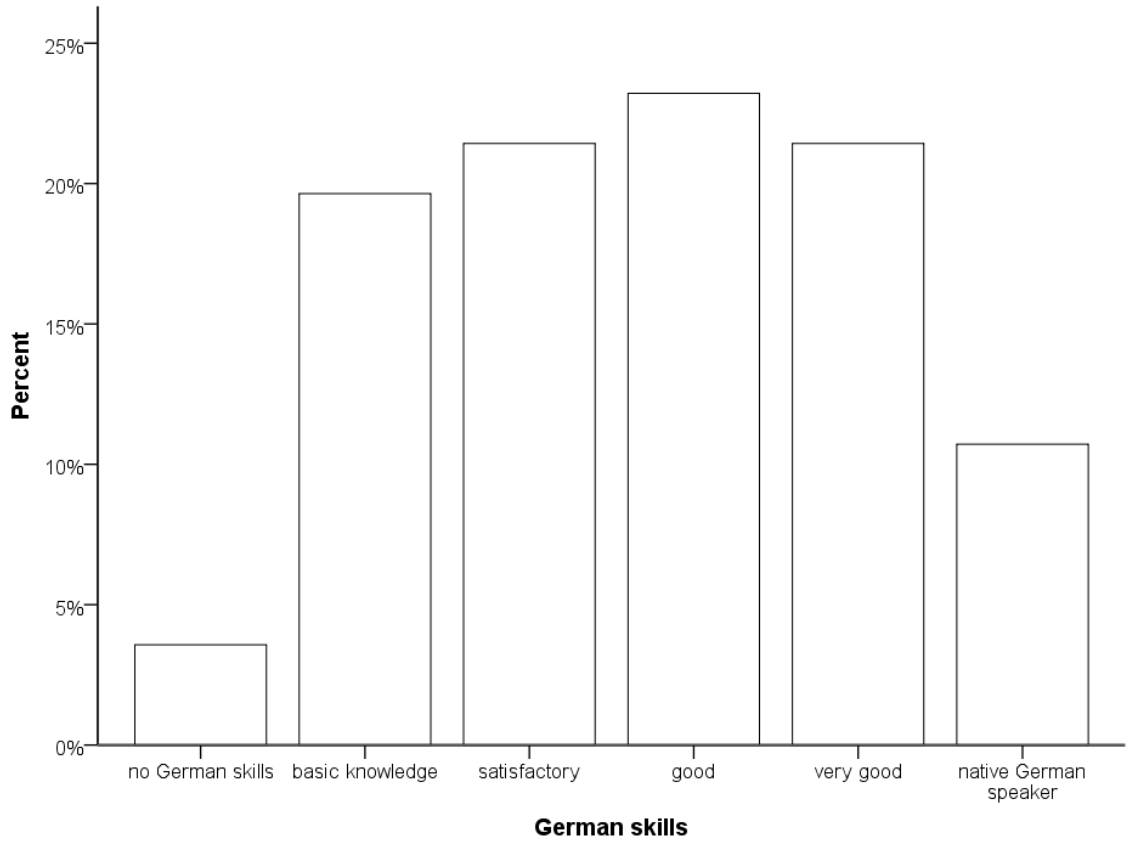

Figure 3 German language skills of patients with migration background as assessed by self-estimation.

3.1.2 Education and Occupation

Differences in education between the group of PMB and native-born German patients are illustrated in figure 4. The present results show a tendency to a u-shaped curve in the PMB group and a Gaussian distribution in the group of native-born German patients in levels of education from “no school-leaving certificate” (“no school degree”) to “Abitur”, the most advanced high school level.

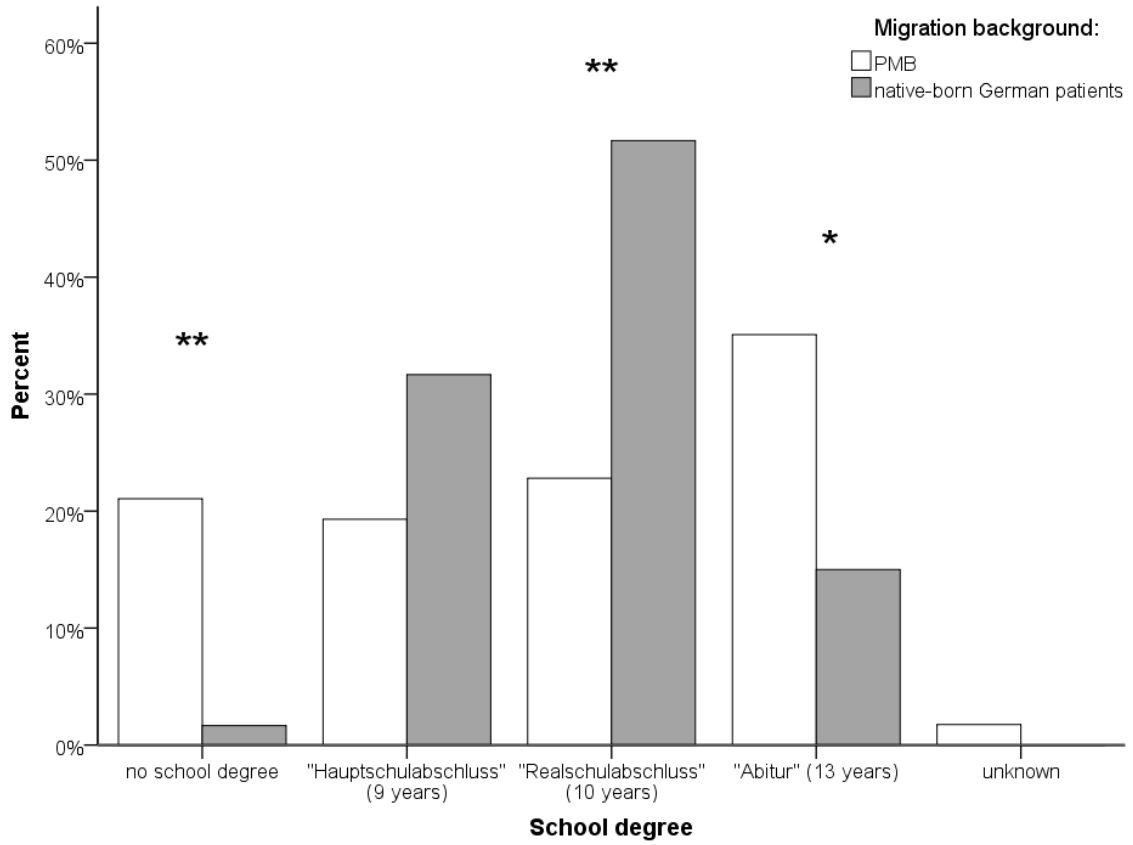

Figure 4 Differences in education between PMB and native-born German patients.
* Significant differences between PMB and native-born German patients ($p < 0.05$)
** Highly significant differences between PMB and native-born German patients ($p < 0.01$)
PMB – patients with migration background

Significant differences between both cohorts could be seen in the number of patients without school-leaving certificate or with less than nine years of education (21.1 percent of PMB and 1.7 percent of native-born German patients, $p = 0.001$, Fisher’s exact test; OR 15.4, CI 2.1 – 681; age adjusted data: $p = 0.001$, Fisher’s exact test; OR 15.4, CI 2.1 – 681). Further dissimilarities between PMB and native-born German patients were

noted in the number of graduates from junior high school. 22.8 percent of PMB and 51.7 percent of native-born German patients had a degree from junior high school with at least 10 years of school education, called “Realschulabschluss” ($p < 0.01$, Fisher’s exact test; OR 3.6 , CI 1.5 – 8.8; age adjusted data: $p = 0.001$, Fisher’s exact test; OR 4.0, CI 1.7 – 9.9). On the other hand, 35.1 percent of PMB and 15.0 percent of native-born German patients graduated from the “Gymnasium” with the “Abitur” certificated of advanced secondary education with at least 12 years of education. This difference was not significant after adjustment for age ($p = 0.018$, Fisher’s exact test; OR 0.3, CI 0.1 – 0.9; p.adjust $p = 0.270$, Fisher’s exact test OR 0.5, CI 0.2 – 1.4).

Additionally, further education like apprenticeship/vocational training, degrees given by universities of applied sciences, the German “Fachhochschule”, and university degree were assessed. The results show significant differences in all subgroups as illustrated in figure 5. More PMB do not have any further education beyond high school (40.4 percent of PMB compared to 1.7 percent of native-born German patients, $p < 0.001$, Fisher’s exact test; OR 38.9, CI 5.8 – 1660; age adjusted data $p < 0.001$, Fisher’s exact test, OR 38.9, CI 5.8 – 1660). Further, significantly more native-born German patients finished an apprenticeship or vocational training (31.6 percent of PMB and 75.0 percent of native-born German patients, $p < 0.001$, Fisher’s exact test, OR 6.4, CI 2.7 – 15.8; age adjusted data $p < 0.001$, Fisher’s exact test, OR 5.9, CI 2.5 – 14.5) or have a degree from a German “Fachhochschule” (3.5 percent of PMB and 18.3 percent of native-born German patients, $p < 0.05$, Fisher’s exact test, OR 6.1, CI 1.2 – 59.3; age adjusted data $p < 0.05$, Fisher’s exact test, OR 6.1, CI 1.2 – 59.3). On the other hand, significantly more PMB have a university degree (24.6 percent of PMB compared to 5.0 percent of native-born German patients, $p = 0.003$, Fisher’s exact test, OR 0.164, CI 0.0285 – 0.639; age adjusted data $p = 0.022$, Fisher’s exact test, OR 0.223, CI 0.0377 – 0.911).

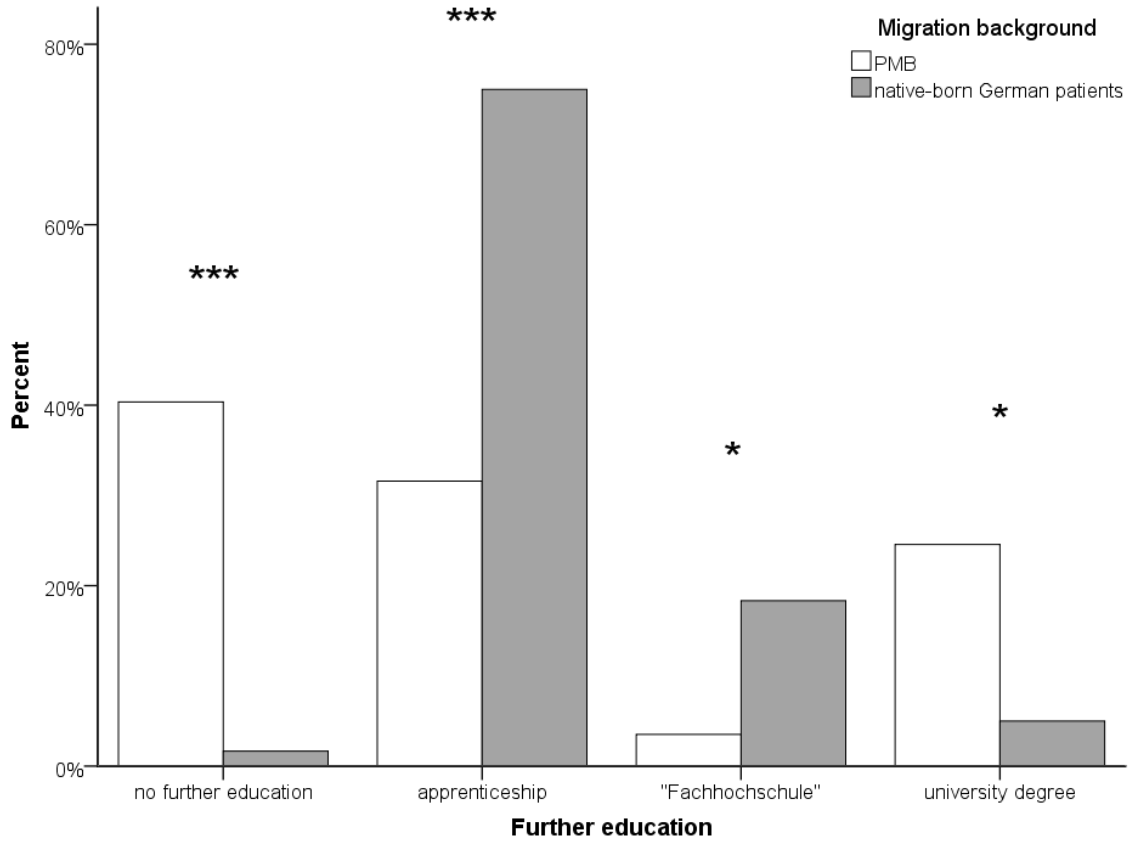

Figure 5 Further education compared between PMB and native-born German patients.

* Significant differences between PMB and native-born German patients ($p < 0.05$)

*** Highly significant differences between PMB and native-born German patients ($p < 0.001$)

PMB – patients with migration background

Although differences in education could be observed, there were no dissimilarities between PMB and native-born German patients with regard to the state of employment except in the number of retired patients, illustrated in figure 6 (14.0 percent of PMB and 20.3 percent of native-born German patients, $p < 0.01$, Fisher's exact test, OR 3.2, CI 1.4 – 7.3; age adjusted data $p = 0.042$, Fisher's exact test, OR 2.2, CI 0.989 – 4.96).

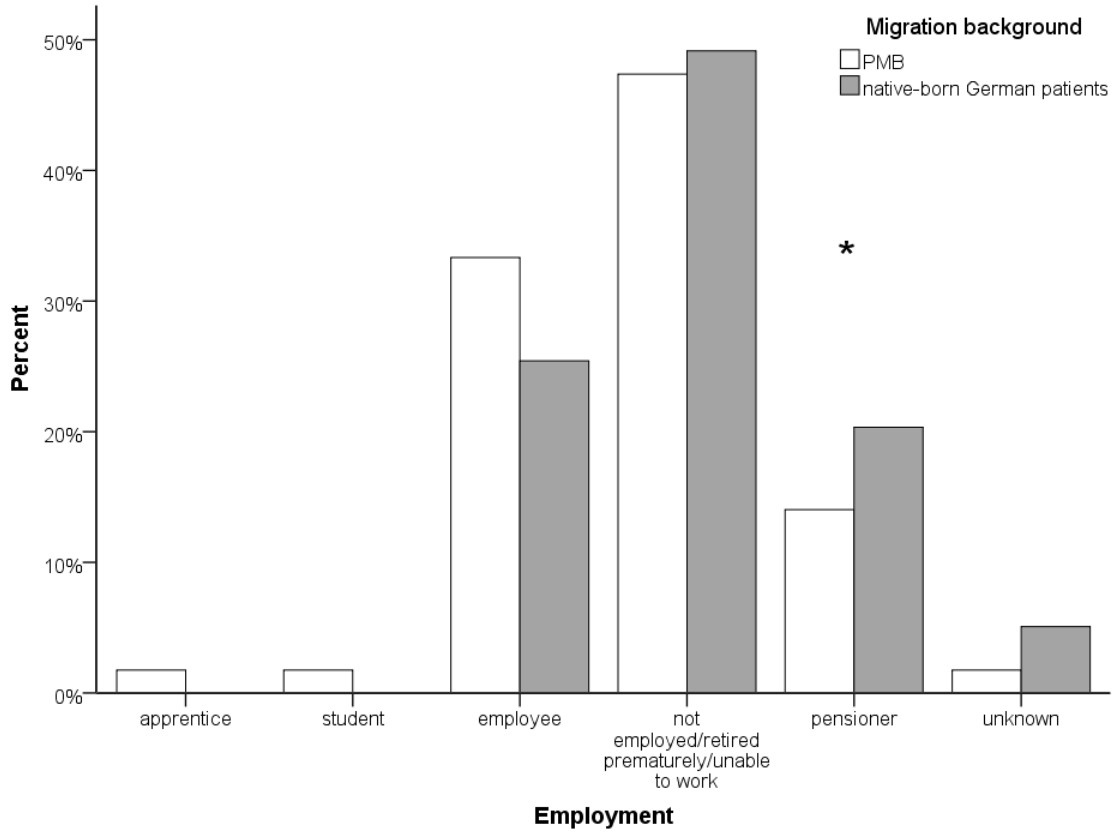

Figure 6 Occupational differences between PMB and native-born German patients.

* Significant differences between PMB and native-born German patients ($p < 0.05$)
PMB – patients with migration background

However, significant differences in the type of employment were found as shown in figure 7. The patients' current or latest profession was classified into three groups, depending on the necessity of an apprenticeship/vocational training or a college degree or no requirement of any education beyond high school education in order to assess occupational differences. Significantly more PMB had an occupation that did not require any further education (49.1 percent for PMB and 8.3 percent for native-born German

patients, p < 0.001, Fisher's exact test, OR 0.1, CI 0.03 – 0.3; age adjusted data p < 0.001, Fisher's exact test, OR 0.1, CI 0.03 – 0.3).

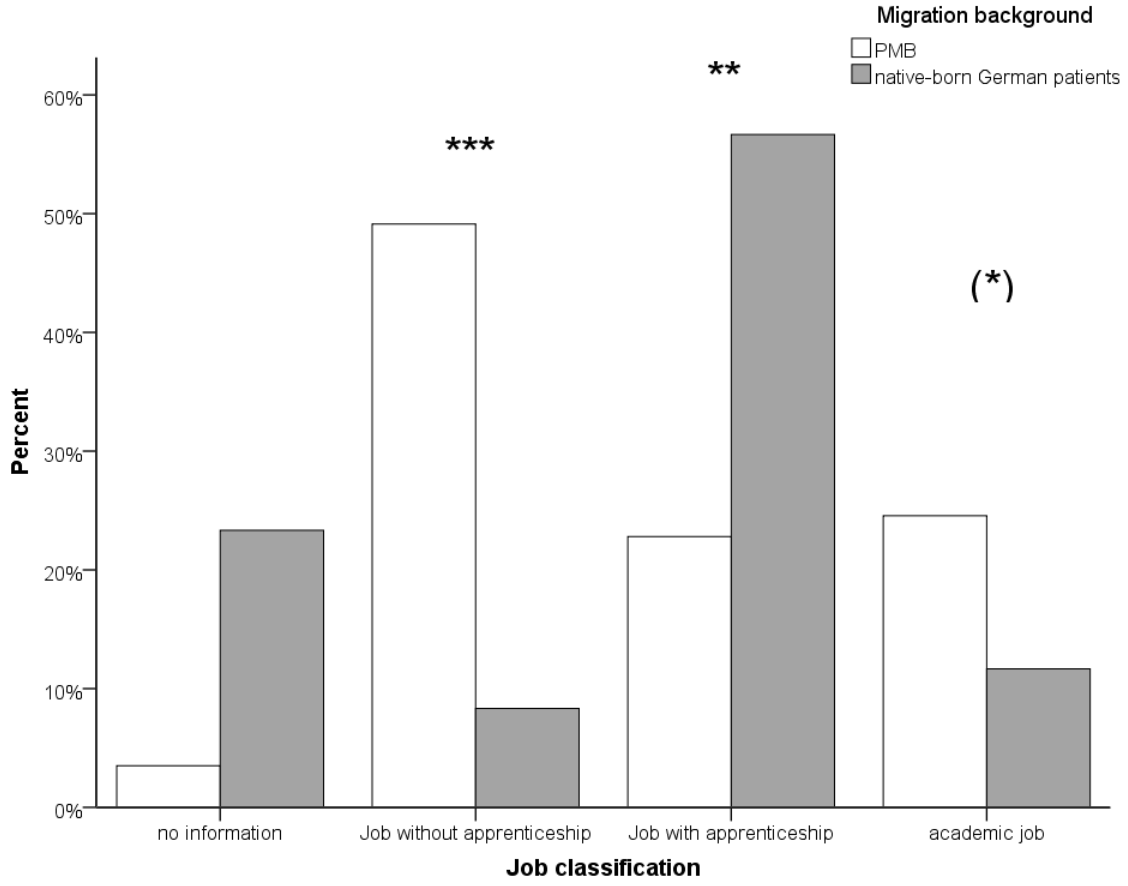

Figure 7 Differences in characteristics of occupation between PMB and native-born German patients.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1)

** Highly significant differences between PMB and native-born German patients (p < 0.01)

*** Highly significant differences between PMB and native-born German patients (p < 0.001)

PMB – patients with migration background

Additionally, there were significantly fewer PMB occupied in jobs requiring at least an apprenticeship/vocational training (22.8 percent PMB and 56.7 percent native-born German patients, p = 0.001, Fisher's exact test, OR 4.4, CI 1.9 – 10.8; age adjusted data p = 0.001, Fisher's exact test, OR 4.4, CI 1.9 – 10.8). Slightly more PMB had academic employments. This trend, however, could not be seen after adjustment for age (24.6 percent and 11.7 percent, respectively, p = 0.092, Fisher's exact test, OR

0.409, CI 0.128 – 1.2; age adjusted data p = 0.213, Fisher's exact test, OR 0.498, CI 0.152 – 1.51; figure 7).

3.2 Graft function (primary hypothesis)

3.2.1 Creatinine and GFR

Figure 8 illustrates levels of creatinine, measured during the first five years after transplantation. Mean creatinine levels of year one and two posttransplant were significantly lower among PMB (1.7 ± 1.0 and 1.4 ± 1.0 mg/dl) compared to creatinine of native-born German patients (2.1 ± 1.3 and 1.5 ± 0.7 mg/dl) (year one: p = 0.001, t-test; year two: p = 0.02, t-test; this item did not show dependency on age or gender, hence, was not adjusted). No significant differences between PMB and native-born German patients during the other years could be observed. Mean creatinine values of year three and five posttransplant for the whole cohort were 1.5 ± 0.6 mg/dl and 1.5 ± 0.7 mg/dl, respectively.

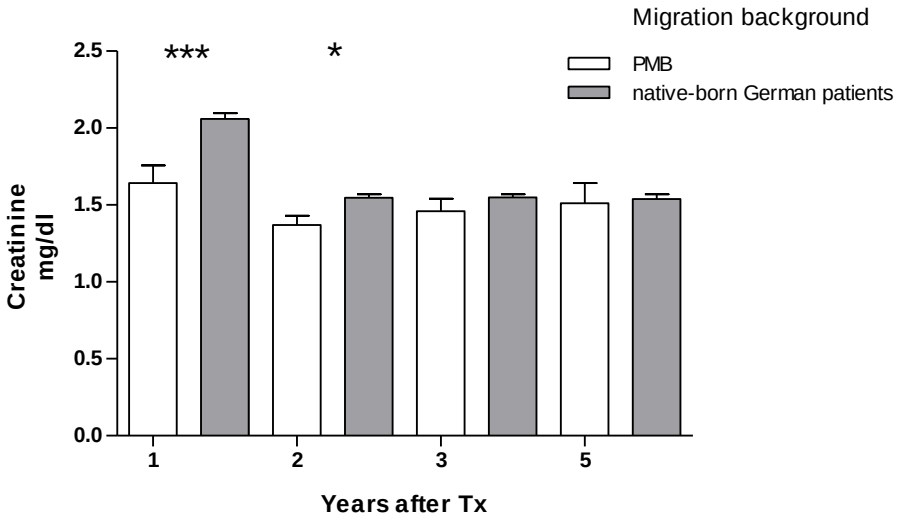

Figure 8 Creatinine levels of PMB and native-born German patients.

* Significant differences between PMB and native-born German patients (p < 0.05)

*** Highly significant differences between PMB and native-born German patients (p < 0.001)

PMB – patients with migration background, Tx – transplantation

Glomerular filtration rate (GFR) is predicted by measurement of creatinine. Correlating to the creatinine values, the GFR also showed significant differences for the first year

after transplantation. Due to age as a central component in the calculation of the GFR, this difference did not reach statistical significance after adjustment for age and gender (see below). In the first year, mean GFR of PMB and native-born German patients was 57.7 ± 21.2 and 51.1 ± 20.6 ml/min, respectively (p = 0.006, t-test; p.adjust p = 0.099, t-test). There were no significant differences between the cohorts in year two, three and five posttransplant. (year two: p = 0.1, t-test, p.adjust p = 0.7, t-test; year three p = 0.4, t-test, p.adjust p = 1, t-test; year five: p = 0.9, t-test, p.adjust, p = 0.6, t-test).

Further, the present study evaluated the frequency of patients with diminished GFR defined as < 50 ml/min. According to this data, there were slightly more native-born German patients with decreased graft function in the first year compared to the group of PMB (50.8 percent and 38.0 percent (467 of 919 and 30 of 79, respectively), p = 0.046, Fischer's exact test, OR 1.7, CI 1.0 – 2.8; after adjustment for age p = 0.034, Fisher's exact test, OR 0.6, CI 0.3 – 0.96). There were no significant differences in the incidence of diminished GFR in the other years without adjustment for age. Interestingly, since this factor was strongly age-dependent, the present data showed significantly more PMB than native-born German patients with a diminished GFR in the fifth year posttransplant after adjustment for age (53.1 percent and 31.7 percent (17 of 32 and 160 of 505, respectively), p = 0.8, Fisher's exact test, OR 1.2, CI 0.5 – 3.0; p.adjust p = 0.02, Fischer's exact test adjusted for age, OR 0.4, CI 0.2 – 0.9).

3.2.2 Rejection

Rejection of the graft is one of the most serious complication posttransplant. This study analyzed rejections during the whole observation period of more than 12 years. In the patient population, 519 patients (41.1 percent) experienced at some point after transplantation one or more rejections. Rejections were defined as histologically proven rejections according to the Banff classification.

The risk of suffering a rejection was equal for the groups and the distribution of rejections throughout the observation period is shown in the Kaplan-Meier estimator in figure 9 (p = 0.7, log rank; p.adjust: p = 0.8, Cox proportional hazard model (PH-Model; sctest), CI 1.08 – 2.52).

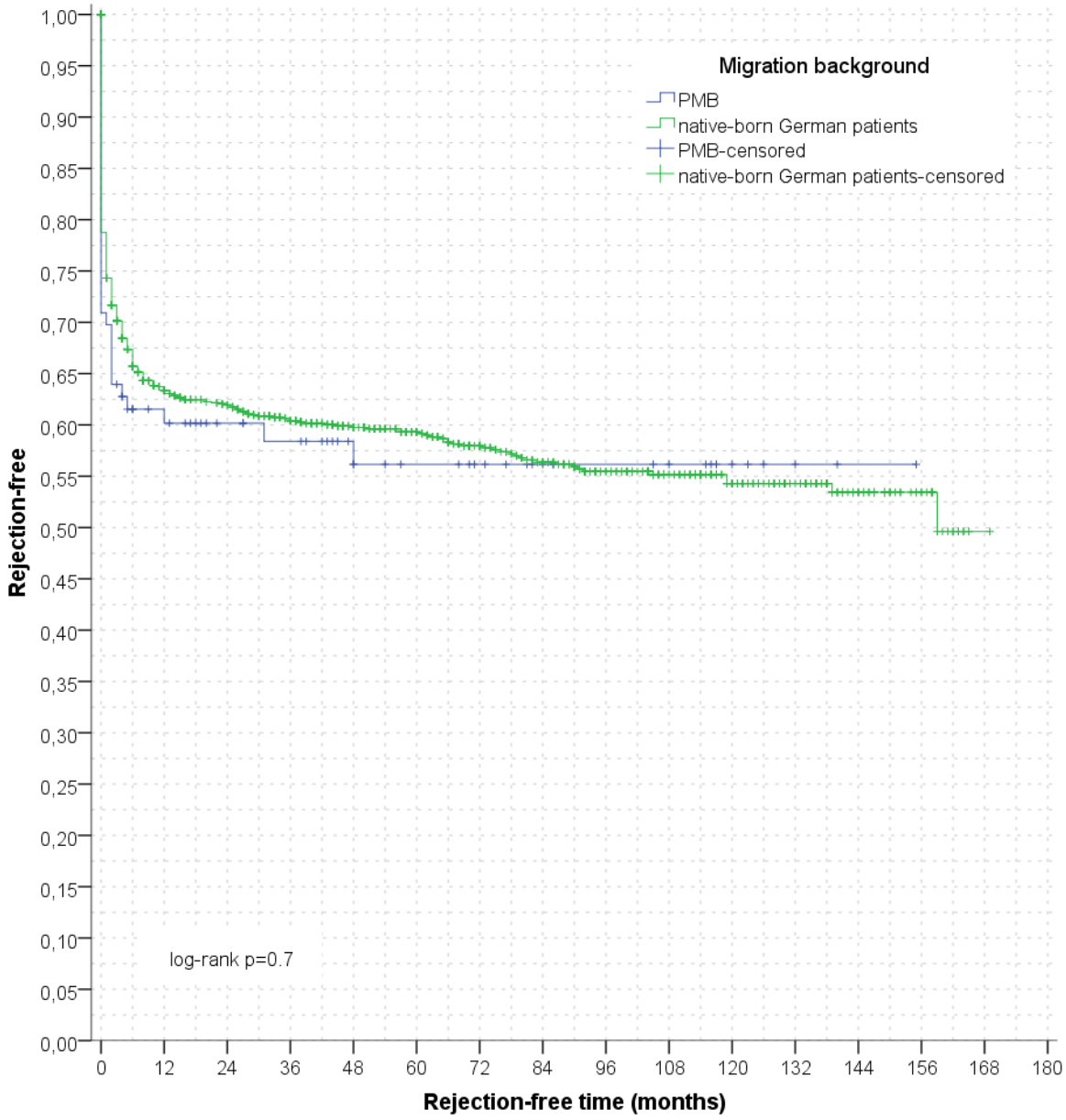

Figure 9 Kaplan-Meier estimator with percentage of PMB and native-born German patients without rejection. The whole observation period is displayed in months.

If a patient suffered more than one rejection, only the first rejection was analyzed
PMB – patients with migration background; Tx – transplantation

There were no differences observed between the group of PMB and the group of native-born German patients in any analysis of the characteristics of transplant rejection with or without adjustment for age except for the rejection-free survival.

Median rejection-free survival (time between transplantation and the first rejection) was significantly shorter among PMB with 11 days (range 1468 days) compared to 26 days (range 4842 days) among native-born German patients, shown in figure 10 (p = 0.008, Wilcoxon test; p.adjust p = 0.005).

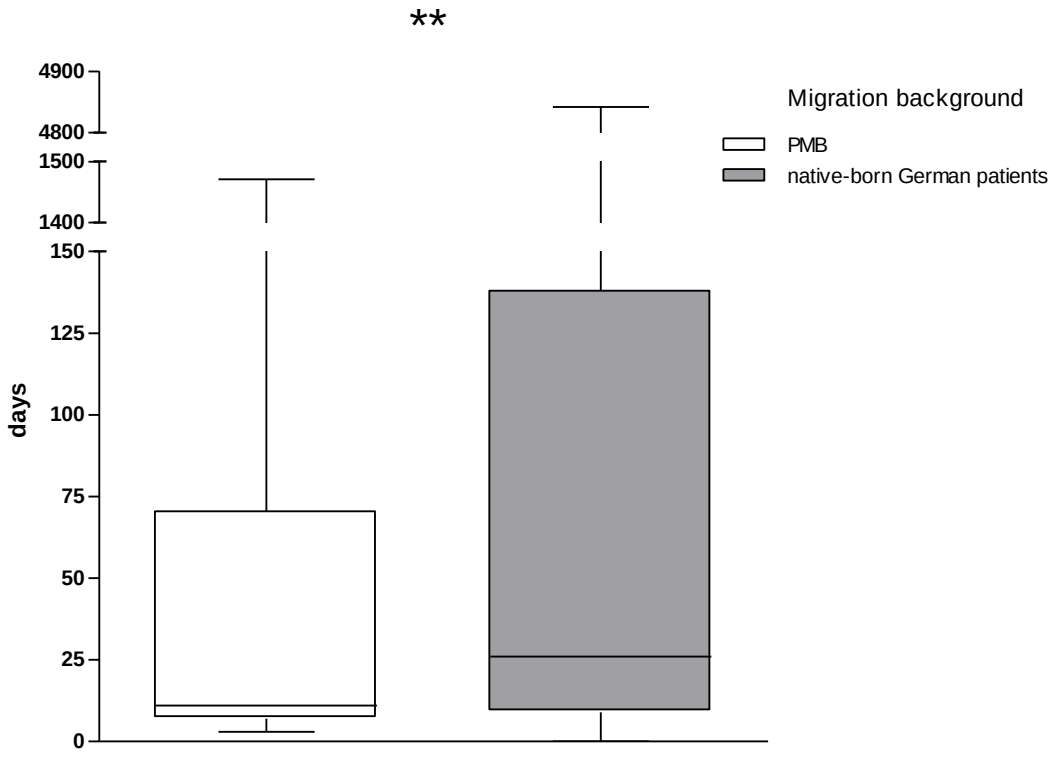

Figure 10 Rejection-free survival of PMB and native-born German patients.

** Highly significant differences between PMB and native-born German patients (p < 0.01)
PMB – patients with migration background

Further, 393 patients (31.1 percent) suffered only one rejection, 95 (7.5 percent) from two and 22 (1.7 percent) from three rejections as shown in figure 11 (number of rejections compared between PMB and native-born German patients: p = 0.7, Wilcoxon test; p.adjust p = 1.0, Wilcoxon test).

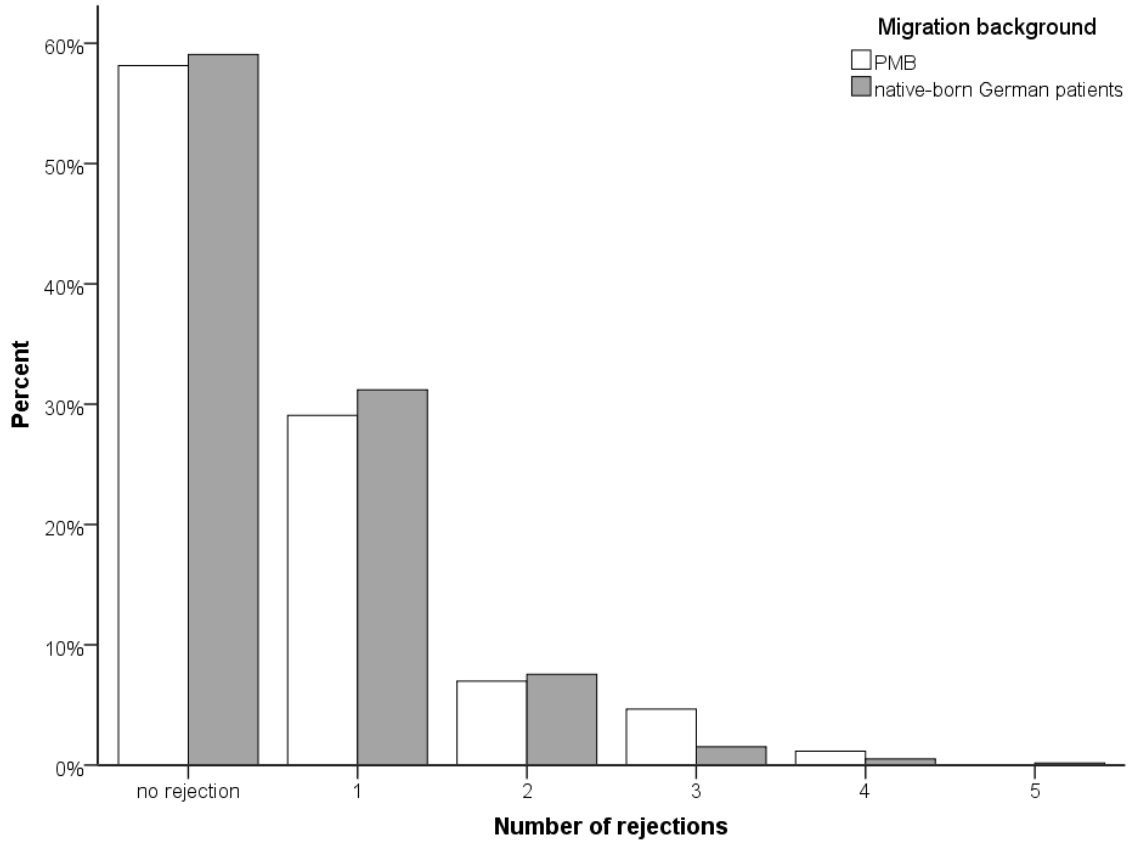

Figure 11 Number of rejections per patient during more than 12 years of observation of PMB compared to native-born German patients.

PMB – patients with migration background

Analyzing the frequency of rejections during the first year after transplantation, there were no significant differences between the cohort of PMB (incidence of 39.5 percent) and of native-born German patients (incidence of 35.8 percent) (p = 0.5, Fisher's exact test). Frequencies of rejections of the PMB group and group of native-born German patients of the years two through five were as following: second year: 0.0 percent and 1.2 percent (p = 0.6), third year: 1.2 percent and 1.2 percent (p = 1), fourth year: 1.2 percent and 0.4 percent (p = 0.3), fifth year: 0.0 percent and 0.3 percent (p = 1).

Moreover the rejection grades were assessed according to the Banff classification, see table 3 and figure 12 (percentages in figure 12 refer to the population which suffered at least one rejection). If patients suffered more than one rejection, only the first rejection was included in this analysis.

Patients with rejection Rejection grade (Banff)	PMB n = 50 (of 86)	Native-born German patients n = 691 (of 1180)	In whole cohort n=1266	p-value/ p.adjust
Borderline rejection	11 (22.0% [a], 12.8% [b])	182 (26.3% [c], 15.4% [d])	n = 193 (15.2%)	>0.1 [e]
Rejection grade Ia	13 (26.0% [a], 15.1% [b])	123 (17.8% [c], 10,4% [d])	n = 136 (10.7%)	>0.1 [e]
Rejection grade Ib	2 (4.0% [a], 2,3% [b])	56 (8.1% [c], 4.7% [d])	n = 58 (4.6%)	>0.1 [e]
Rejection grade IIa	5 (22.0% [a], 5.8% [b])	60 (8.7% [c], 5.1% [d])	n = 65 (5.1%)	>0.1 [e]
Rejection grade IIb	4 (8.0% [a], 4.7% [b])	32 (4.6% [c], 2.7% [d])	n = 36 (2.8%)	>0.1 [e]
Rejection grade III	0	11 (1.6% [c], 0.9% [d])	n = 11 (0.9%)	>0.1 [e]

Table 3 Rejection grade of suffered rejection* according to Banff classification of PMB and native-born German patients with their distribution for each population.

* If a patient suffered more than one rejection only the first rejection was analyzed

[a] Percentage within patients with at least one rejection among PMB

[b] Percentage within the whole population of PMB

[c] Percentage within patients with at least one rejection among native-born German patients

[d] Percentage within the whole population of native-born German patients

[e] Fisher's exact test

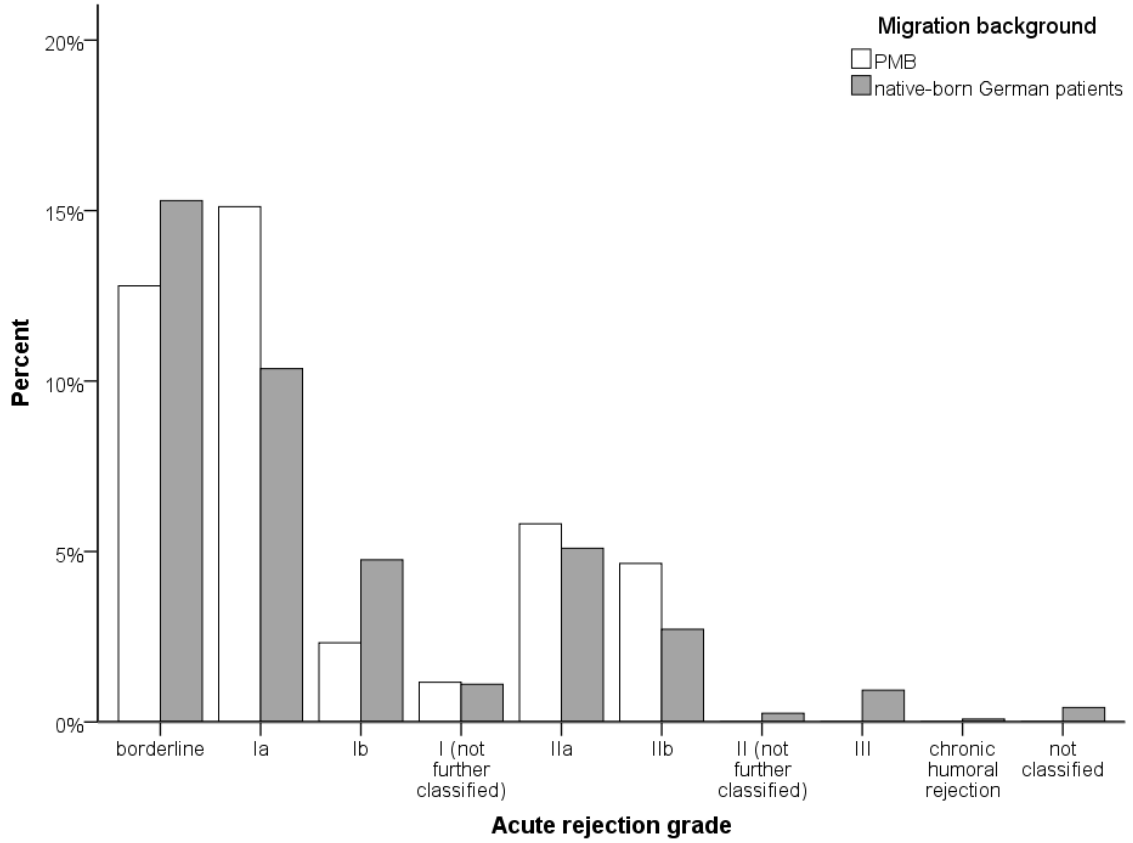

Figure 12 Rejection grade of suffered rejection* according to Banff classification of PMB and native-born German patients.**

* if a patient suffered more than one rejection, only the first rejection was analyzed

** Percentages refer to the population which suffered at least one rejection

PMB – patients with migration background

3.2.3 Ischemia times (cold, warm and mixed)

The cold ischemia time (CIT) is one of the principal factors to influence short and long-term graft survival (Isabel Quiroga et al., 2006). In the present study, the mean cold ischemia time was 9.3 ± 4.8 hours for the group of PMB and 10.1 ± 5.4 hours for native-born German patients, (p = 0.3, Wilcoxon test; p.adjust: p = 0.4), Wilcoxon test). Mean mixed ischemia time was 30.2 ± 7.9 and 30.7 ± 8.6 minutes in PMB and native-born German patients, respectively (p = 0.6, Wilcoxon test). Warm ischemia time in PMB and native-born German patients was 0.2 ± 0.6 and 0.5 ± 2.7 minutes, respectively (p = 0.9, Wilcoxon test).

3.2.4 Graft loss

Graft loss was defined as the initiation of dialysis in patients on account of insufficient graft function. Graft loss within more than 12 years of observation occurred in 167 patients (13.2 percent). Significantly fewer PMB suffered graft loss than native-born German patients: 4 of 86 (4.7 percent) and 163 of 1180 (13.8 percent), respectively, shown as Kaplan-Meier estimator in figure 13 (p = 0.045, log-rank; p.adjust p = 0.031 sctest).

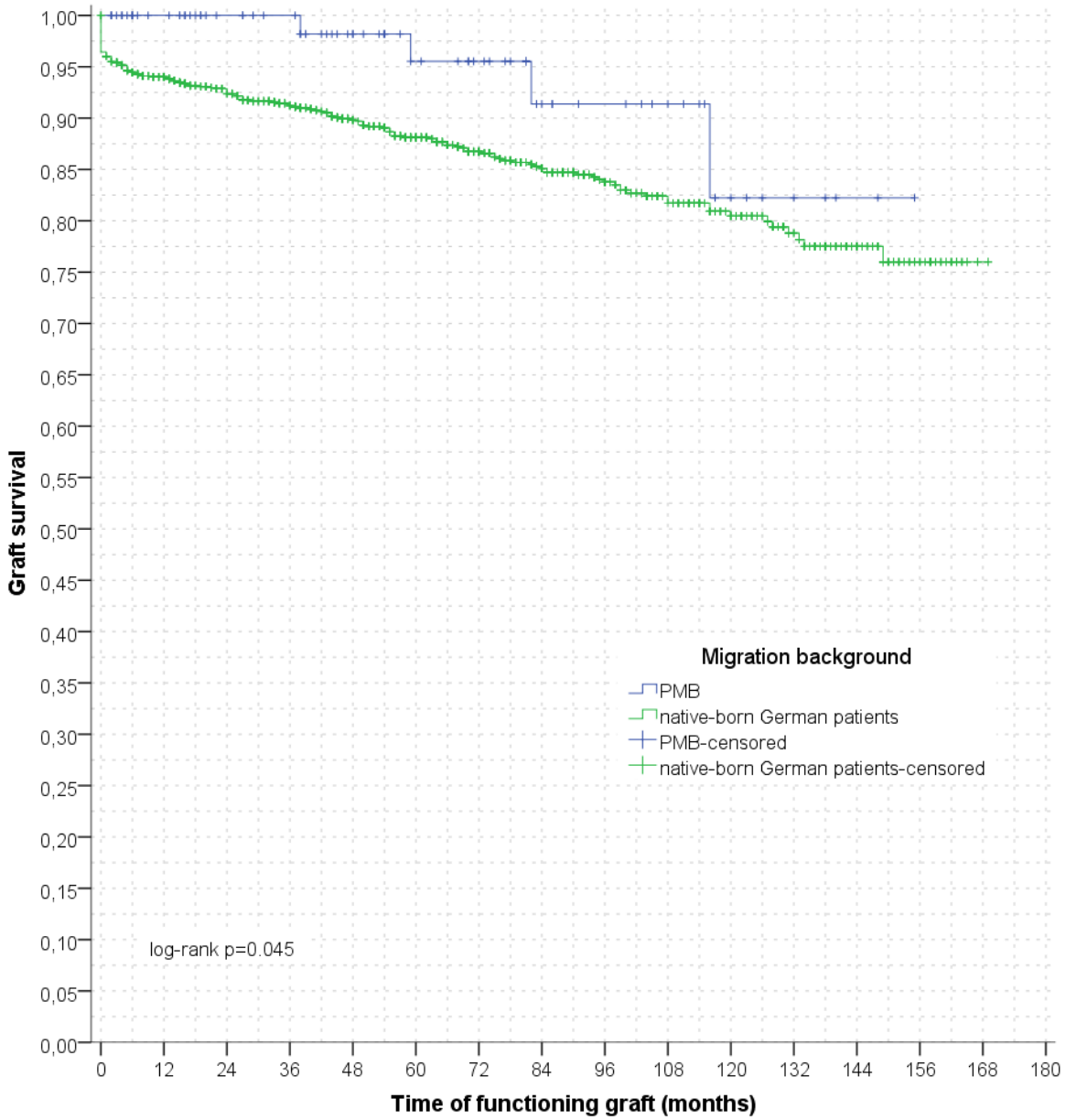

Figure 13 Kaplan-Meier estimator with time in months from transplantation to graft failure or the end of observation compared between PMB and native-born German patients. Major differences in graft loss during the first six months are apparent, especially when compared with the Kaplan-Meier estimator excluding the first six months, shown in figure 14 (p = 0.045 vs. p = 0.4, log-rank).

PMB – patients with migration background; Tx – transplantation

Median time elapsed from transplantation until graft failure was significantly longer among the cohort of PMB (median 71, range 78 months, 25% and 75% percentile: 43 and 108 months) compared to the cohort of native-born German patients (median 22,

range 149 months, 25% and 75% percentile: 0 and 57 months; p = 0.045, Wilcoxon test). However, the difference did not reach statistical significance after adjustment (p.adjust p = 0.14, Wilcoxon test). Median time to graft failure in the whole cohort was 24.0, range 149 months, 25% and 75% percentile: 0 and 63 months.

Nevertheless, no difference in graft loss can be seen when excluding the first six months posttransplant and focusing on the observation period after six months until the end of observation, shown in the Kaplan-Meier estimator in figure 14 (log-rank p = 0.4).

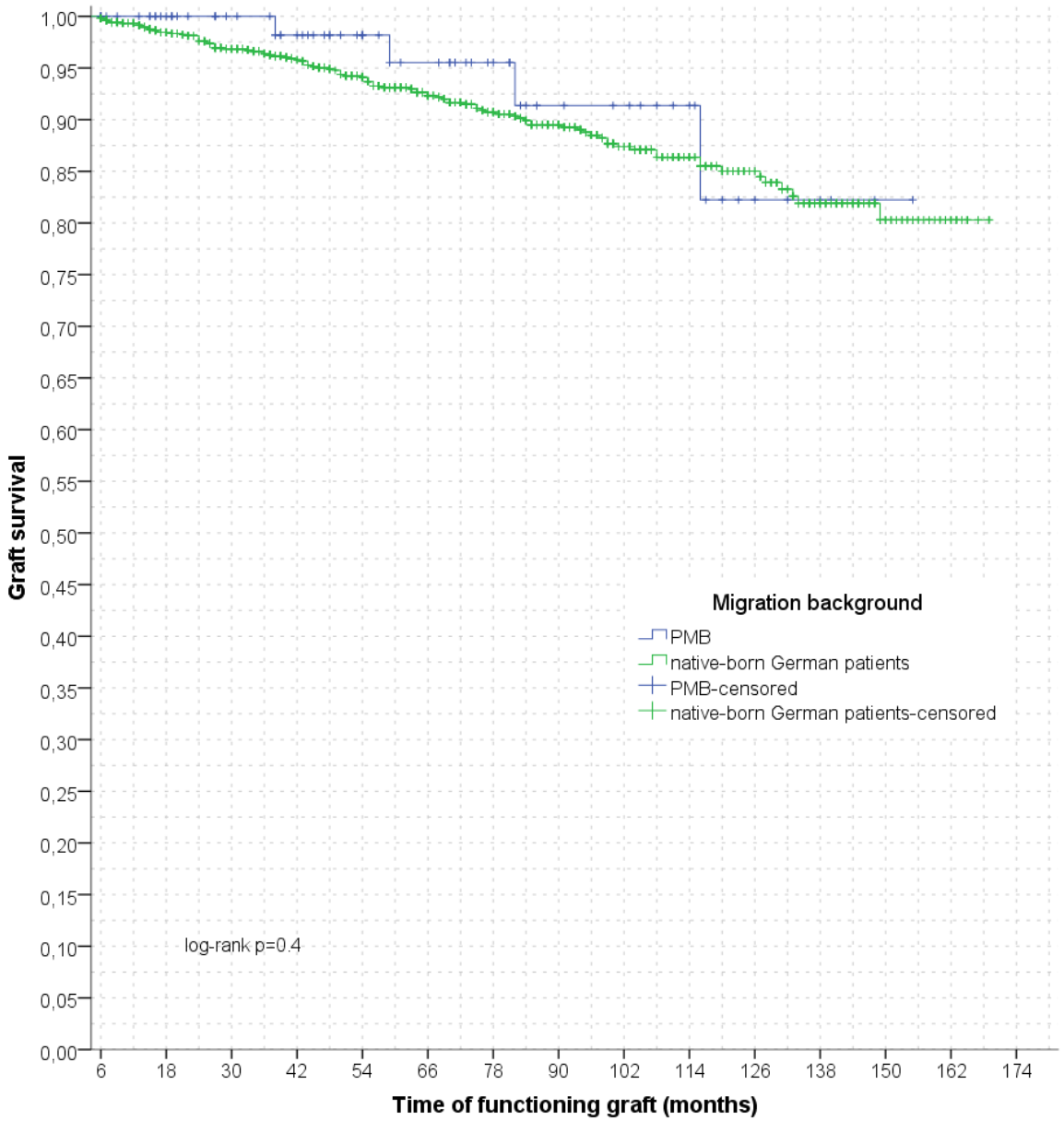

Figure 14 Kaplan-Meier estimator of graft loss among PMB and native-born German patients. In this graph the first six months posttransplant are excluded.

PMB – patients with migration background; Tx – transplantation

Graft survival at three, five and ten years posttransplant was as follows: at three years posttransplant: 100 percent of PMB (graft failure: 0 of 56 remaining cases) and 91 percent of native-born German patients (graft failure: 98 of 831 remaining cases); at five years posttransplant: 96 percent of PMB (graft failure: 2 of 35 remaining cases) and 88 percent of native-born German patients (123 of 617 remaining cases). Graft survival after 10 years for PMB and native-born German patients was 82 percent (graft failure: 4 of 7 remaining cases) and 81 percent (graft failure: 157 of 174 remaining cases), respectively. See also figure 13.

3.2.5 Infection risks

Immunosuppressive therapy has reduced the incidence of rejections on a great scale, while the susceptibility to opportunistic infections has risen (Fishman, 2007). In the present study, the risk of infections as positive reactions to tests for common transplantation-associated infections (BKV, CMV, EBV) and urinary tract infections were measured. No differences between the two groups could be seen, as shown in figure 15. A trend toward more positive reactions to tests for BK virus was found in the cohort of PMB compared to native-born German patients: 11.2 percent (n = 9 of 80) PMB tested compared to 10.1 percent (n = 98 of 967) native-born German patients tested (p = 0.08, Wilcoxon test). Positive reactions to tests of CMV were found in 20.0 percent (n = 17 of 85) and 18.7 percent (n = 203 of 1083) of PMB and native-born German patients, respectively (p = 0.3, Wilcoxon test). Positive reactions to tests for EBV were found in 13.7 percent (n = 10 of 63) and 10.8 percent (n = 84 of 780) of PMB and native-born German patients, respectively (p = 0.4, Wilcoxon test). Positive bacterial cultures for urinary tract infections were found in 51.4 percent (n = 36 of 70) and 42.4 percent (n = 380 of 895) of PMB and native-born German patients, respectively (p = 0.2, Wilcoxon test).

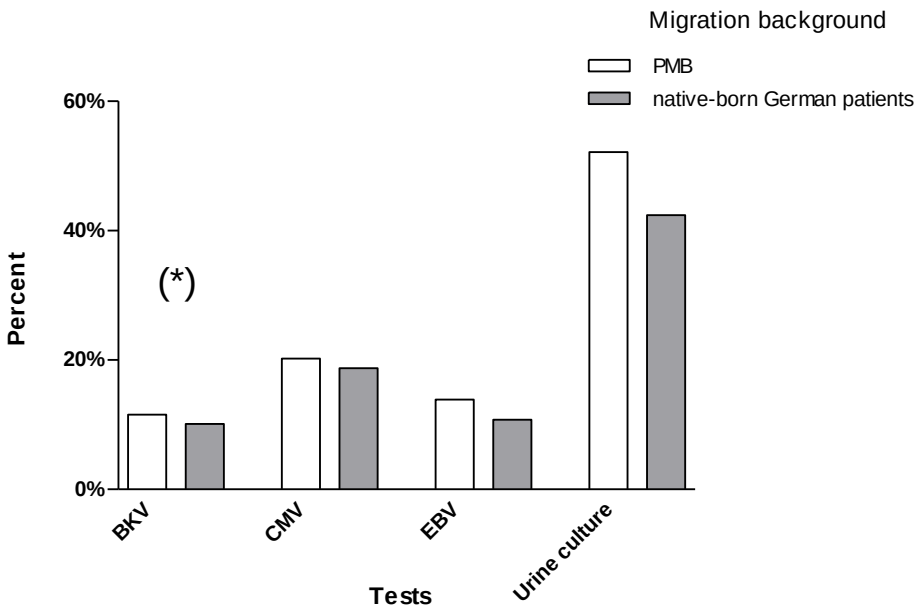

Figure 15 Infection risks of PMB and native-born German patients measured as patients with ≥1 positive test.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1)

PMB – patients with migration background; BKV – BK virus; CMV – Cytomegalovirus; EBV – Epstein-Barr virus

3.3 Waiting time (secondary hypothesis)

Waiting time was defined as months elapsed from the day of first dialysis to the date of transplantation. Median waiting time was 72 months (range 146; mean: 64.0 ± 36.4) and 56 months (range 251; mean: 56.8 ± 37.8) for the cohort of PMB and native-born German patients, respectively, shown as box-plot in figure 16. The data of the present study show a trend toward longer waiting times of PMB. After adjustment for age and gender this difference reached statistical significance (partial proof of secondary hypothesis; p = 0.07, Wilcoxon test, p.adjust, p = 0.04, Wilcoxon test).

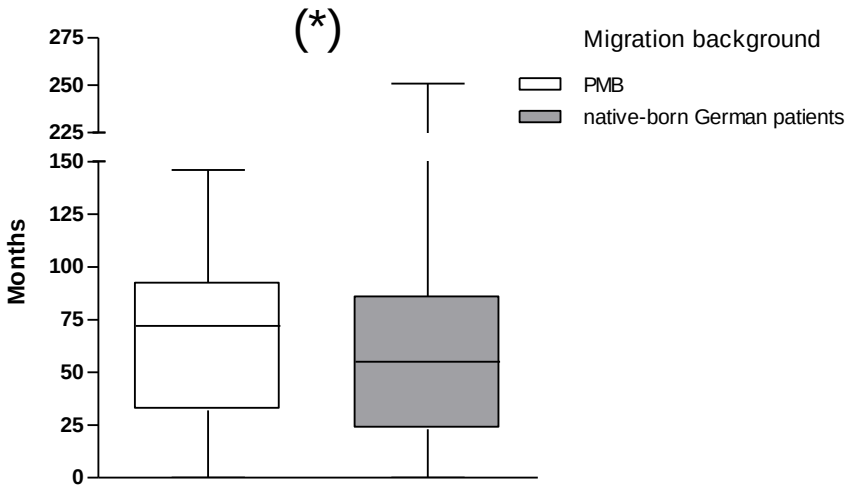

Figure 16 Waiting time for PMB and native-born German patients.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1). Significant differences were observed after adjustment for age and gender (p.adjust, p = 0.04). PMB – patients with migration background

A later listing on the Eurotransplant waiting list could contribute to different waiting times. However, there was no difference between time of first dialysis and listing on the Eurotransplant waiting list between PMB and native-born German patients (p > 0.1, Wilcoxon test).

Interestingly, two peaks of waiting times shown in the histogram in figure 17 could be observed; one after 25 months and another after 75 months. Subanalysis showed that in the whole cohort, recipients of 65 years and older had a mean waiting time of 51.1 ± 26 months.

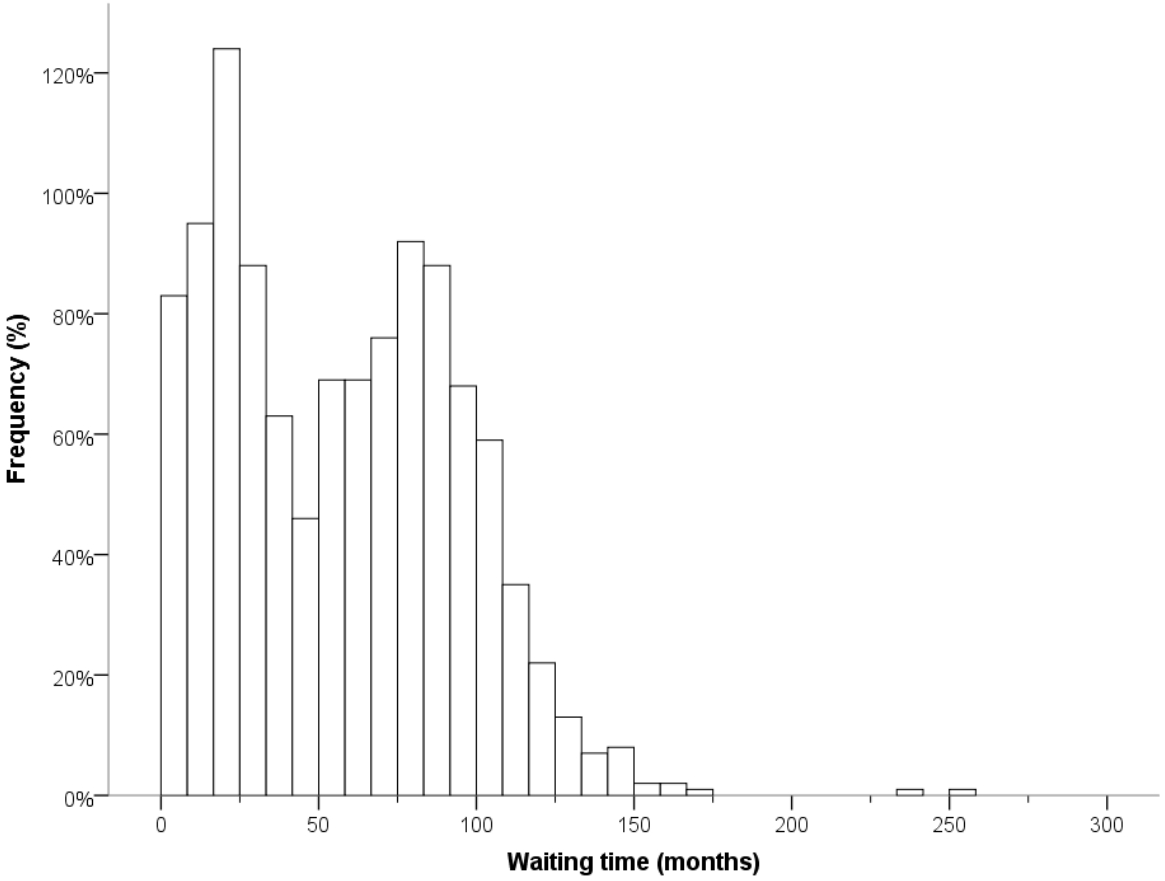

Figure 17 Histogram of waiting time in months of the whole cohort (patients with migration background (PMB) and native-born German patients).

3.3.1 First sub-hypothesis: HLA match

The antigens of the HLA system have the greatest influence on the acceptance or rejection of a renal transplant by the recipient (Brennan, 2012). The number of some HLA mismatches was significantly different between PMB and native-born German patients, shown in table 3.

Patient group Patient characteristics	**PMB** **n = 86**	**Native-born German patients** **n = 1180**	**p-value**	**p.adjust[c]**
Median mismatches overall (HLA-A, -B, and –DR (broad)) (25% and 75% percentile)	3 (2 – 5)	3 (1 – 4)	0.048 [a]	0.01 [a]
Median HLA–A mismatches (25% and 75% percentile)	1 (0 – 2)	1 (0 – 1)	0.049 [b]	0.02 [b]
Median HLA–B mismatches (25% and 75% percentile)	1 (1 – 2)	1 (0 – 2)	0.04 [b]	0.03 [b]
Median HLA–DR mismatches (25% and 75% percentile)	1 (1 – 2)	1 (0 – 2)	0.2 [b]	0.07 [b]

Table 4 HLA mismatches of PMB and native-born German patients.

[a] Wilcoxon test

[b] Fisher's exact test

[c] p-value adjusted for age and gender

PMB – patients with migration background

3.4 Adherence (=compliance; tertiary hypothesis)

The Essener Compliance-Score (ECS) categorizes patients' adherence (compliance) into low, medium and high compliance. It was possible to interview 57 of 86 patients (66 percent) in our experimental group of PMB and compare these data with 60 patients of our cohort of native-born German patients. 32.5 percent (n = 38 of 117) of the patients interviewed had an ESC corresponding to high compliance. 31.6 percent (n = 37 of 117) and 35.9 percent (n = 42 of 117) of the patients interviewed had medium and low compliance, respectively, results are shown in figure 18. There were no significant differences between the cohort of PMB and native-born German patients (partially disprove of tertiary hypothesis) (p = 0.2, Fisher's exact test, OR 0.58, CI 0.2 – 1.4; age adjusted data: p = 0.12, OR 0.54, CI 0.2 – 1.3). PMB showed a higher number of patients with a high score and a smaller number of patients with a medium or low score.

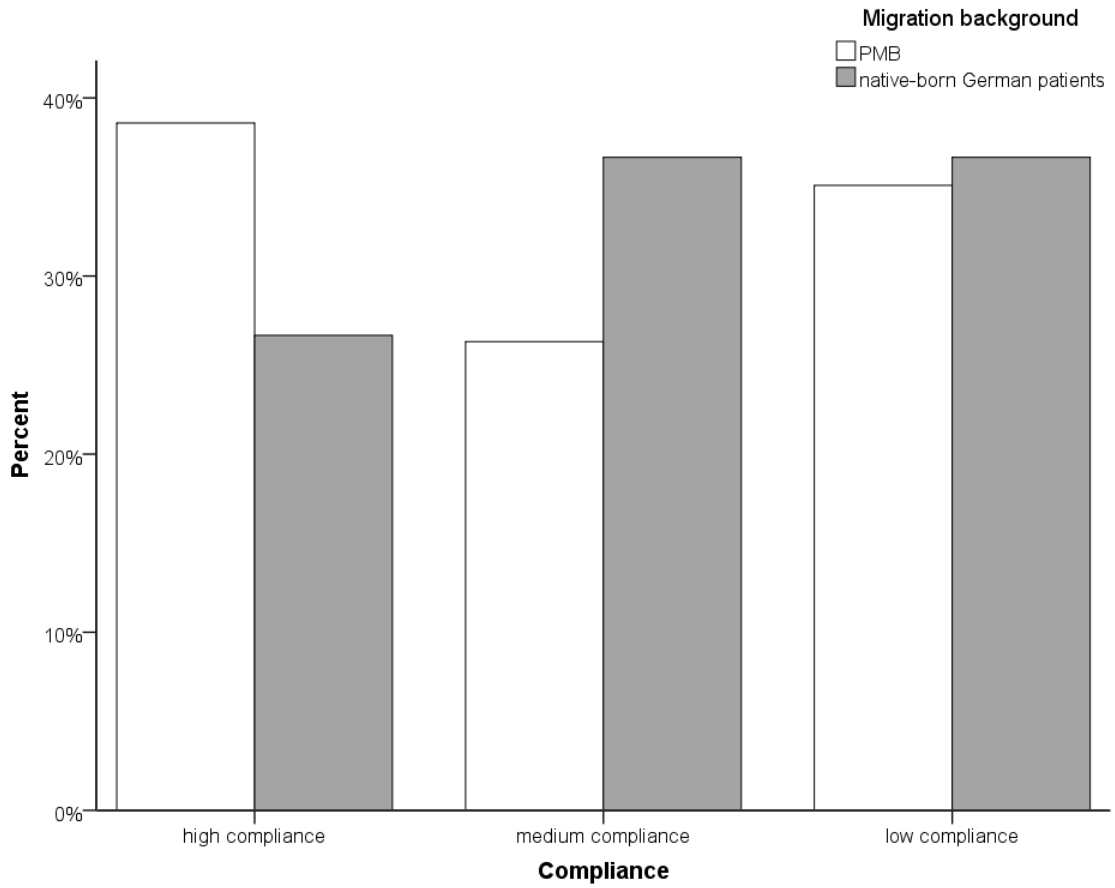

Figure 18 Compliance of PMB and native-born German patients.

PMB – patients with migration background

Also evaluated in the present study were the number of visits in the outpatient department of the transplantation center, regarding the visits as an indirect indicator of compliance as well. The results show significantly more visits by PMB compared to native-born German patients, as shown in figure 19 (partially confirmed tertiary hypothesis). Since female patients had been undergoing more controls during the second and third year post transplantation (p = 0.06 and 0.03, respectively), the data were adjusted to gender. Data in detail: first year, PMB and native-born German patients: median 17 and 13 visits, respectively (p < 0.001, Wilcoxon test; p.adjust p = 0.003, Wilcoxon test); second year: 6 and 5 visits (p = 0.02, Wilcoxon test; p.adjust p = 0.057, Wilcoxon test); third year: 7 and 4 visits (p < 0.001, Wilcoxon test; p.adjust p = 0.001, Wilcoxon test); fifth year: 5 and 4 visits (p = 0.048, Wilcoxon test; p.adjust p = 0.078, Wilcoxon test).

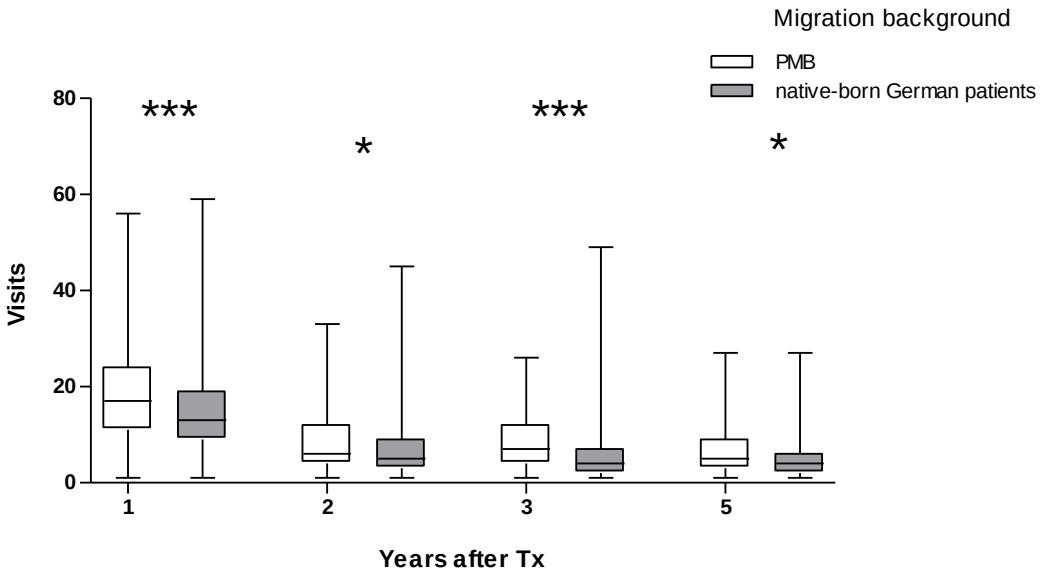

Figure 19 Annual visits to the outpatient department by PMB and native-born German patients.

* Significant differences between PMB and native-born German patients (p < 0.05)

*** Highly significant differences between PMB and native-born German patients (p < 0.001)

PMB – patients with migration background; Tx – transplantation

3.4.1 Second sub-hypothesis: metabolism and cardiovascular risk factors

3.4.1.1 Metabolism

The mean glycated haemoglobin (haemoglobin A1C, HbA1C) was 5.9 percent in the first, second, third and fifth year after transplantation (SD: ± 0.8-0.9 depending on the year) without significant differences between the groups shown in figure 20.

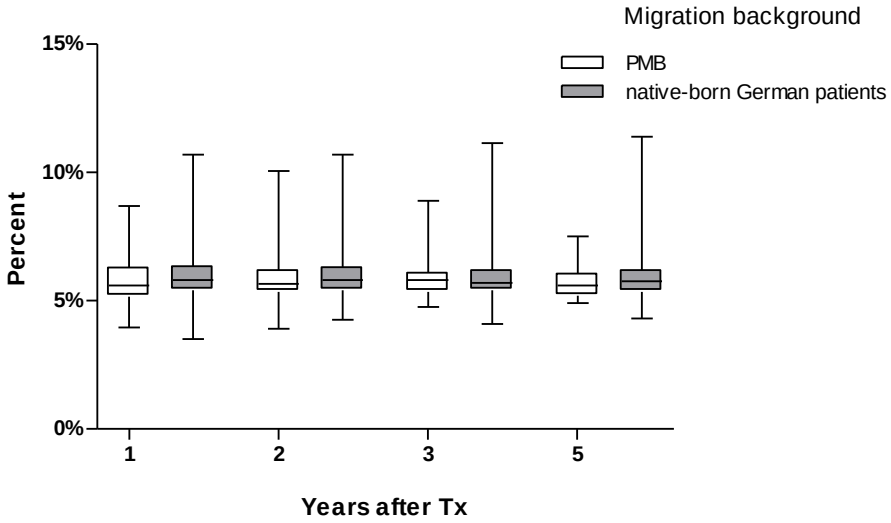

Figure 20 Mean HbA1C (glycated haemoglobin) of PMB and native-born German patients.
PMB – patients with migration background; Tx – transplantation

Other important metabolic data which affect patients' health include cholesterol and obesity. Mean cholesterol was between 189.0-194.0 mg/dl. Raw data showed a trend and adjusted data showed significantly higher cholesterol values in the cohort of PMB compared to native-born German patients in the first year after transplantation as shown in figure 21 (198 mg/dl and 188 mg/dl, respectively; p = 0.06, Wilcoxon Test; p.adjust: p = 0.03, Wilcoxon Test). In the other years, there were no significant differences between the groups.

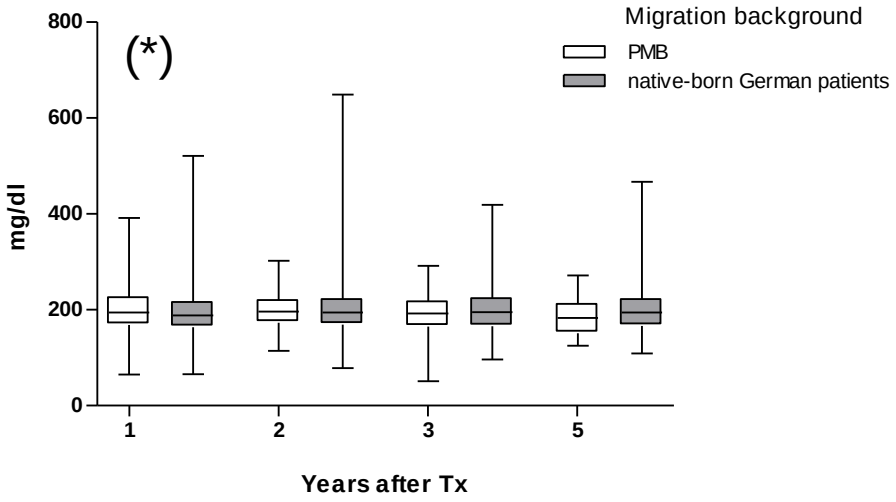

Figure 21 Mean cholesterol of PMB and native-born German patients.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1)

PMB – patients with migration background; Tx – transplantation

The body mass index (BMI) was assessed to evaluate patients' weight and obesity. Mean BMI in the first, second, third and fifth year was as follows: 24.3 ± 4.0, 25.0 ± 4.3, 25.3 ± 8.8, 25.4 ± 10, also shown in figure 22. There were no significant differences between the groups.

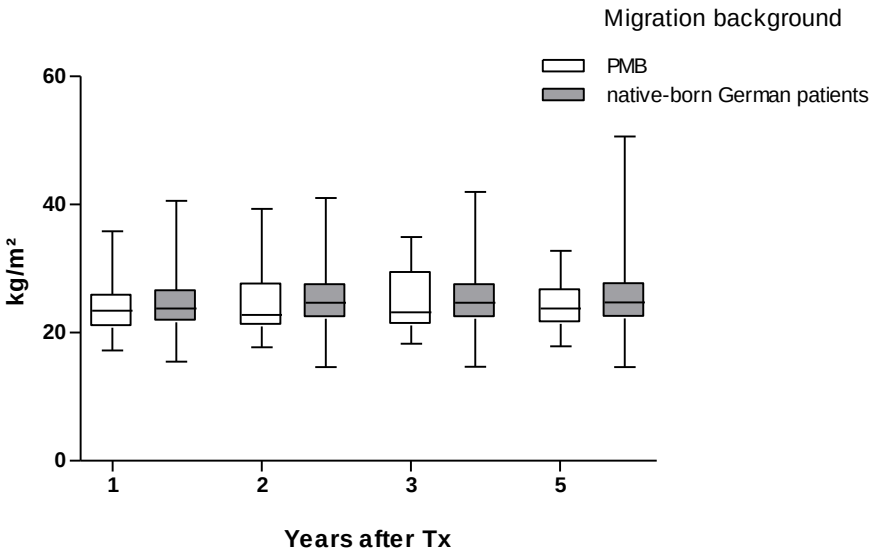

Figure 22 Mean BMI of PMB and native-born German patients.

PMB – patients with migration background; BMI – Body mass index; Tx – transplantation

3.4.1.2 Bone metabolism

Parathyroid hormone (PTH), one of the most important hormones regulating calcium and phosphate homeostasis, was checked in both patient cohorts. Mean PTH was not significantly different between the groups. However, the results showed a trend toward lower PTH levels in the group of PMB during the first year (p = 0.07, Wilcoxon test; p.adjust: p = 0.06, Wilcoxon test).

The mean PTH for PMB and for native-born German patients in the first, second, third and fifth year after transplantation was as follows, also shown in figure 23 (listed as mean, first for PMB then for native-born German patients): first year: 114.7 ± 91.6 pg/ml and 159.9 ± 180.6 pg/ml, second year: 113.7 ± 94 pg/ml and 145.8 ± 189 pg/ml, third year: 115.2 ± 180 pg/ml and 138.8 ± 279 pg/ml and fifth year: 75 ± 55 and 114 ± 120 pg/ml.

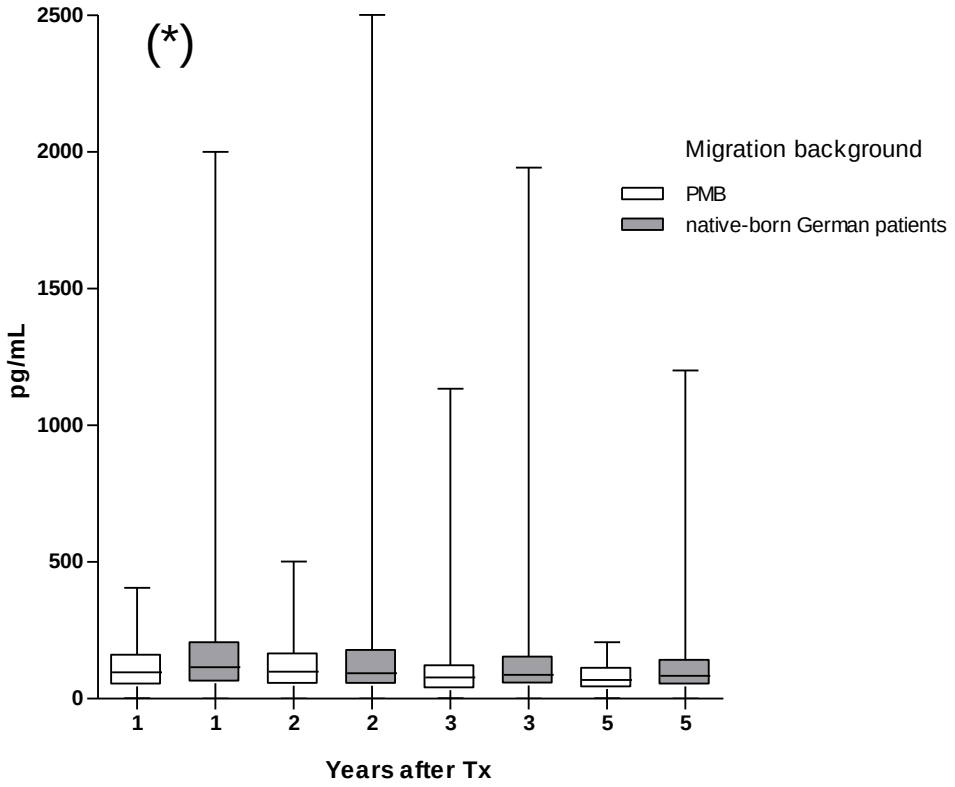

Figure 23 Mean PTH of PMB and native-born German patients.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1)

PMB – patients with migration background; PTH – Parathyroid hormone; Tx – transplantation

The subgroup analysis of patients with a PTH ≥ 300 pg/ml showed significantly higher levels of PTH in the group of native-born German patients compared to PMB in the first year (median of 425 pg/ml vs. 327 pg/ml; $p < 0.05$, Wilcoxon test). The incidence of PTH levels above 300 pg/ml after transplantation was higher, though not significant, in the group of native-born German patients during the first and second years after transplantation, respectively (incidence in the first year: 12.0 percent (110 of 915) and

6.8 percent (5 of 74); p = 0.3, Fisher's exact test; and in the second year: 10.1 percent (69 of 683) and 2.2 percent (1 of 45); p = 0.1 Fisher's exact test, for native-born German patients and PMB, respectively).

3.4.1.3 Cardiovascular risk factors

Median systolic blood pressure (BP) in the overall group was 124 – 128 mmHg throughout the first five years (25% and 75% percentile: 118 – 120 and 130 – 135 mmHg). Whereas median diastolic BP was 75-77 mmHg (25% and 75% percentile: 70 - 71 and 80 mmHg) during the first five years, shown in figure 24 and figure 25. Systolic BP was lower in PMB in the first year and third year posttransplant as shown in figure 24 (first year after transplantation: median of 121 and 128 mmHg in the cohort of PMB and native-born German patients, respectively; p = 0.001, Wilcoxon test; p.adjust p = 0.03, Wilcoxon test; third year after transplantation 121 and 125 mmHg in the cohort of PMB and native-born German patients, respectively, p = 0.03, Wilcoxon test; p.adjust p = 0.14, Wilcoxon test). However, data of year three posttransplant did not reach statistical significance after adjustment for age and gender.

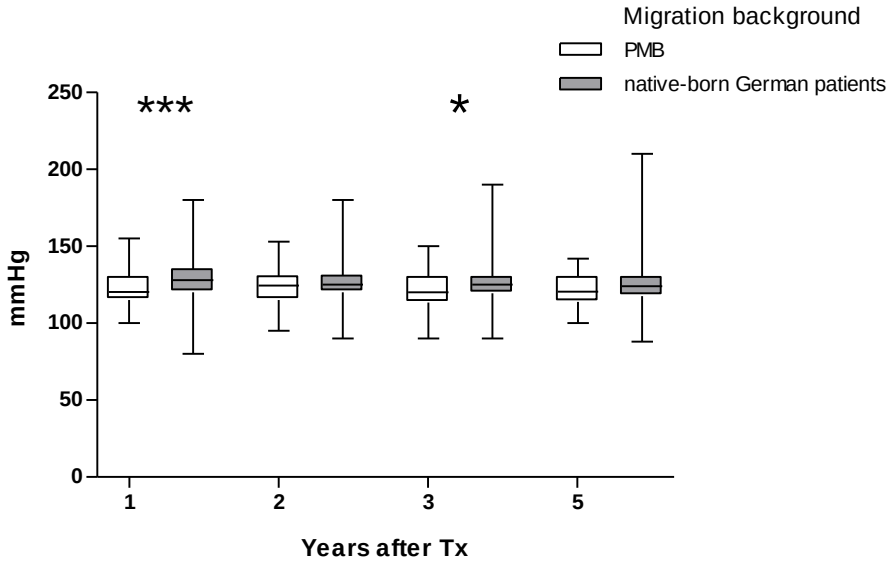

Figure 24 Systolic blood pressure of PMB and native-born German patients.

* Significant differences between PMB and native-born German patients ($p < 0.05$)

*** Highly significant differences between PMB and native-born German patients ($p < 0.001$)

PMB – patients with migration background; Tx – transplantation

Diastolic BP showed a trend to higher values in the cohort of PMB in the fifth year posttransplant shown in figure 25. This trend was not present after adjustment for age and gender (78 and 75 mmHg, p = 0.08, Wilcoxon test; p.adjust p = 0.11, Wilcoxon test). Data on other time periods did not differ significantly between the groups.

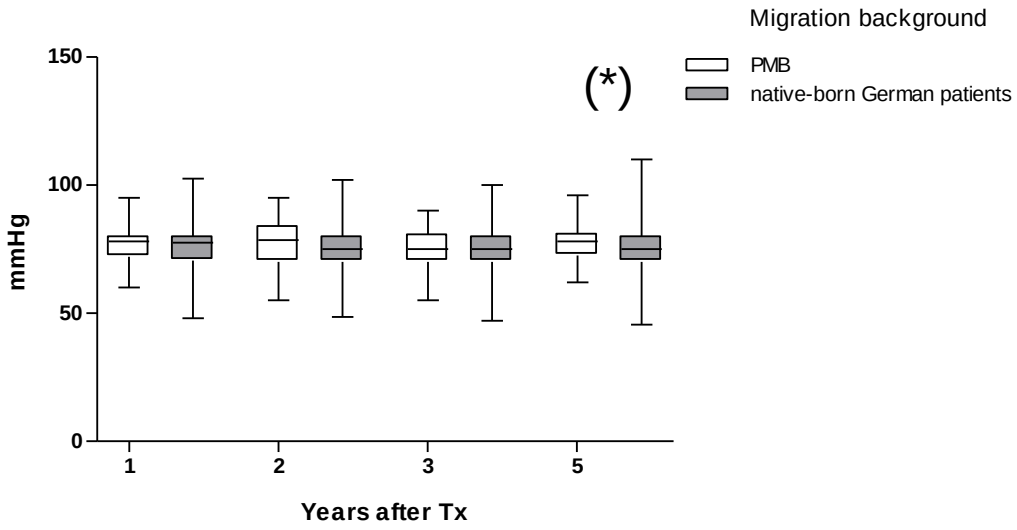

Figure 25 Diastolic blood pressure of PMB and native-born German patients.

(*) Statistical trend toward differences between PMB and native-born German patients (p = 0.05 – 0.1)

PMB – patients with migration background; Tx – transplantation

4 Discussion

4.1 Migration background and transplantation

While the number of studies about migration and general health care rises, information about migration and transplant medicine in Europe is still scarce. In contrast, there has been a reasonable amount of investigation concerning this topic in the United States.

In the United States, African Americans have a lower long-term allograft survival rate compared to white Americans and other ethnic minorities. This disparity was first demonstrated by Opelz and colleagues and has been confirmed by numerous other studies since (Braun, 2007; Opelz, Mickey, & Terasaki, 1977; Pallet et al., 2005; Patzer et al., 2012; Peters, 2005; Press et al., 2005; Young & Gaston, 2000). The 2010 annual report of the Organ Procurement and Transplant Network (OPTN) / Scientific Registry of Transplant Recipients (SRTR) declares that the adjusted 5-year renal allograft survival rate is 66.3 percent for African Americans compared to 74.8 percent for Whites (*OPTN / SRTR 2010 Annual Data Report*, 2011). Interestingly, the adjusted 5-year renal allograft survival rate of deceased donors of “Asians”, “Hispanic/Latino” and “Other/Multi-race” ethnic groups in the United states is impressively higher than that of African Americans (80.8 percent, 78.5 percent, and 73.6 percent, respectively)(*OPTN / SRTR 2010 Annual Data Report*, 2011). Potential reasons for this discrepancy include immunologic, genetic and pharmacologic aspects and have been extensively discussed (Braun, 2007; Pallet et al., 2005; Young & Gaston, 2000). However, socioeconomic factors, education and access to health care are other possible factors to influence outcome after renal transplantation (Chakkera et al., 2005; Goldfarb-Rumyantzev et al., 2006).

In Europe there has not been much noteworthy investigation in the field of migration background and transplantation until 2005. In 2005, Pallet and colleagues published a study analyzing the correlation of race and ethnicity in the outcome after renal transplantation of 952 Caucasian patients and 140 African European patients in a French population (Pallet et al., 2005). Pallet et al. showed that ethnic origin does not influence allograft outcome after renal transplantation in France. Their study may be the most prominent study in this matter in Europe and is an answer to numerous studies evaluating this subject in the United States.

A smaller study concerning this subject was published in Spain in 2009 by Mérida and co-authors. The authors matched 27 African emigrants with 49 Caucasian patients from

Spain and confirmed previous results from France (Mérida et al., 2009). Mérida and colleagues found similar results for both groups for incidence of acute rejection and patient and graft survival (Mérida et al., 2009). The studies by Pellet et al. and Mérida et al. reinforce the hypothesis that there must be other than immunological factors that are responsible for the differences between Caucasians and Africans and their ancestors which influences allograft survival in the United States.

Oztek and colleagues studied the outcome after renal transplantation in children with and without migration background in Austria in a cohort of 196 children (Oztek et al., 2011). They show equal outcomes of renal transplantation in children with migration background and native-born Austrian children. There were no differences in the HLA mismatch observable, while a higher rate of living donation in the group of children with migration background could be noticed (Oztek et al., 2011). However, a limitation of the study mentioned above is the small number of subjects and events.

To further investigate this field, this single center study was carried out analyzing the data of 1266 patients, 86 (7 percent) of whom were patients with migration background (PMB). To the knowledge of our working group, no study investigating this subject in Germany has been published to date.

4.2 Patient population

The cohorts for analysis consisted of 1180 (93 percent) native-born German patients and 86 (7 percent) patients with migration background (PMB) distributed throughout different years posttransplant. This results in reduced patient groups the later the time point of focus after transplantation. For this reason it was concentrated for most variables on data up to the fifth year posttransplant, since the cohort of PMB after five years posttransplant was too small for many analyses.

With a mean age of 43 years at transplantation, PMB were significantly younger than native-born German patients, with a mean age of 48 years at transplantation. Reasons for this include the higher proportion of inhabitants with migration background in this age group in Germany. In 2010, 67.7 percent of persons with migration background were younger than 45 years, compared to 46.7 percent of native-born German citizen younger than 45 years (*Migration Report 2010*, p. 192). Another reason for younger

PMB could be that the sicker or elderly migrate to their country of origin – the so called “salmon bias hypothesis” (Pablos-Mendez, 1994). This hypothesis is intensively discussed as a cause for the “Latino mortality paradox” in the United States.

Any further analysis was adjusted to age, to exclude any influence that this age difference at transplantation might have on the data.

4.2.1 Origin, year of immigration and language skills

Patients with Turkish background (32 percent) represent by far our largest sub-group in the cohort of PMB. This finding is comparable with demographic data of Germany. In 2010, persons with Turkish migration background formed the largest group with 15.8 percent (*Migration Report 2010*, p. 192). The second largest group formed inhabitants with migration background from Poland: in the present study 7.0 percent, in the whole population 8.3 percent (*Migration Report 2010*, p. 192). In Germany, a large group of 49.4 percent could not be classified by country or had migration background from countries with a percentage less than 1.6 percent (*Migration Report 2010*, p. 192).

The majority (54 percent) of PMB estimated their language skills as “good”, “very good” or considered themselves as a “native speakers”. Hence, it was supposed that the German language was not a barrier between PMB and the health care staff.
Findings about outstanding German language skills amongst PMB are congruent with the present data about the year of immigration: The majority (59 percent) of PMB migrated to Germany before 1991. Thus, the majority of PMB had more than 20 years to acquire their German language skills.

However, we have to keep in mind that this study cannot make a general statement about inhabitants with migration background and kidney failure or even migrants and general health in Germany. The study investigated only transplanted patients. It is possible that a number of inhabitants with migration background and kidney failure were missed, who, due to insufficient language skills or other reasons, were neither put on dialysis nor received transplantation care. This possibility is supported when comparing national statistics with the percentage of PMB in our cohort. The rate of seven percent of PMB in the present study is very low compared to nearly 20 percent inhabitants with migration background of Germany’s population (*Migration Report 2010*). However, a 20

percent rate of transplant recipients wouldn't reflect the young age pattern of inhabitants with migration background in Germany.

Nevertheless, experience showed a rate of approximately seven percent PMB in dialysis care in Berlin/Germany (personal communication), which corresponds to the seven percent of PMB among transplanted patients in the present study. Hence, it was assumed that most PMB on dialysis also underwent transplantation in Berlin. If there were more than seven percent of inhabitants with migration background with kidney failure in Berlin, the point where they fail to enter treatment must be before dialysis. One potential explanation would be the above mentioned "salmon bias hypothesis" (Pablos-Mendez, 1994).

4.2.2 Education and Occupation

The present data provide a comprehensive orientation about education and occupation of the PMB and the native-born German patients in the study. Interpreting these data, one has to consider that there might be some factors which influence the results discussed later.

The results show significantly more PMB without a high school leaving certificate. Further, more native-born German patients than PMB had graduated from the "Realschule". Students graduate from this school after 10 years of education. This difference was highly significant as well. Nonetheless, significantly more PMB graduated with the "Abitur" from the "Gymnasium". This difference was not significant after adjustment for age, hence, a difference was stated in the present study but it cannot be transposed to other transplanted PMB in Germany.

School systems vary widely among different countries. In Germany, which has a tripartite school system, students obtain their first level of secondary education after completing nine, or ten years of secondary modern school, the so-called "Hauptschulabschluss" at the "Hauptschule". Everything less than graduation from such a school, or less than nine years of education at other secondary modern schools with higher standing ("Realschule" or "Gymnasium"), is not considered a high school diploma. The years of education in other countries were, if necessary, adapted to the German equivalent of high school diplomas, since school systems of some other

countries are not easily comparable. German students are most likely to complete at least nine years of education, whereas students in other countries might obtain a high school diploma after less than nine years of education. This may be a reason for the disparity of school leaving certificates between PMB and native-borne German patients.

Further education after secondary school differed significantly, in some cases highly significantly, in all aspects between PMB and native-born German patients. Explanations and limitations to the results about further education are comparable to the above noted explanations and limitations to the results about high school education. Again, educational systems vary tremendously in the international context. In Germany, most citizens obtain some kind of further education after secondary school, often an apprenticeship or vocational training. In other countries, however, this may not be the case.

On the other hand, significantly more PMB with university degree compared to native-born German patients (see also 3.1.2) were found. One explanation for this finding may be the increasing deficit of highly educated experts in Germany in recent decades and increasing efforts to attract experts from outside of Germany.

Though there were many significant, in some measures highly significant, differences in aspects of education between PMB and native-born German patients, these differences did not seem to result in a difference in the state of employment (see also 3.1.2). The only item differing significantly between the two cohorts in this matter was the higher rate of “retired” native-born German patients compared to PMB. To evaluate the state of employment in a cohort of patients with seriously impeding conditions is more challenging than in healthy individuals. Underlying fundamental reasons include the definition of the state of employment by the health care system when an employee is unable to work for a longer period of time as a consequence of an illness. Depending on the severity and on the length of time the employee is unable to work, he/she submits a statement of work disability, whereupon they receive long term disability or are retired prematurely. In this context it may be challenging for PMB to distinguish between formal descriptions although their language skills might be very good.

Correlating to the differences in the percentage of graduates of secondary schools between PMB and native-born German patients, there were differences in the type of employment between the two cohorts. To be able to evaluate occupational differences,

professions were classified according to the educational demands of each profession. The present data show highly significant differences in the number of patients with an occupation requiring or not requiring an apprenticeship or vocational training: More native-born German patients had a profession requiring an apprenticeship/vocational training, while more PMB worked in a situation not requiring further education beyond secondary school or not requiring education at all. When interpreting these results, it has to be considered that academic degrees of other countries, especially outside of the European Union, may not be accepted as such in Germany. Hence, not all PMB with an academic degree might be able to work in their profession like native-born German patients with a German academic degree are able to. This may have an effect on the number of patients in a job which demands an apprenticeship/vocational training and on academic jobs in the cohort of PMB. Further, evaluating the present data, it was challenging at times to differentiate between academic jobs and non-academic ones, which may have resulted in some inaccuracy in the results relating to this item.

Interpreting and analyzing these results, the above noted differences in educational systems have to be considered, challenging the comparison of PMB and native-born German patients. Additionally, this aspect of the present study was evaluated with a relatively limited cohort of 57 PMB and a control group of 60 native-born German patients (see also 2.2). Yet, differences in education between PMB and native-born German patients could be seen. Although this was not the main point of focus, it has to be stated that obviously PMB in Berlin find themselves in different conditions in terms of high school and further education. These conclusions are mostly comparable with data about education of the Ministry of Migration and Refugees, see table 4 and table 5. To investigate this subject further studies with greater cohorts are needed.

School degree in Germany, Microcensus 2006 →	**No school-leaving certificate**	**"Hauptschul-abschluss" (9 yr)**	**"Realschul-abschluss" (10 yr)**	**"Abitur" (13 yr)**	**Poly-technical high-school**
Inhabitants Germany 2006 ↓					
Persons with migration background	13.0%	40.0%	19.8%	25.9%	0.6%
Native-born German persons	1.8%	43.7%	22.0%	23.9%	8.0%

Table 5 School degree of all persons not (anymore) attending a general high school in Germany.

Reference: Federal Statistical Office, 2008, adapted from the Federal Office for Migration and Refugees (Siegert, 2008, p. 47).

yr – year

Educational degree of ≥ 25 yr olds in Germany, Microcensus 2006 → / Inhabitants Germany 2006 ↓	No further education	Apprentice-ship	"Fachhoch-schule" and university degree	Others*
Persons with migration background	42.0%	37.1%	13.7%	8.3%
Native-born German persons	36.6%	56.6%	13.9%	10.2%

Table 6 Type of educational degree/further education of ≥ 25 year olds in Germany with and without migration background, Microcensus 2006.

Reference: Federal Statistical Office, 2008, adapted from the Federal Office for Migration and Refugees (Siegert, 2009, p. 57).

In the present study, a distinction was made between "Fachhochschule" and "university degree". To compare the data of the present study with the one above please summate entries of "Fachhochschule" and "university degree" of the present study.

yr – year; * master craftsperson/technician/internships/technical training school/vocational preparatory class

4.3 Discussion of primary hypothesis: outcome

4.3.1 Graft function: Creatinine and GFR

As shown in figure 8, mean creatinine values of PMB were significantly lower during years one and two posttransplant compared to native-born German patients. During years three and five no significant differences between the groups could be noted. The tendency of differences in creatinine values between the group of PMB and native-born German patients in the years directly following transplantation, but not later during follow up, may be explained by a declining number of patients at a longer posttransplant period. This was of special importance in the group of PMB, since this group was much smaller than the cohort of native-born German patients. Consequently, statistical tests are less likely to show significance (patients with creatinine measurements in the groups of PMB and native-born German patients during years one, two, three, and five posttransplant were as following: 83 and 1156; 65 and 917; 54 and 788; 35 and 580, respectively).

Age is a factor when calculating the GFR on the basis of creatinine to predict the filtration of the kidneys. Consequently, it is not surprising to find, in accordance with the creatinine values, the GFR to be significantly lower among the relatively young cohort of PMB prior, but not after adjustment for age and gender. Creatinine levels and the GFR were significantly lower, so was the frequency of patients with diminished GFR in year one posttransplant among PMB also after adjustment for age (see also 3.2.1).

As one of the first studies, this study shows better graft function among PMB compared to native-born patients: In 2005, Pallet and co-workers investigated differences after renal transplantation between a cohort of African European patients and Caucasian patients (Pallet et al., 2005). The authors did not find any difference in serum creatinine clearance during the first five years after transplantation and conclude that they did not find an influence of ethnic background on allograft outcome after renal transplantation (Pallet et al., 2005). Another study investigated the influence of migration background on outcomes after renal transplantation in children in Austria (Oztek et al., 2011). As Pallet et al. five years earlier with African European patients, Oztek and colleagues did not find any differences in glomerular filtration rate (estimated glomerular filtration rate (eGFR)) between patients with migration background and native recipients (Oztek et al., 2011). Other studies demonstrating equal graft function of the study groups (creatinine or eGFR) in a comparable setting include the investigations by Dooldeniya or Molnar et al. (Dooldeniya et al., 2006; Molnar et al., 2012).

Creatinine is a useful marker of pathological processes, since it ensures accuracy, measurement precision, and has a quite consistent individual daily rate of creatinine levels (Nankivell & Kuypers, 2011). Therefore a rise of about 25 percent above the creatinine baseline value is sensitive for alterations in renal allograft function (Nankivell & Kuypers). Graft failure is reliably predicted by a decline in inverse serum creatinine of less than -30 percent (relative risk [RR] 2.56 with 30 percent reduction) (Kasiske, Andany, & Danielson, 2002). Another study underlines the importance of serum creatinine, or calculated GFR levels, as markers of renal function and graft failure (OR=2.2 for an increase of 1 mg/dl) (Kaplan, Schold, & Meier-Kriesche, 2003). However, the authors stress the predictive power of these markers as the area under the receiver operating characteristic curve (AUC) was unsatisfactory (0.627) (Kaplan et al., 2003). A second study compared various eGFR formulae to mortality six months

after renal transplantation and graft failure three and five years posttransplant (He et al., 2009). In the case of unsatisfying areas under the receiver operating characteristic curve for mortality (0.63 and 0.61 for 3- and 5-year mortality), and graft failure (0.66 and 0.60 for 3- and 5-year graft failure), the authors conclude that eGFR equations foresee graft failure and mortality only in a limited way (He et al., 2009).

Significantly poorer creatinine and GFR values among native-born German patients during the first two years posttransplant are consistent with significantly more graft losses in this cohort during the first two years and especially in the first six months after transplantation.

4.3.2 Immunologic complications

4.3.2.1 Rejections and ischemia times

In the study's patient population, 519 patients (41.1 percent) experienced, at some point after transplantation, one or more rejections, while the results didn't show differences between the cohort of PMB and native-born German patients in any analysis of rejection, except a longer rejection-free survival in the group of native-born German patients (time period between transplantation and the first rejection, see also Figures 9 through 11). Most rejections occurred during the first year after transplantation with an incidence of 39.5 percent in the cohort of PMB and 35.8 percent in the cohort of native-born German patients.

To our knowledge, this is the first study to compare the grade of acute rejection episodes according to the Banff classification criteria between patients with migration background and native patients. Analyzing the first rejection, most patients suffered from a rather mild acute rejection: 36.8 percent of patients with a rejection experienced a borderline rejection (15.2 percent of the whole cohort) and 37.2 percent a rejection graded as I according to the Banff classification (15.3 percent of the whole cohort, see also Figure 12).

Though potent immunosuppression has dramatically reduced rejections and graft loss, acute and chronic rejections of the kidney allograft are still the most important immunologic complications after renal transplantation. At the same time it remains challenging to optimize immunosuppression therapy and find an equilibrium between

sufficient immunosuppression with the least amount of drug toxicity, danger of opportunistic infections, and the risk of malignancy. The task becomes even more challenging because non-invasive monitoring of acute rejections is far from perfect to date, whilst renal allograft biopsy is still the gold standard for diagnosing acute allograft rejection in a patient with poor kidney function (see also review (Nankivell & Alexander, 2010)). Acute rejection episodes are of special importance, since they are a significant independent variable for long-term survival (Flechner et al., 1996).

The present findings are predominantly consistent with the literature showing similar frequencies of acute rejection episodes after renal transplantation among immigrant and native recipients. This is also backed up by the studies by Pallet et al. and Mérida et al. mentioned earlier (2009; 2005).

Investigating outcome after renal transplantation in children, Oztek and colleagues did not find any significant differences in the frequency of acute rejection episodes (2011). However, in this study, PMB had a significantly shorter rejection-free survival compared to native-born German patients. In Vienna, rejection-free survival did not differ between native children and immigrant children (Oztek et al., 2011).

Comparing results from the United Kingdom (UK) with the current findings, one notices both parallels and discrepancies. Dooldeniya et al. investigated the renal transplant outcome among Indo-Asians and Caucasians, finding biopsy-proven acute rejection rates among the two cohorts similar to those of this present study, but showing a significantly longer mean rejection-free survival in Indo-Asian patients (46 ± 5.7 days) compared to Caucasians (33 ± 6.3 days) (Dooldeniya et al., 2006). In contradiction to the findings of Dooldeniya et al., the present study revealed fewer mean overall rates of acute rejection in the whole cohort and longer rejection-free survival in native-born German patients than reported by the colleagues from the UK (median 26, mean 251 ± 631 days for native-born German patients and median 11 days, mean 105 ± 288 days for PMB (skewed deviation, therefore the median was chosen for statistics but the mean also mentioned to compare it to Dooldeniya's data) (Dooldeniya et al., 2006). Shorter rejection-free survival among PMB, that can be explained by the greater mismatches in the HLA system, didn't affect the transplant outcome, since PMB showed a better graft function compared to native-born German patients.

The incidence of acute rejections during the first year after transplantation in current national data shows low rates of “acute rejections with necessity of therapy” of 13.5 percent, according to the AQUA-Institute (AQUA-Institute, 2012). Further, as noted above, data from the United States Renal Data System from the current 2012 Annual Data Report showed a rate of 11 percent acute rejections in the course of the first year after transplantation for deceased donor recipients transplanted in 2009 ("U S Renal Data System," 2012, p. 284). However, it is not surprising to find a lower first year rejection rate in current data compared to the present report, since the mean year of transplantation in this whole cohort was 2004, when rejection rates were still much higher (see also section 1.1.3.2.2 and the "U S Renal Data System" 2012, p. 289). Further, acute rejection episodes with biopsy-proven borderline changes were also classified as rejection. Other studies didn’t classify borderline changes as acute rejection (Uslu & Nart, 2011). If borderline changes were not taken into account, the frequency of rejection would be markedly lower (see section 3.2.2). Moreover, as no other indicator, the low rates of graft loss demonstrated good outcome and underlined the rather low effect of mild acute rejections, as borderline changes, on graft survival.

Another principal factor to influence the probability of acute rejection is the ischemia time before and during the transplantation. Mean cold (10.0 ± 5.0 hours), mixed (30.6 ± 8.6 minutes), and warm ischemia time (0.5 ± 2.7 minutes) did not significantly differ between the groups ($p > 0.1$).

Longer cold ischemia time (CIT) increases the immune response and the risk of rejection (see also review (Nankivell & Alexander, 2010)). Additionally, in a study by Quiroga and co-workers, CIT was determined as an important independent factor of graft failure, which increased in a linear manner, the longer CIT was documented (I. Quiroga et al., 2006).

Comparable studies on this field showed heterogeneous results. In the already mentioned study by Pallet et al., CIT was remarkably longer than in the present study, and significantly longer in African Europeans (28.5 ± 10 hours), compared to Caucasians (24.5 ± 11 hours) (Pallet et al., 2005). Pallet et al. attribute this difference, to some extent, the time the recipients needed to travel from their home to, in most cases, Paris, France (Pallet et al., 2005). In a study by Cantrelle et al., CIT was significantly different between native French patients transplanted in mainland France

(21.2 ± 8.0 hours), and French patients in overseas territories (33.3 ± 24.0 hours), Greek patients (30.4 ± 8.4 hours), and Italian patients (24.1 ± 9.8 hours) (Cantrelle, Laurens, Luciolli, Loty, & Tuppin, 2006).
Oztek and co-workers report in a study mentioned above a mean CIT of 16.0 ± 1.7 without differences between the groups (Oztek et al., 2011).

A recent study by Gondos and co-authors compared outcome after renal transplantation between Europe and the United States (2012). In Europe and the United States the majority of allografts was transplanted with a CIT between 13 and 18 hours, which is considerably longer than the CIT reported in the present study (Gondos et al., 2012). In conclusion, one can state that the mean CIT in the present study was shorter than the average in Europe and the United States without disadvantage for ethnic minorities.

After summarizing and comparing the results to current literature one may conclude that there were no differences in rejection rates and CIT between the groups, in contrast to studies in the US and Europe. First year rejection rates were high compared to 2012 data. Nevertheless, the mean transplant year was 2004, with considerable improvement in immunosuppressive therapy since then. Further, the majority of rejections were mild.

4.3.2.2 Graft loss

Graft loss was defined as starting dialysis on account of a patient's insufficient graft function. Fewer PMB (4.7 percent) suffered a graft loss than the cohort of native-born German patients (13.8 percent) within an overall observation period of more than 12 and 14 years of PMB and native-born German patients, respectively (maximum transplant age of 154 and 168 months in PMB and native-born German patients, respectively; Figure 13). PMB who suffered a graft loss had longer graft survival prior to graft loss (median 70.5, range 78 months) than native-born German patients (median 22.0, range 149 months, $p = 0.045$).

Graft survival at three years posttransplant for PMB and native-born German patients was 100 percent and 91 percent, respectively (graft failure: 0 of 56 and 98 of 831 remaining cases). Graft survival after 10 years for PMB and native-born German patients was 82 percent and 80 percent, respectively (graft failure: 4 of 7 and 157 of 174 remaining cases). See also figure 13.
This rate of graft survival is high compared to current national and United States

reference data. In Germany, graft survival at three years posttransplant is 89.3 percent (AQUA-Institute, 2012). In the United States, in 2009, there is a 0.39 and 0.56 probability of a graft failure within ten years posttransplant in patients with a living donor and a deceased donor allograft, respectively, ("U S Renal Data System," 2012, p. 289).

As discussed earlier, it has been reported that acute rejection episodes influence long-term graft survival (Flechner et al., 1996). Though overall acute rejection rates have diminished with modern immunosuppressive protocols, overall graft survival has not significantly improved (Meier-Kriesche, Schold, Srinivas, & Kaplan, 2004).

Factors having an impact on graft survival include delayed graft function and CIT (Isabel Quiroga et al., 2006). Further, organ quality plays an increasing role, since failure to meet the demand for organs leads to the exploration of alternatives. For example, expanded-criteria donors (ECDs) are donors aged ≥60 years or donors at an age of 50 to 59 years with two of the following risk factors: Death from cerebrovascular accident, hypertension, or terminal serum creatinine >1.5 mg/dl (Rao & Ojo, 2009). However, ECD renal transplants have a 70 percent greater risk of failure in comparison with a allograft from a standard-criteria donor (SCD) (Metzger et al., 2003). Other non-standard-criteria donor kidneys include donations after cardiac death (DCDs) and donations after brain death (DBDs), which result in a poorer outcome as well (for further information please see review (Rao & Ojo, 2009)).

Influence of medication non-adherence on rejection and graft survival is discussed in another section (4.5 Discussion of tertiary hypothesis: compliance).

The majority of studies investigating graft survival of patients with migration background and native patients in Europe did not find significant differences of graft survival between the groups (Dooldeniya et al., 2006; Loucaidou et al., 2004; Mérida et al., 2009; Oztek et al., 2011; Pallet et al., 2005). However, one recent study in a Hungarian center compared outcome after renal transplantation of patients with Roma ethnicity with Caucasian patients and found a higher death-censored graft loss among Roma patients (Molnar et al., 2012). The authors attribute these results to socio-economic factors, greater cardiovascular risks and possible different genetic background in the cohort of Roma (Molnar et al., 2012). Two studies in the United Kingdom demonstrated a trend toward decreased transplant survival in black patients after three years post transplantation (Rudge, Johnson, Fuggle, Forsythe, & Kidney and Pancreas Advisory

Group, 2007) and after five years posttransplant in Asian patients (Jeffrey, Woodrow, Mahler, Johnson, & Newstead, 2002).

Especially in the United States, outcome of renal transplantation still shows racial disparities. A current review by Malek and co-workers discuss many details relating to this topic (Malek, Keys, Kumar, Milford, & Tullius, 2011).

This discrepancy between ethnic groups was already noticed by Pallet and co-workers in 2005, who state the hypothesis that differences in access to the health care system may result in different outcomes in the United States, but not in France (Pallet et al., 2005). Other possible explanations for racial disparities in the United States include the question whether patients´ adherence to complex and costly medication regimens diverge between racial groups (Pallet et al., 2005). Moreover, a recent study compared the outcome of renal transplantation in Europe and the United States and found comparable results for data one year posttransplant but higher overall 5- and 10-year graft survival rates in Europe. A possible explanation might be the 3-year limitation in immunosuppression coverage in the United States by Medicare (Gondos et al., 2012).

In Germany, health care provides allograft recipients with unlimited medication coverage independent of socio-economic factors and thus provides PMB and native-born German patients with comparable access to the health care system (see also section 1.1.4). Hence, a low socio-economic status as possible reason for inferior outcome, as may be the case for some minorities in the United States, is not given. Further, the majority of PMB immigrated to Germany more than 20 years ago (see also 3.1.1); consequently, a good integration into German society can be assumed, which makes appropriate usage of the health care system very likely. Whereas good medication adherence by patients in the cohort of PMB may well be the reason for the present finding of significantly fewer graft failure in PMB (4.7 percent) compared to native-born German patients (13.8 percent) after more than 12 years of observation. Hence, low level of education and lower classification of employment of PMB compared to native-born German patients did not have a negative effect or did not override other positive effects of the PMB cohort on graft survival as hypothesized in other studies (Molnar et al., 2012).

4.3.2.3 Infections

As discussed in the introduction, infections are a major complication and increasing risk with potent immunosuppression. The present results show no significant differences between the groups concerning the risk of infections, in terms of numbers of patients with positive reactions to tests (CMV, BKV, EBV and urinary tract infections; see also figure 15). Only a trend toward more positive reactions to tests of BK virus could be seen. In this study the ratio of positive compared to negative tests in PMB and native-born German patients during routine controls were analyzed. The purpose of this analysis was to get an impression of common transplantation-associated infections in PMB and native patients as there has been little investigation in this field. Considering related results between the groups, one can state that the larger number of visits to the outpatient department among PMB cannot be explained by greater complications concerning infections in the PMB group.

It can be concluded that the primary hypothesis of a difference in outcome between the cohort of patients with migration background and native-born German patients was proven by this study in one important aspect: Graft function was better in terms of better creatinine and GFR values in the group of PMB. There were fewer immunologic complications in PMB in terms of fewer and late graft failures. With regard to immunologic complications, no differences for rates of infections or acute rejections, despite worse HLA-match in the group of PMB, were observed. This could be the result of good compliance without an overriding effect of lower level of education.

4.4 Discussion of secondary hypothesis: waiting time

Median waiting time (wait time) of PMB and native-born German patients was 72 and 56 months, respectively (mean of 64.0 ± 36.4 and 56.8 ± 37.8 months, respectively). This difference was a trend observed in the present study (p = 0.07), which reached statistical significance after adjustment for age and gender (p.adjust: p = 0.04, figure 16). With results ranging in p-values around the value considered statistically significant (0.05) one has to be careful in interpretation, since there is a very low possibility of a false positive result. Especially when testing many variables as in this study, there is a chance of receiving a significant false positive result. Since this study is rather exploratory, it was not corrected for multiplicity and discusses these findings as well (see also section on limitations 4.7).

Nevertheless, when adjusted for age and gender, this result demonstrated significant longer waiting times for PMB. Hence, the present study with the given cohort shows a trend toward longer wait times of PMB. Transferring the results to the population of Berlin (age and gender adjusted) one has to consider the possibility of longer wait times for inhabitants with migration background. A possible explanation for longer wait times among PMB is a more difficult HLA match, indicated also in more mismatches among PMB.

To date there is limited investigation about waiting times of patients with migration background in comparison with native patients in Europe. Rudge and co-authors found wait times for Asian and black patients to be almost twice as long as for white patients in the United Kingdom (Rudge et al., 2007). Cantrelle et al. studied waiting times, HLA matching and cold ischemia time in “foreign patients and French patients living in mainland France or in French overseas territories” (Cantrelle et al., 2006). Wait times differed significantly between mainland French patients (median of 13.8 months) and other ethnic groups (Italians 17.8 months, Greeks 21.9 months etc.) in their study (Cantrelle et al., 2006). Cantrelle and co-authors mention challenges encountering HLA matching and challenging logistics in overseas territories as possible reasons for this difference (Cantrelle et al., 2006). A difficult HLA match is also addressed by Jeffrey and colleagues as a reason for longer waiting times in their cohort of Indo-Asian patients (55 percent transplanted at 3 years) compared to native patients (72 percent transplanted at 3 years) in Yorkshire, United Kingdom (Jeffrey et al., 2002).

There was one study comparing the outcome after renal transplantation in children with and without migration background in Austria mentioning waiting times of 1.5 ± 1.7 years for the whole cohort without difference between the groups (Oztek et al., 2011). However, the study population consisted of children and is, particularly in the context of waiting times, hardly comparable with the present results.

In the United States, overall median waiting time was 2.6 years in 2010, while white patients have a significantly shorter waiting time than other ethnic groups including African Americans ("U S Renal Data System," 2012, p. 286). Other data collected during the period from 1998 to 2003 showed a median waiting time in the United States to be about 1100 to 1200 days (3.0 to 3.3 years), with a median wait time of 769 days for white patients and more than 1300 days for all other races in 2002 (Leichtman et al., 2008).

Waiting time depends to a great extent on blood types. In the United States, patients with blood group 0 and B wait twice as long as candidates with blood group A and four times as long as patients with blood group AB (Danovitch et al., 2005).

In the United States, it is not completely understood why African Americans wait longer for a renal transplant than whites. One reason is earlier wait-listing, often prior to treatment by dialysis in white patients compared to African Americans (Kutner, Zhang, Huang, & Johansen, 2012). Other reasons for long waiting times may be rare blood and HLA groups of Sub-Saharan African patients (Cantrelle et al., 2006) and consequently, African Americans with Sub-Saharan African ancestry.

Interestingly, the present results show two peaks in waiting times. The first peak after 19 months and the second peak after 75 months as shown in figure 17.

There are two possible reasons for a peak after a relatively small period of time. Many living donors may decide to donate a kidney to a relative/friend after an initial period of dialysis. Further subanalysis could show detailed results in this matter. Another reason could be the European Senior Program, ESP (Old-for-Old Program), with earlier transplantations of grafts donated by elderly persons 65 years and older to recipients of 65 years and older on the waiting list. However, subanalysis in the present cohort showed that the mean waiting time of recipients aged 65 and older was 51.1 ± 26 months. This data is consistent with data from Eurotransplant: most patients receiving a graft via the ESP wait between 24 and 59 months (Oosterlee & Rahmel, 2012, p. 61).

Thus, wait time for elderly in the ESP is shorter than the mean or median wait time in the present study and influences the first peak of the present findings.

4.4.1 Discussion of sub-hypothesis HLA match

Mean overall mismatches and median mismatches of HLA-A and HLA-B were significantly greater in the cohort of PMB than in native-born German patients (see table 2). Since the values describing the number of mismatches were discrete numbers, the results demonstrate significant differences, even though the difference in question was quite slim, in this case, only the percentiles differed between the groups. In the present study most patients with migration background were of Caucasian ancestry and therefore should have a comparable HLA genotype with native-born German patients. Further analysis would be needed to reveal details in this case.

Poor HLA matching is associated with increased rejections and decreased graft survival, hence poorer outcome (more on this topic, e.g. (Nankivell & Alexander, 2010; Nankivell & Kuypers, 2011). Another study demonstrated HLA DR mismatches even as the most important predictor of rejection if the patient did not have a delayed graft function (I. Quiroga et al., 2006).

In Europe, studies comparing HLA mismatches of migrant patients and native patients show divergent results. The majority of studies showed a similar level of mismatches between their cohorts (Dooldeniya et al., 2006; Mérida et al., 2009; Oztek et al., 2011; Pallet et al., 2005), while some studies found significant differences (Cantrelle et al., 2006; Crippin, 2007; Jeffrey et al., 2002). In the United States, one study found that the amount of allografts with 4 to 6 HLA mismatches is higher in Asian, African American and other race/ethnic recipients than in non-Hispanic Caucasians (Schold et al., 2005). A comparison between transplantations in Europe and the United States showed that most transplants have a HLA mismatch level of 3 and 4 in Europe and the United States, respectively (Gondos et al., 2012).

Though HLA mismatches did not differ to a great extent, the difference was still significant (proven first sub-hypothesis). Surprisingly, PMB could reach better graft function and graft survival posttransplant despite these differences in matching. Further analysis of genotypes among the major ethnic groups of our PMB and genotype

analysis of renal allografts will be needed to obtain a deeper understanding of this aspect.

Summarizing our secondary hypothesis, a trend toward longer waiting times in patients with migration background (PMB) can be said to exist (partially proven secondary hypothesis). One potential reason for this is the fact that PMB had a more challenging HLA match resulting in longer wait times and more poorly matched allografts. Another possible reason may be miscommunication between patients and health care staff about future transplantation prior to starting dialysis treatment.

4.5 Discussion of tertiary hypothesis: adherence to medical regimen

Adherence or compliance is the extent to which patients adhere to the medical regimen designed by the health care staff, e.g., taking medications (see also introduction 1.1.3.3).

To our knowledge, this is the very first study to investigate patients' adherence in the context of outcome after renal transplantation, comparing patients with and without migration background.

To evaluate compliance, the Essener Compliance Score (ECS) was used. In the present study, 32.5 percent of the patients interviewed had an ESC corresponding to high compliance, 31.6 percent and 35.9 percent of them had medium and low compliance, respectively, without significant differences between the cohorts of PMB and native-born German patients (see also figure 18). Although not significant, PMB showed a greater number of patients with a high score and a smaller number of patients with a medium or low score.

Analyzing the number of visits to the outpatient department as another indicator for adherence, significantly more visits by PMB during years one, two, three and five after transplantation were found (see figure 19). However, after adjustment, a significant difference could only be seen in years one and three posttransplant with statistical trends in years two and five posttransplant.

As discussed in the introduction, adherence to the medication regimen and taking advice from the health care staff are extremely important factors in the years following renal transplantation.

A systemic review by Butler and colleagues (see introduction) showed that about 20 percent of transplant recipients are non-adherent (2004). In another meta-analysis of 147 studies by Dew and co-workers, kidney allograft recipients showed a non-adherence rate of 36 percent to immunosuppressant treatment (2007). With 35.9 percent non-adherent patients in the present whole cohort, the rate of noncompliance in the present study lies at the upper end. The wide range of non-adherence rates can, to some extent, be explained by non-standardized assessment methods.

The questionnaire used in the present study, the ECS, contains 18 items including detailed questions about habits of medication-taking (14 items) as well as knowledge about the medication (4 items). Response options were to be marked on a 5-level-scale. The ECS proved to be valid as a questionnaire for compliance (Franke et al., 2009). In 418 patients after renal transplantation, Franke et al. demonstrated high compliance in 29.2 percent, medium compliance in 40.5 percent and low compliance in 30.7 percent of transplanted patients (Franke et al., 2009). The present data is comparable to the data by Franke et al., even though they showed lower rates of adherence. Explanations for lower adherence rates include misinterpretation of a phrasing of especially one item with possible higher misinterpretation in the present cohort compared to others. Patients who misinterpreted this item quickly dropped into medium or low compliance, which explains the rather high rates of low compliance. Nevertheless, low adherence rates of 35.9 percent cannot be ignored. Further investigation, for instance electronic monitoring and rephrasing of the discussed item of the questionnaire, will be necessary.

One basic aspect of adherence is to keep regular appointments at the outpatient clinic (see more on this topic (Bunzel & Laederach-Hofmann, 2000; Dew et al., 2007)). In various years after transplantation, PMB had more visits compared to the cohort of native-born German patients. One has to keep in mind that this is the total number of visits during one year without comparison to regular appointments. Therefore the number of visits is influenced by the number and severity of complications. Nevertheless, data about graft function (creatinine, GFR) indicated significantly better kidney function in the PMB group during the first year posttransplant and results about

graft loss also show better kidney function in the cohort of PMB. Further, there were no differences between the groups with regard to possible reasons for complications such as infections. Thus, it is very unlikely that the higher number of visits among the PMB is associated with frequent complications but rather with higher adherence and less missed appointments at the outpatient department than in the case of the native-born German patients.

4.5.1 Non-immunologic complications (secondary sub-hypothesis)

4.5.1.1 Cardiovascular disease

One of the major risk factors for graft loss or patient death is related to blood pressure (BP) (Fellström et al., 2005). Systolic BP was lower among PMB in the first year and third year posttransplant shown in figure 24. Median systolic and diastolic BP of the whole cohort during the first five years after transplantation ranged from 124 – 128 mmHg and 75 – 77 mmHg, respectively. Lower BP among PMB deserves to be taken a closer look at. This may be attributed to the Mediterranean diet which many PMB are presumably on. In the future closer insight into this and other related topics will give us “The National Cohort”, a large-scale population study with long observation periods (for further information see http://www.nationale-kohorte.de/informationen_en.html).
Further, the present data show that the average patient had normal systolic (definition: 120 – 129 mmHg) and optimal diastolic BP (definition: < 80 mmHg), according to the generally accepted criteria by World Health Organisation (WHO).

One study by Dooldeniya et al. compared many factors of non-immunologic complications between Indo-Asian and Caucasian patients and is, along with the present study, one of the only European studies to investigate these data in a group of migrant and native patients after renal transplantation (Dooldeniya et al., 2006). The authors found similar systolic and diastolic BP in the two cohorts at one year posttransplant with higher mean systolic and comparable diastolic BP in comparison with the present results (app. 137 – 142 and app. 75 – 80 mmHg, respectively (Dooldeniya et al., 2006).

4.5.1.2 Metabolism: diabetes, cholesterol, obesity

Diabetes is one of the major metabolic risk factors for the kidney function and thus for the function of the transplant. Measurement and control of glycated haemoglobin provides information about the mean blood glucose of the past 8 to 12 weeks (McCulloch, 2012). Mean glycated haemoglobin was at a constant 5.9 percent (normal: 4-6 percent) in years one, two, three and five after transplantation with slight differences of SD depending on the year (see figure 20). There were no significant differences between the two groups. Thus, comparable glucose metabolism in the two cohorts can be expected. Further, one can state that diabetic patients of both cohorts are equally well adjusted concerning blood glucose. In contrast to the present findings, Dooldeniya et al. showed significantly more post-transplant diabetes mellitus among the Indo-Asian population in the United Kingdom (Dooldeniya et al., 2006). Nevertheless, in Indo-Asian patients studied, the group of patients with migration background differed in their ancestry to a great extent from our PMB.

Pathologically high cholesterol, dyslipidemia, is a common condition in the Western world and a known risk factor for cardiovascular disease. Further, dyslipidemia is a risk factor for allograft loss (Wissing, Abramowicz, Broeders, & Vereerstraeten, 2000). Mean cholesterol during the years one to five after transplantation was 189.0-194.0 mg/dl, which is within the normal range (see figure 21). During the first year posttransplant, PMB showed higher values of cholesterol (raw data revealed a statistical trend and adjusted data showed a significant difference). This may be explained by differences in diet and lifestyle rather than non-adherence. Nevertheless, mean values remained below pathological references. Dooldeniya and colleagues found comparable results after three years post transplantation between Caucasian and Indo-Asian patients (189 and 186 mg/dl, respectively) (Dooldeniya et al., 2006).

Another important metabolic factor is obesity, which is correlated with a higher risk of acute rejection, delayed graft function (DGF), longer hospitalization and diminished overall graft survival after renal transplantation (Gore et al., 2006). The present data show a mean BMI of 24.3 to 25.4 kg/m² through years one, two, three and five after transplantation without differences between the two cohorts.

According to Gore et al., about half of all transplant patients can be regarded as obese (BMI ≥ 25 kg/m²) or morbidly obese (BMI ≥ 30 kg/m²) (Gore et al., 2006). Since the

present findings are in the neighborhood of a mean BMI of 25 kg/m², the present results are comparable to the above noted study. Corresponding to the present findings, Dooldeniya and colleagues showed equal rates of patients with a BMI ≥ 30 kg/m² among Indo-Asians and Caucasians (Dooldeniya et al., 2006). Taking into account the serious adverse effects of obesity, the present data underlines the importance of professional help for transplanted patients in the field of diet and lifestyle.

4.5.1.3 Bone metabolism

Parathyroid hormone (PTH) is one of the major hormones regulating calcium and phosphate homeostasis (Potts & Juppner, 1996), minerals essential for bone metabolism. Impairment in bone metabolism, including bone loss and osteonecrosis, appear frequently after renal transplantation (see also section 1.1.3.2.3 and other information on this topic, e.g., (Heaf, 2003)). To the best knowledge of the author, this study has been the first one to investigate PTH levels after renal transplantation in connection with migration background in Europe. Mean PTH levels for the whole cohort in the years 1, 2, 3 and 5 posttransplant were 156.6 ± 176, 143.8 ± 184, 137.3 ± 273 and 112.0 ± 118 pg/ml, respectively, without significant differences between the groups. In the first year after transplantation, however, a trend toward lower mean PTH levels in the group of PMB was found (114.7 ± 91.6 and 159.9 ± 180.6 pg/dl, respectively; $p < 0.1$; see also figure 23 and sections 3.4.1.2 and 1.1.3.2.3).

The present data show pathological levels above normal laboratory references (10 – 65 pg/ml) for all years with a considerable decline throughout the years of observation, indicating an improvement of bone metabolism with a functioning renal allograft. Interestingly, in the subgroup analysis of patients with a very high PTH of ≥ 300 pg/ml the present results show significantly higher levels of PTH in the group of native-born German patients during the first year posttransplant ($p < 0.05$).

Slightly better PTH levels can be explained by better adherence concerning visits to the outpatient department and a better renal function among PMB compared to native-born German patients.

Concerning non-immunologic complications, a partially proven secondary sub-hypothesis regarding lower values of systolic blood pressure among PMB but a trend

toward higher cholesterol measurements in PMB during year one posttransplant was observed.

Further, one can conclude that a tertiary hypothesis of differences in compliance between patients with migration background (PMB) and native-born German patients has been partially proven: one possible reason for better graft function in some years after transplantation and fewer graft losses with longer time to graft loss in case of graft failure is better adherence shown by more visits to the outpatient department by the PMB cohort. Electronic monitoring, for instance, would help to better understand adherence and the discrepancy between compliance scores of the two cohorts but more visits in the outpatient department of PMB.

4.6 Perspectives on renal transplantation and migration background

This study offers a first thorough insight into renal transplantation in the context of migration background in Germany. Moreover, it may be the first study to show – in this degree - a better outcome after renal transplantation among patients with migration background (PMB) compared to native-born patients.

Explanations for these results include better adherence in some means with, in the international comparison, surely a German health care system which treats patients independently of their socio-economic standing.

Pallet et al. hypothesized in 2005 that socio-economic factors and consequently less resources for immunosuppressive treatment are the major potential explanations for ethnic disparities in the United States. The authors could not evaluate the impact of compliance and educational levels in their study. Today, equal compliance scores (ECS) and better compliance in terms of controls in the outpatient department among PMB despite lower educational standings can be demonstrated in the present study.

Further studies could investigate medical adherence even closer, e.g. with electronic monitoring. Nevertheless, at this point one can already be sure that good patient adherence is essential for a satisfactory outcome after renal transplantation. Good compliance includes not only adherence to the medical regimen but also following advice from the health care staff and having regular and frequent checks at the

outpatient department after renal transplantation. Further, it would be very interesting to see effects of patient instruction about adherence – one tool clinicians can use to improve patient adherence and thus, the general outcome after transplantation. Yet unpublished data by Weber and Schaefer, Charité, may soon give us further insight (Weber & Schaefer, *unpublished manuscript*).

4.7 Limitations

One potential limitation of this study is the national definition of migration background in the German census of 2005. Adapted from this definition, patients were classified as immigrants if they are not German citizens, or if they were born in a country other than Germany, or if they, or at least one of the two parents, immigrated to Germany after 1949. Consequently there are some patients included in the study cohort who are defined to have migration background but would be considered native-born in other countries definition. Further subanalysis of patients' migration background in our cohort could provide additional insight.

One possible problem for data gathered with the questionnaire are misunderstandings and inadequate patient replies. Typically, patients were asked to complete the questionnaire during their visits in the outpatient department. To minimize bias, patients with trouble understanding the questionnaire were called by the study author and interviewed on the phone. If communication in German, English or Spanish was not possible, a patient's family member was asked to translate the questions.

Another problem is a possible placing of some patients into the wrong group. Thus, the first filtering into the groups was done by the health care staff at the outpatient clinic who are very well trained and know each patient well by their numerous checks. Hence, patients with possible migration background who were not available at the outpatient department could be classified as such. These patients were also called and interviewed on the phone. Although the health care staff knows the patients at the outpatient department very well, another potential bias is missing some patients with migration background during this phase of the study. To minimize this problem every member on the team with intense patient contact was asked to verify the patient lists including patients with potential migration background. Afterwards every patient was asked explicitly via the questionnaire or during the interview about ancestry.

The study was a retrospective study with a large cohort. This study design may show some problems. For instance data which was not collected during a specific period in the past may no longer be obtainable. This is true for this study in some aspects. Since the vast majority of patients are still followed in the outpatient department, data, if not bound to a specific time point, could be gathered afterwards. However, patients who passed away during the retrospective observation time could obviously not be interviewed and hence could not be included in the study.

Further, statistical tests may show quite rapidly significant differences within large cohorts though differences may be fairly minor. Consequently variables with hardly significant p-values may need to be interpreted with caution. However, the character of this study is exploratory rather than confirmatory. Applying correction methods for multiple testing in such studies increases the number of type 2 errors, which poses the risk of losing promising leads and enhances problems of data interpretation. Therefore, no correction for multiplicity (multiple testing) was done (see also (Streiner & Norman, 2011)). Moreover, multiple variables were tested, increasing the possibility of false positive tests (multiple testing problem). However, the hypotheses tested were mostly independent, thus the multiple testing problem loses its importance.

With this study, the outcome after renal transplantation of patients with migration background and native-born German patients in Berlin was described. The study group hypothesizes comparable characteristics of follow-up in other major transplant centers in other cities in Germany with corresponding distributions of patients with migration background. However, it will be difficult to make prognoses about the outcome of patients in regions with completely different social structures.

5 Bibliography

AQUA-Institute. (2012). Qualitätsreport 2011. Göttingen: AQUA-Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen. from http://www.ukaachen.de/go/show?ID=21939140&DV=0&COMP=download&NAVID=21229036&NAVDV=0

Arend, S. M., Mallat, M. J., Westendorp, R. J., van der Woude, F. J., & van Es, L. A. (1997). Patient survival after renal transplantation; more than 25 years follow-up. Nephrol Dial Transplant, 12(8), 1672-1679.

Berger, J. T. (2012). Culture and Ethnicity in Clinical Care. Archives of Internal Medicine, 158(19), 2085-2090.

Braun, W. E. (2007). The rocky road of limited immunosuppression for renal transplantation in African Americans. Transplantation, 83(3), 267-269.

Brennan, D. C. (2012). HLA matching and graft survival in kidney transplantation. In UpToDate & D. S. Basow (Eds.), UpToDate. Waltham, MA: UpToDate.

Bunnapradist, S., & Danovitch, G. M. (2007). Evaluation of adult kidney transplant candidates Am J Kidney Dis (Vol. 50, pp. 890-898). United States.

Bunzel, B., & Laederach-Hofmann, K. (2000). Solid organ transplantation: are there predictors for posttransplant. Transplantation, 70(5), 711-716.

Butler, J. A., Roderick, P., Mullee, M., Mason, J. C., & Peveler, R. C. (2004). Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review Transplantation (Vol. 77, pp. 769-776). United States.

Cantrelle, C., Laurens, C., Luciolli, E., Loty, B., & Tuppin, P. (2006). Access to kidney transplantation in France of non-French patients and French. Transplantation, 81(8), 1147-1152.

Chakkera, H. A., O'Hare, A. M., Johansen, K. L., Hynes, D., Stroupe, K., Colin, P. M., & Chertow, G. M. (2005). Influence of race on kidney transplant outcomes within and outside the Department of Veterans Affairs. J Am Soc Nephrol, 16(1), 269-277.

Chertow, G. M., Levin, N. W., Beck, G. J., Depner, T. A., Eggers, P. W., Gassman, J. J., . . . Kliger, A. S. (2010). In-center hemodialysis six times per week versus three times per week. N Engl J Med, 363(24), 2287-2300. doi: 10.1056/NEJMoa1001593

Clinical practice guidelines for hemodialysis adequacy, update 2006. (2006) Am J Kidney Dis (Vol. 48 Suppl 1, pp. S2-90). United States.

Crippin, J. S. (2007). Kidney and Liver Transplantation in Nonresident Aliens: How Open Is the Door? Transplantation, 84(12), 1557-1558

Danovitch, G. M., Cohen, D. J., Weir, M. R., Stock, P. G., Bennett, W. M., Christensen, L. L., & Sung, R. S. (2005). Current status of kidney and

pancreas transplantation in the United States, 1994-2003. Am J Transplant, 5(4 Pt 2), 904-915.

de Souza, R. M., & Olsburgh, J. (2008). Urinary tract infection in the renal transplant patient Nat Clin Pract Nephrol (Vol. 4, pp. 252-264). England.

Dew, M. A., DiMartini, A. F., De Vito Dabbs, A., Myaskovsky, L., Steel, J., Unruh, M., . . . Greenhouse, J. B. (2007). Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation, 83(7), 858-873.

Dew, M. A., Switzer, G. E., Goycoolea, J. M., Allen, A. S., DiMartini, A., Kormos, R. L., & Griffith, B. P. (1997). Does transplantation produce quality of life benefits? A quantitative analysis of the literature. Transplantation, 64(9), 1261-1273.

Dooldeniya, M. D., Dupont, P. J., He, X., Johnson, R. J., Joshi, T., Basra, R., . . . Warrens, A. N. (2006). Renal transplantation in Indo-Asian patients in the UK Am J Transplant (Vol. 6, pp. 761-769). Denmark.

Einbinder, L. C., & Schulman, K. A. (2000). The effect of race on the referral process for invasive cardiac procedures. Med Care Res Rev, 57 Suppl 1, 162-180.

Eknoyan, G., Beck, G. J., Cheung, A. K., Daugirdas, J. T., Greene, T., Kusek, J. W., . . . Toto, R. (2002). Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med, 347(25), 2010-2019.

Fan, P. Y., Ashby, V. B., Fuller, D. S., Boulware, L. E., Kao, A., Norman, S. P., . . . Leichtman, A. B. (2010). Access and outcomes among minority transplant patients, 1999-2008, with a focus on determinants of kidney graft survival Am J Transplant (Vol. 10, pp. 1090-1107). United States.

The Federal Government (2010). 8. Bericht der Beauftragten der Bundesregierung für Migration, Flüchtlinge und Integration über die Lage der Ausländerinnen und Ausländer in Deutschland
Retrieved from http://www.bundesregierung.de/Content/DE/_Anlagen/2010/2010-07-07-langfassung-lagebericht-ib.pdf?__blob=publicationFile

The Federal Statistical Office (2007). Bevölkerung und Erwerbstätigkeit. Bevölkerung mit Migrationshintergrund – Ergebnisse des Mikrozensus 2005
Retrieved from https://www.destatis.de/DE/Publikationen/Thematisch/Bevoelkerung/MigrationIntegration/Migrationshintergrund2010220057004.pdf?__blob=publicationFile

Fellström, B., Holdaas, H., Jardine, A. G., Nyberg, G., Grönhagen-Riska, C., Madsen, S., . . . Pedersen, T. R. (2005). Risk factors for reaching renal endpoints in the assessment of Lescol in renal transplantation (ALERT) trial. Transplantation, 79(2), 205-212

Fishman, J. A. (2007). Infection in solid-organ transplant recipients. The New England Journal of Medicine, 357(25), 2601-2614

Flechner, S. M., Modlin, C. S., Serrano, D. P., Goldfarb, D. A., Papajcik, D., Mastroianni, B., . . . Novick, A. C. (1996). Determinants of chronic renal allograft rejection in cyclosporine-treated recipients. Transplantation, 62(9), 1235-1241.

Franke, G. H., Jagla, M., Reimer, J., Haferkamp, L., Türk, T., Witzke, O., . . . Witzke, O. (2009). Erfassung von Medikamenten-Compliance bei erfolgreich Nierentransplantierten mit einer erweiterten Version des Morisky-Scores - dem Essener Compliance Score (ECS). PPmP - Psychotherapie · Psychosomatik · Medizinische Psychologie, 59(02).

Frei, U., & Schober-Halstenberg, H. J. (2008). Renal replacement therapy in Germany. Report on dialysis treatment and renal transplantation in Germany, 2006/2007. QUASI Niere, Report.
Retrieved from http://www.bundesverband-niere.de/files/QuaSi-Niere-Bericht_2006-2007.pdf

Goldfarb-Rumyantzev, A. S., Koford, J. K., Baird, B. C., Chelamcharla, M., Habib, A. N., Wang, B. J., . . . Isaacs, R. B. (2006). Role of socioeconomic status in kidney transplant outcome. Clin J Am Soc Nephrol, 1(2), 313-322.

Gondos, A., Dohler, B., Brenner, H., & Opelz, G. (2012). Kidney Graft Survival in Europe and the United States: Strikingly Different Long-term Outcomes. Transplantation.

Gore, J. L., Pham, P. T., Danovitch, G. M., Wilkinson, A. H., Rosenthal, J. T., Lipshutz, G. S., & Singer, J. S. (2006). Obesity and outcome following renal transplantation. Am J Transplant, 6(2), 357-363.

He, X., Moore, J., Shabir, S., Little, M. A., Cockwell, P., Ball, S., . . . Borrows, R. (2009). Comparison of the predictive performance of eGFR formulae for mortality and graft failure in renal transplant recipients Transplantation (Vol. 87, pp. 384-392). United States.

Heaf, J. G. (2003). Bone disease after renal transplantation. Transplantation, 75(3), 315-325.

Herter-Eschweiler, R. (2012). Weniger Menschen ohne Krankenversicherungsschutz.
Retrieved from https://www.destatis.de/DE/PresseService/Presse/Pressemitteilungen/2012/08/PD12_285_122.html

Icks, A., Haastert, B., Gandjour, A., Chernyak, N., Rathmann, W., Giani, G., . . . Koch, M. (2010). Costs of dialysis--a regional population-based analysis Nephrol Dial Transplant (Vol. 25, pp. 1647-1652). England.

Jeffrey, R. F., Woodrow, G., Mahler, J., Johnson, R., & Newstead, C. G. (2002). Indo-Asian experience of renal transplantation in Yorkshire: results of a 10-year survey. Transplantation, 73(10), 1652-1657.

Joswig, MD., Weber, K., Dang-Heine, C., Jürchott, K., Hörstrup, J., Hinrichs, C., Reinke, P., & Babel, N. Renal transplantation in patients with migration background and native-born German patients: differences in outcome and compliance. Manuscript submitted for publication.

Kaplan, B., Schold, J., & Meier-Kriesche, H. U. (2003). Poor predictive value of serum creatinine for renal allograft loss. Am J Transplant, 3(12), 1560-1565.

Kasiske, B. L., Andany, M. A., & Danielson, B. (2002). A thirty percent chronic decline in inverse serum creatinine is an excellent predictor of late renal allograft failure Am J Kidney Dis (Vol. 39, pp. 762-768). United States: 2002 by the National Kidney Foundation, Inc.

Kohls, M. (2011). Morbidität und Mortalität von Migranten in Deutschland 9. Forschungsbericht Retrieved from http://www.bamf.de/SharedDocs/Anlagen/DE/Publikationen/Forschungsberichte/fb09-mortalitaet.pdf?__blob=publicationFile

Kotton, C. N., Fishman, J. A., Kotton, C. N., & Fishman, J. A. (2005). Viral Infection in the Renal Transplant Recipient. Journal of the American Society of Nephrology, 16(6), 1758-1774.

Kutner, N. G., Zhang, R., Huang, Y., & Johansen, K. L. (2012). Impact of race on predialysis discussions and kidney transplant preemptive wait-listing. Am J Nephrol, 35(4), 305-311.

Laupacis, A., Keown, P., Pus, N., Krueger, H., Ferguson, B., Wong, C., & Muirhead, N. (1996). A study of the quality of life and cost-utility of renal transplantation. Kidney Int, 50(1), 235-242.

Leichtman, A. B., Cohen, D., Keith, D., O'Connor, K., Goldstein, M., McBride, V., . . . Ashby, V. B. (2008). Kidney and pancreas transplantation in the United States, 1997-2006: the HRSA Breakthrough Collaboratives and the 58 DSA Challenge. Am J Transplant, 8(4 Pt 2), 946-957.

Levey, A. S., & Coresh, J. (2012). Chronic kidney disease Lancet (Vol. 379, pp. 165-180). England: 2012 Elsevier Ltd.

Levey, A. S., Eckardt, K. U., Tsukamoto, Y., Levin, A., Coresh, J., Rossert, J., . . . Eknoyan, G. (2005). Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO) Kidney Int (Vol. 67, pp. 2089-2100). United States.

Liem, Y. S., Bosch, J. L., Arends, L. R., Heijenbrok-Kal, M. H., & Hunink, M. G. (2007). Quality of life assessed with the Medical Outcomes Study Short Form 36-Item Health Survey of patients on renal replacement therapy: a systematic review and meta-analysis Value Health (Vol. 10, pp. 390-397). United States.

Loucaidou, M., Prasad, S., Van Tromp, J., Cairns, T. D., Griffith, M., Hakim, N., . . . Taube, D. (2004). Outcome of renal transplantation in South Asian recipients is similar to that in non-Asians. Transplantation, 78(7), 1021-1024.

Malek, S. K., Keys, B. J., Kumar, S., Milford, E., & Tullius, S. G. (2011). Racial and ethnic disparities in kidney transplantation. Transplant International: Official Journal of the European Society for Organ Transplantation, 24(5), 419-424

McCulloch, D. (2012). Estimation of blood glucose control in diabetes mellitus. In UpToDate & D. S. Basow (Eds.), UpToDate. Waltham, MA: UpToDate.

Meier-Kriesche, H. U., Schold, J. D., Srinivas, T. R., & Kaplan, B. (2004). Lack of improvement in renal allograft survival despite a marked decrease in. Am J Transplant, 4(3), 378-383.

Mérida, E., Rodríguez, A., Hernandez, G., Huerta, A., Gonzalez, J., Hernández, A., . . . others. (2009). Renal Transplantation in Emigrants From Africa in Spain: Similar Results but Different Infectious Profile Compared With Spanish People Transplant Proc (Vol. 41, pp. 2363–2365).

Metzger, R. A., Delmonico, F. L., Feng, S., Port, F. K., Wynn, J. J., & Merion, R. M. (2003). Expanded criteria donors for kidney transplantation. Am J Transplant, 3 Suppl 4, 114-125.

Migration Report 2010 (2011). Federal Office for Migration and Refugees, Unit 222 Retrieved from http://www.bamf.de/SharedDocs/Anlagen/EN/Publikationen/Migrationsberichte/migrationsbericht-2010.html?nn=1452220

Molnar, M. Z., Langer, R. M., Remport, A., Czira, M. E., Rajczy, K., Kalantar-Zadeh, K., . . . Rosivall, L. (2012). Roma ethnicity and clinical outcomes in kidney transplant recipients. Int Urol Nephrol, 44(3), 945-954.

Nankivell, B. J., & Alexander, S. I. (2010). Rejection of the kidney allograft. N Engl J Med, 363(15), 1451-1462.

Nankivell, B. J., & Kuypers, D. R. (2011). Diagnosis and prevention of chronic kidney allograft loss. Lancet, 378(9800), 1428-1437.

Nissenson, A. R., Pereira, B. J., Collins, A. J., & Steinberg, E. P. (2001). Prevalence and characteristics of individuals with chronic kidney disease in a large health maintenance organization Am J Kidney Dis (Vol. 37, pp. 1177-1183). United States.

Ojo, A. O., Hanson, J. A., Wolfe, R. A., Leichtman, A. B., Agodoa, L. Y., & Port, F. K. (2000). Long-term survival in renal transplant recipients with graft function Kidney Int (Vol. 57, pp. 307-313). United States.

Oosterlee, A., & Rahmel, A. (2012). Eurotransplant International Foundation Annual Report 2011. from http://www.eurotransplant.org/cms/index.php?page=annual_reports

Opelz, G., Mickey, M. R., & Terasaki, P. I. (1977). Influence of race on kidney transplant survival. Transplant Proc, 9(1), 137-142.

Opelz, G., Wujciak, T., & Ritz, E. (1998). Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. Kidney Int, 53(1), 217-222.

OPTN / SRTR 2010 Annual Data Report (2011). Organ Procurement and Transplant Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). Retrieved from http://srtr.transplant.hrsa.gov/

Osterberg, L., & Blaschke, T. (2005). Adherence to medication N Engl J Med (Vol. 353, pp. 487-497). United States.

Oztek, F. Z., Tekin, P., Herle, M., Mueller, T., Arbeiter, K., & Aufricht, C. (2011). Does immigration background influence outcomes after renal transplantation? Pediatr Nephrol, 26(2), 309-315.

Pablos-Mendez, A. (1994). Mortality among Hispanics. JAMA, 271(16), 1237.

Page, T. F., & Woodward, R. S. (2009). Cost-effectiveness of Medicare's coverage of immunosuppression medications for kidney transplant recipients. Expert Rev Pharmacoecon Outcomes Res, 9(5), 435-444.

Pallet, N., Thervet, E., Alberti, C., Emal-Aglae, V., Bedrossian, J., Martinez, F., . . . Legendre, C. (2005). Kidney Transplant in Black Recipients: Are African Europeans Different from African Americans? American Journal of Transplantation, 5(11), 2682-2687

Patzer, R. E., Amaral, S., Klein, M., Kutner, N., Perryman, J. P., Gazmararian, J. A., & McClellan, W. M. (2012). Racial disparities in pediatric access to kidney transplantation: does socioeconomic status play a role? Am J Transplant, 12(2), 369-378.

Peters, T. G. (2005). Racial disparities and transplantation Am J Kidney Dis (Vol. 46, pp. 760-762). United States.

Potts, J. T., & Juppner, H. (1996). Parathyroid hormone: molecular biology and regulation. (Principles of Bone Biology, Academic Press), 325.

Press, R., Carrasquillo, O., Nickolas, T., Radhakrishnan, J., Shea, S., & Barr, R. G. (2005). Race/ethnicity, poverty status, and renal transplant outcomes. Transplantation, 80(7), 917-924.

Quiroga, I., McShane, P., Koo, D. D., Gray, D., Friend, P. J., Fuggle, S., & Darby, C. (2006). Major effects of delayed graft function and cold ischaemia time on renal. Nephrol Dial Transplant, 21(6), 1689-1696.

Quiroga, I., McShane, P., Koo, D. D. H., Gray, D., Friend, P. J., Fuggle, S., & Darby, C. (2006). Major effects of delayed graft function and cold ischaemia time on renal allograft survival.

Rao, P. S., & Ojo, A. (2009). The alphabet soup of kidney transplantation: SCD, DCD, ECD--fundamentals for the. Clin J Am Soc Nephrol, 4(11), 1827-1831.

Razum, O., Zeeb, H., Meesmann, U., Schenk, L., Bredehorst, M., Brzoska, P., . . . Ulrich, R. (2008). Migration und Gesundheit Schwerpunktbericht der Gesundheitsberichterstattung des Bundes
Retrieved from

http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsT/migration.pdf?__blob=publicationFile

Rudge, C., Johnson, R. J., Fuggle, S. V., Forsythe, J. L., & Kidney and Pancreas Advisory Group, U. K. T. N. B. (2007). Renal transplantation in the United Kingdom for patients from ethnic minorities. Transplantation, 83(9), 1169-1173.

Schnitzler, M. A., Lowell, J. A., Hardinger, K. L., Boxerman, S. B., Bailey, T. C., & Brennan, D. C. (2003). The association of cytomegalovirus sero-pairing with outcomes and costs following cadaveric renal transplantation prior to the introduction of oral ganciclovir CMV prophylaxis Am J Transplant (Vol. 3, pp. 445-451). Denmark.

Schold, J. D., Kaplan, B., Chumbler, N. R., Howard, R. J., Srinivas, T. R., Ma, L., & Meier-Kriesche, H. U. (2005). Access to quality: evaluation of the allocation of deceased donor kidneys for transplantation. J Am Soc Nephrol, 16(10), 3121-3127.

Schulz, K. H., & Thaiss, F. (2012). [Long-term outcome with end-stage renal disease - survival is not enough: does dialysis or kidney transplantation matter?]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 55(4), 543-551.

Siegert, M. (2008). Schooling of migrants in Germany Integration report (Vol. Working paper 13).

Siegert, M. (2009). Professional and academic training of migrants in Germany Integration report (Vol. Working Paper 22, pp. 57): Federal Office for Migration and Refugees.

Streiner, D. L., & Norman, G. R. (2011). Correction for multiple testing: is there a resolution? Chest, 140(1), 16-18.

Uslu, A., & Nart, A. (2011). Treatment of first acute rejection episode: systematic review of level I evidence Transplant Proc (Vol. 43, pp. 841-846). United States: 2011 Elsevier Inc.

USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. (2011) U S Renal Data System (Vol. 59, pp. e247-e294). Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. (2012) U S Renal Data System (pp. 286). Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Wissing, K. M., Abramowicz, D., Broeders, N., & Vereerstraeten, P. (2000). Hypercholesterolemia is associated with increased kidney graft loss caused by chronic rejection in male patients with previous acute rejection. Transplantation, 70(3), 464-472.

Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y., . . . Port, F. K. (1999). Comparison of mortality in all patients on

dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med, 341(23), 1725-1730.

Woodward, R. S., Schnitzler, M. A., Baty, J., Lowell, J. A., Lopez-Rocafort, L., Haider, S., . . . Brennan, D. C. (2003). Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients Am J Transplant (Vol. 3, pp. 590-598). Denmark.

Young, C. J., & Gaston, R. S. (2000). Renal transplantation in black Americans. N Engl J Med, 343(21), 1545-1552.

Malte D. Joswig
malte.joswig@charite.de

Conflict of Interest Statement

The author declares no conflicts of interest.

Affidavit

“I, Malte D. Joswig certify under penalty of perjury by my own signature that I have submitted the thesis on the topic Renal Transplantation in Patients with Migration Background and Native-born German Patients: Differences in Setting, Outcome and Compliance. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

Curriculum Vitae

My curriculum vitae will not be shown in the digital version of this dissertation for reasons of data protection.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Complete list of publications and presentations

Malte D. Joswig had the following share in the following publications:

Publication: Malte D. Joswig, Katja Weber, Chantip Dang-Heine, Karsten Jürchott, Jan Hörstrup, Carl Hinrichs, Petra Reinke and Nina Babel, *Renal transplantation in patients with migration background and native-born German patients: differences in outcome and compliance*, submitted to Kidney International. Contribution in detail: Malte D. Joswig participated as a main contributor to writing of the paper, research design, performance of the research and data analysis.

Oral presentation: *Migration and Transplantation,* World Transplant Congress, Malte D. Joswig, Chantip Dang-Heine, Karsten Jürchott, Jan Hörstrup, Carl Hinrichs, Katja Weber, Petra Reinke and Nina Babel, Berlin, Germany (July 2014). Contribution in detail: Malte D. Joswig participated as a main contributor to research design, performance of the research, data analysis and preparation of the presentation.

Oral presentation: *Migration und Transplantation,* Charité – Kidney Transplant Symposium 2012, Malte D. Joswig, Chantip Dang-Heine, Karsten Jürchott, Jan Hörstrup, Carl Hinrichs, Katja Weber, Petra Reinke and Nina Babel, Berlin, Germany (June 2012). Contribution in detail: Malte D. Joswig participated as a main contributor to research design, performance of the research, data analysis and preparation of the presentation.

Oral presentation: *Migranten und Nierentransplantation,* Congress of Nephrolgoy, 3. Annual Meeting of the German Society of Nephrology, Malte D. Joswig, Chantip Dang-Heine, Karsten Jürchott, Jan Hörstrup, Carl Hinrichs, Katja Weber, Petra Reinke and Nina Babel, Berlin, Germany (September 2011). Contribution in detail: Malte D. Joswig participated as a main contributor to research design, performance of the research, data analysis and preparation of the presentation.

_____

Signature, date and stamp of PD Dr. Nina Babel, supervising University teacher

_____

Signature Malte D. Joswig, doctoral candidate

Acknowledgments

First of all I would like to express my deep gratitude to PD Dr. med. Nina Babel, leader of the working group, for the opportunity to execute this dissertation, for her patient guidance, enthusiastic encouragements and useful critiques of this research work. Furthermore, I'd like to offer my special thanks to Dr. med. Jan Hörstrup, Senior Medical Advisor of the transplant outpatient clinic, for all his help in collecting the necessary data. I am particularly grateful for the kind and patient help given by Dr. rer. nat. Karsten Jürchott with all advanced statistical analyses, particularly the adjusted data. I would also like to thank Dr. med. Carl Hinrichs for his kind training in classifying the histopathological findings in renal allograft biopsies and the data I could generously use.

I would like to extend my thanks to Ms. Katja Weber for the cooperation with the Institute for Clinical Pharmacology and Toxicology and especially for her help in analyzing the compliance scores. Advice given by Dr. Chantip Dang-Heine has been a great help in daily questions. Kind aid provided by the assistances of the transplant outpatient clinic in distributing and collecting the patient questionnaires and aid was greatly appreciated. Further I wish to acknowledge all patients who participated in this study. Without you, obviously this work would not have been possible.

I wish to express special thanks to Ms. Anna Kochs for her great support in everyday problems and questions and difficult situations.

Moreover, I would like to thank all my friends who supported me with this research work or during this time in any manner, among them Ms. Elena Escouflaire and Ms Ulrike Scheurer, Mr. Robert Hoffmann and Ms. Helena Velten.

Finally, I wish to thank my parents, Ursula Frömming and Dr. jur. Walter Joswig, who made my medical studies possible and who encouraged me throughout this time.