"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

DOCTORAL SCHOOL
FIELD OF MEDICINE

POSTOPERATIVE COMPLICATIONS OF THE LIVING KIDNEY DONOR

SUMMARY OF THE DOCTORAL THESIS

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2026

CONTENTS

INTRODUCTION

Living kidney transplantation represents the optimal therapeutic option for the patient with end-stage chronic kidney disease, offering superior graft and patient survival compared with deceased-donor transplantation, a reduction in time spent on the waiting list, and a superior quality of life[1]. Nevertheless, the discrepancy between organ demand and supply remains a major global problem, and transplant programs must find a balance between expanding the pool of potential donors and maintaining strict safety standards for them.

The topic of the thesis is justified by the radical transformation of the demographic profile of potential donors: whereas in the past donation was reserved for healthy young individuals, an increasing proportion of candidates now present cardiometabolic risk factors such as obesity, arterial hypertension, prediabetes, or tobacco exposure[2-5]. In parallel, international guidelines have evolved from categorical exclusion of candidates with risk factors toward an individualized approach based on quantitative risk stratification, beginning with the 2017 KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors[6].

Living kidney donation is, in essence, a major surgical procedure performed on a healthy individual without a direct medical benefit. Consequently, the principle of "primum non nocere" carries a particular ethical weight, and careful assessment of the perioperative risk and of long-term complications becomes a professional and moral obligation[1]. At the national level, the Center of Surgical Urology and Kidney Transplantation of the Fundeni Clinical Institute is one of the principal kidney transplant centers in Romania, which allows the analysis of clinical cohorts relevant to the local context.

The research hypothesis of the thesis is the following: the cardiometabolic risk factors — obesity, smoking, prediabetes, and arterial hypertension — increase the incidence of certain early postoperative complications and of some late events (chronic kidney disease, new-onset hypertension, diabetes mellitus, cardiovascular events); however, under judicious selection, performant surgical management, and adequate monitoring, the overall outcome of these donors remains favorable, and the absolute risk of severe complications stays within acceptable limits. The presence of risk factors should not

constitute an absolute contraindication, but rather an argument for an individualized approach.

The methodology is mixed: the general part is a narrative synthesis of the literature, based on documentation in the PubMed/MEDLINE, Embase, and Cochrane databases, prioritizing large cohort studies, meta-analyses, and clinical practice guidelines; the original part uses a retrospective, observational, cohort design, followed by multivariate statistical analysis. The interdisciplinary character is evident, the topic integrating urology, nephrology, transplantology, endocrinology, cardiology, pathology, and medical statistics. The limitations of the research — the retrospective nature of the data, the size of the local cohort, and the follow-up duration — suggest clear directions for future research.

I. GENERAL PART — CURRENT STATE OF KNOWLEDGE

1. LIVING KIDNEY DONATION — OVERVIEW

Living kidney donation is the procedure by which a healthy person voluntarily gives one of their two kidneys to a recipient, followed by transplantation of the graft, an intervention that transforms the dialysis patient into an individual with autonomous renal function[1]. Globally, living-donor kidney transplantation accounts for approximately 30–40% of all kidney transplants, with more than 6,000 living-donor transplants performed in the United States in 2023 and an annual European number between 3,000 and 5,000; in Romania the proportion remains modest compared with the European average. The disproportion between the number of patients on the waiting list and the number of available organs makes the safe expansion of the living-donor pool a public health priority[6].

The history of donor selection reflects the tension between protecting the donor and expanding transplantation opportunities. The historical, categorical, and rigid criteria were called into question by data showing that the absolute risk of end-stage kidney disease remains low even in the presence of moderate risk factors[7-8], by the transformation of the population's epidemiological profile, and by the development of risk prediction models, in particular the Grams et al. model, published in 2016[9]. The turning point was the 2017 KDIGO guideline, which recommended replacing categorical exclusion criteria with an individualized assessment based on the candidate's overall risk profile[6], a recommendation reinforced by the 2020 KDOQI commentary[10].

Donor evaluation is a complex, multidisciplinary process that includes detailed history-taking, clinical examination, repeated blood pressure measurement (with ambulatory monitoring in borderline cases), determination of the glomerular filtration rate, assessment of proteinuria and albuminuria, the lipid profile, fasting glucose, glycated hemoglobin, and the oral glucose tolerance test in candidates with metabolic risk[6,10]. Imaging includes ultrasound and computed tomography with vascular reconstruction, with renal volume measurement becoming an important element because it correlates with the number of functioning nephrons. The psychosocial aspects and explicit, documented informed consent are as important as the medical ones.

The surgical technique has evolved from open nephrectomy to minimally invasive techniques — transperitoneal laparoscopic, hand-assisted, retroperitoneal, and robotic — which provide a reduction in hospital stay, pain, and recovery period, without compromising graft function[11]. The choice of technique depends on the surgeon's experience, renal anatomy, and logistical considerations, with the general principles remaining constant: minimizing warm ischemia time, preserving the vascular and ureteral integrity, and rigorous hemostasis. The benefits of living-donor transplantation for the recipient include superior graft and patient survival, reduced time on the waiting list, and the possibility of preemptive transplantation[1].

2. POSTOPERATIVE COMPLICATIONS OF THE LIVING KIDNEY DONOR

The Clavien-Dindo classification represents the universal standard for reporting postoperative complications, stratifying them into five grades of severity according to the treatment required. Applied to living donors, the retrospective cohort study by Lentine et al. of 14,964 donors from 97 academic institutions in the United States reported an overall rate of complications of any grade of 16.8%, with life-threatening complications (grade IV or higher) occurring in 2.5% of donors[11].

Perioperative mortality has decreased significantly over recent decades. In the North American cohort, 90-day mortality was 3.1 per 10,000 donations[12], data confirmed by other international cohorts, with values between 1 and 5 per 10,000 donations[13-14]. The main causes include massive pulmonary thromboembolism, hemorrhage, acute cardiac complications, and, more rarely, sepsis[11-12]. Intraoperative complications are rare; the frequency of conversion to open surgery ranges between 1% and 5%, the independent risk factors being morbid obesity, complex anatomical variants, and limited surgeon experience, with the risk being reduced in high-volume centers[13,15-17].

Early postoperative complications (the first 30 days) include venous thromboembolism — below 1% under adequate prophylaxis — cardiac, pulmonary, gastrointestinal, renal, and metabolic complications, alongside surgical complications such as hemorrhage, hematoma, wound infection, and incisional hernias[11]. Wound infection (1–5%) is more frequent in obese donors and smokers[18]. Heimbach et al., in 553 hand-assisted laparoscopic nephrectomies, reported a complication rate of 5% in donors with a BMI below 25 kg/m² and 16% in those with a BMI ≥35 kg/m²[18]. Late complications

include incisional hernia, chronic pain, testicular symptoms, and psychological and social complications[19-22].

After donation, the donor is left with an approximately 50% reduction in nephron mass, but through compensatory hypertrophy and increased per-nephron filtration, the remaining kidney reaches 65–75% of the preoperative glomerular filtration rate, placing the donor in stage 2 or 3 of chronic kidney disease[6,23]. Muzaale et al., in 96,217 donors, reported an absolute risk of end-stage kidney disease at 15 years of 30.8 per 10,000, compared with 3.9 per 10,000 in the control group: an approximately 8-fold relative risk increase, but an absolute risk below 0.5%[24]. The Norwegian study by Mjøen reported an increase in all-cause mortality (HR 1.3) and cardiovascular mortality (HR 1.4)[25], whereas subsequent American and Korean studies did not confirm this increase after adjustment for socioeconomic factors[25-26].

3. RISK FACTORS ASSOCIATED WITH POSTOPERATIVE COMPLICATIONS

The presence of cardiometabolic risk factors statistically modifies both the incidence of early complications and the long-term outcome; these factors rarely occur in isolation, and their interaction may be synergistic[10,24]. The contemporary approach has replaced categorical exclusion based on a single factor with individualized, quantitative risk stratification[6,9].

3.1. Obesity

The mean body mass index of donors has increased substantially, following the trend in the general population. In the study by Locke et al. of 119,769 donors, the risk of end-stage kidney disease increased above a critical BMI threshold of 27 kg/m²: obese donors had a 20-year cumulative incidence of 93.9 per 10,000, compared with 39.7 per 10,000, with an adjusted hazard ratio of 1.86[2]. The 20-year cumulative mortality was 304 per 10,000 for obese donors, compared with 209 per 10,000, with an adjusted hazard ratio of 1.32, an association attributed, however, to obesity itself rather than to the act of donation[27].

Central adipose tissue distribution appears to be a predictor superior to BMI. The prospective study by Westenberg demonstrated that waist circumference and the waist-to-height ratio are significantly associated with progressively lower renal function over 10

years[28]. Major surgical complications appear similar to those of normal-weight donors in experienced centers, although national American data identified obesity as an independent risk factor for life-threatening complications (adjusted OR 1.55)[11]. An underestimated phenomenon is post-donation weight gain: 74.8% of donors gain weight, and those who lost weight pre-donation and regained it presented an increased risk of incisional hernias and of hypertension and type 2 diabetes mellitus[29]. Obesity-related glomerulopathy, characterized by glomerular hypertrophy, hyperfiltration, and focal segmental glomerulosclerosis, involves ectopic accumulation of renal lipids[30-37].

The standard recommendation is for overweight patients to lose weight before donation and maintain an optimal weight thereafter, although lifestyle-only approaches are frequently insufficient[29]. GLP-1 receptor agonists have demonstrated efficacy in weight management and diabetes prevention in the SCALE, STEP, SELECT, and SURMOUNT-1 trials[7-8,38-41], and pre-donation bariatric surgery represents a valid alternative for severe obesity[42].

3.2. Smoking

The prevalence of smoking among donors varies between regions: 32% in a Korean cohort[3], 34.4% in Mexico[43], 13% in Canada[44], up to 37% in Germany[45] and 47% preoperatively in Turkey[46]. The number of pack-years is the most robust predictor: Yoon et al. demonstrated a dose-response relationship with eGFR, identifying an odds ratio of 7.5 for post-donation chronic kidney disease in former smokers with more than 12 pack-years[3], as well as risk thresholds for graft loss in recipients[47-48]. Donation itself is not an effective smoking-cessation intervention (74% of smokers continue), whereas 88% of those who quit before donation remain abstinent[44].

Underwood et al. did not identify significant differences in perioperative complications between smokers and non-smokers[49], an observation that must be interpreted with caution given the rigorous preoperative screening; extrapolation from the general surgical literature nevertheless suggests risks of delayed wound healing, infections, and altered tissue oxygenation, mediated by the vasoconstriction and endothelial dysfunction induced by smoking[50-56]. Idiopathic nodular glomerulosclerosis, described by Markowitz et al., is a distinct renal lesion associated with smoking that occurs in non-hypertensive and non-diabetic individuals, establishing smoking as an independent cause; in candidates with more than 20 pack-years, protocol biopsy should be considered[47-48].

3.3. Prediabetes and impaired glucose tolerance

Prediabetes comprises impaired fasting glucose, impaired glucose tolerance, and an intermediate elevation of HbA1c[4], with individuals with IFG having an approximately 25% risk of developing type 2 diabetes mellitus within 3–5 years[4,57-58]. The ADA definitions and the role of OGTT as the gold standard are essential, given that HbA1c has reduced sensitivity for detecting prediabetes[59-60]. The outcome of donors with prediabetes is favorable: in the study by Hebert of 8,280 donors, of whom 22% had IFG, the outcome was similar to that of normoglycemic donors, with end-stage kidney disease in only 0.5%[4]; the study by Chandran of 143 donors with IFG reported zero cases of end-stage kidney disease at 10 years[57]; and Okamoto did not identify an increased incidence of perioperative complications in donors with IGT[11,61-62].

A history of gestational diabetes is not an absolute contraindication but constitutes a significant risk factor requiring mandatory OGTT and intensive monitoring[6,63-67]. Lifestyle interventions reduce the risk of progression to diabetes by 58%, and metformin by approximately 31% in high-risk patients[59,68]; recent data on GLP-1 receptor agonists (liraglutide, semaglutide, tirzepatide) are particularly promising[69-71].

3.4. Arterial hypertension

Hypertension affects approximately 10–25% of candidates; among those initially normotensive, hypertension develops in approximately 21% at 5 years and over 50% at 15 years post-donation[5-6,72]. The 2017 KDIGO guideline recommends measuring blood pressure on at least two occasions and using ambulatory monitoring in ambiguous cases[6]; in a Mayo Clinic study, ABPM identified hypertension in 25.5% of patients previously considered normotensive[73-74]. Donors with hypertension controlled on 1–2 medications, with blood pressure below 140/90 mmHg and without target-organ damage, may be acceptable candidates; assessment of target-organ damage (echocardiography, albumin-to-creatinine ratio, ophthalmologic examination, ankle-brachial index) is mandatory, any evidence constituting a contraindication[6,10,72,75-81].

A Portuguese study of 300 donors found the development of hypertension in 30% of subjects[5], and a meta-analysis showed a 5 mmHg increase in systolic blood pressure at 5–10 years post-donation[82]. In a cohort of 24,533 donors aged ≥50 years, pre-donation hypertension conferred a 15-year risk of end-stage kidney disease of 0.8% versus 0.2% (adjusted HR 3.04), the absolute risk remaining, however, below 1%[83]. APOL1 genetic

variants contribute to the risk of African-American donors, with testing being recommended[24,84-88]. The conclusion of the chapter is that none of the four factors, in isolation and under adequate management, represents a categorical contraindication[6].

II. SPECIAL PART — PERSONAL CONTRIBUTIONS

4. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

The synthesis of the literature highlights a fundamental tension: the contemporary paradigm requires individualized risk stratification[6,10], while cohort data continue to identify cardiometabolic risk factors as potential predictors of unfavorable outcomes[89]. The fundamental clinical question is to what extent the metabolic comorbidities present at donation independently influence renal function and long-term survival, when selection and management follow current standards. To this is added the psychosocial and socioeconomic dimension of donation[90], insufficiently characterized in the Romanian donor population. The research arose from the desire to contribute to filling these two gaps, starting from a real cohort of living donors evaluated and operated on at the Center of Surgical Urology and Kidney Transplantation of the Fundeni Clinical Institute, between 2015 and 2019, with a median postoperative follow-up of approximately 8.4 years.

Primary hypothesis: in donors selected according to contemporary standards, the metabolic comorbidities present at the time of donation — obesity, arterial hypertension, and dyslipidemia — do not constitute independent predictors of a composite endpoint comprising a decline in eGFR below 45 mL/min/1.73 m² or death from any cause, when adjusting for demographic variables and baseline renal function. **Secondary hypothesis:** psychosocial and socioeconomic outcomes remain favorable in the long term, but deterioration of renal function below the 45 mL/min/1.73 m² threshold is associated with a less favorable retrospective attitude toward the decision to donate, manifested in particular by the refusal to repeat the decision under the hypothetical conditions of a repeated choice. The two hypotheses are interconnected through the eGFR threshold of 45 mL/min/1.73 m², which marks the transition between stages 3a and 3b of chronic kidney disease[6].

The general objectives were: (1) characterization of the cohort of donors operated on at the Fundeni Clinical Institute between 2015 and 2019; (2) assessment of the long-term evolution of renal function; (3) identification of the independent predictors of the composite endpoint; (4) assessment of psychosocial and socioeconomic outcomes through the investigation of 12 distinct domains; (5) investigation of the association between renal function evolution and psychosocial outcomes; (6) comparison of the results with the

international literature; (7) formulation of clinical recommendations and directions for future research, adapted to the local context.

5. GENERAL RESEARCH METHODOLOGY

The research is structured as two retrospective observational studies, conducted on the same base cohort. Study 1 has a longitudinal retrospective observational design, while Study 2 has a cross-sectional retrospective design. All surgical procedures were performed at the Center of Surgical Urology and Kidney Transplantation of the Fundeni Clinical Institute, Bucharest. The cohort comprised all consecutive living donors who underwent nephrectomy between 1 January 2015 and 31 December 2019, a total of 142 donors meeting the inclusion criteria, with no loss to follow-up. For Study 2, 6 donors who could not be interviewed were excluded, resulting in a sub-cohort of 136 donors.

All donors were evaluated preoperatively according to the institutional protocol, aligned with the 2017 KDIGO guideline[6], including complete medical evaluation, eGFR determination using the CKD-EPI 2009 formula, imaging evaluation by CT angiography (or MR angiography), and cardiologic evaluation. Obesity was defined as a BMI ≥ 30 kg/m^2; arterial hypertension by a documented diagnosis or chronic antihypertensive medication; dyslipidemia by a documented diagnosis or lipid-lowering medication. Only candidates with mild hypertension, controlled with a maximum of two medications and without target-organ damage, were considered eligible. The number of metabolic comorbidities was calculated as the sum of hypertension, dyslipidemia, and obesity.

The primary endpoint of Study 1 was a composite endpoint defined by a decline in eGFR below 45 mL/min/1.73 m^2 at the last evaluation or death from any cause. The outcomes of Study 2 were assessed through a structured, institutionally developed questionnaire covering twelve dichotomously coded domains. The studies were conducted in accordance with the Declaration of Helsinki, the protocol being approved by the Ethics Committee of the Fundeni Clinical Institute (protocol code 15380, date 14 April 2025). Statistical analysis used the Student t-test, the Mann-Whitney U test, the chi-square test or Fisher exact test, as well as univariate and multivariate binary logistic regression (variables with $p < 0.15$ included in the multivariate model). All analyses were performed using SPSS version 26.0, the significance threshold being $p < 0.05$ two-tailed.

6. STUDY 1. IMPACT OF METABOLIC COMORBIDITIES ON RENAL FUNCTION AND SURVIVAL IN LIVING KIDNEY DONORS

6.1. Introduction

The transformation of the epidemiological profile of the population eligible for donation has imposed a reflection on the eligibility criteria[6,12,91]. Western data suggest that donors with mild or moderate metabolic comorbidities present favorable outcomes: obesity increases the absolute risk of end-stage kidney disease, but this remains below 1% over 15–20 years[2,92], and pre-donation hypertension confers an increase in relative risk, with an absolute risk below 1% at 15 years[83]. Eastern European data remain limited, and the particularities of the Romanian population — older mean age, high prevalence of hypertension and dyslipidemia, female predominance — make the investigation of a Romanian cohort a relevant original contribution. The specific hypothesis is that, in donors selected according to contemporary standards, metabolic comorbidities do not constitute independent predictors of the composite endpoint after adjustment for age and baseline renal function.

6.2. Materials and methods

The study represents a longitudinal retrospective observational analysis of the cohort of 142 consecutive living donors operated on between January 2015 and December 2019, evaluated and selected according to the 2017 KDIGO guideline[6]. The mean follow-up was 100.88 ± 17.75 months (approximately 8.4 years), with all 142 donors included in the primary analysis and no loss to follow-up. The variable definitions and statistical methodology are those presented in Chapter 5.

6.3. Results

The cohort included 142 donors, with a mean age at donation of 52.44 ± 11.27 years, with 39 donors (27.5%) male and 103 (72.5%) female. The mean body mass index was 26.96 ± 4.99 kg/m². The comorbidities present at donation included arterial hypertension (28.2%, n=40), dyslipidemia (34.5%, n=49), and obesity (12.7%, n=18); current or former smoking status was present in 21.8% (n=31). 57 donors (40.1%) presented at least one comorbidity, and 17 (12.0%) two or more. Baseline renal function was 0.86 ± 0.18 mg/dL for creatinine and 88.66 ± 18.44 mL/min/1.73 m² for eGFR.

Table II.6.1. Baseline characteristics of the cohort, comparing donors who reached the composite endpoint and those who did not.

Variable	Whole cohort (n=142)	With endpoint (n=24)	Without endpoint (n=118)	p
Age at donation (years)	52.44 ± 11.27	61.48 ± 6.72	50.68 ± 11.15	< 0.001
Male sex, n (%)	39 (27.5)	7 (29.2)	32 (27.1)	0.80
BMI (kg/m²)	26.96 ± 4.99	28.86 ± 4.10	26.47 ± 5.12	0.12
Obesity, n (%)	18 (12.7)	6 (25.0)	12 (10.2)	0.07
Arterial hypertension, n (%)	40 (28.2)	10 (41.7)	30 (25.4)	0.11
Dyslipidemia, n (%)	49 (34.5)	14 (58.3)	35 (29.7)	0.009
Creatinine at donation (mg/dL)	0.86 ± 0.18	0.98 ± 0.16	0.83 ± 0.17	< 0.001
eGFR at donation (mL/min/1.73 m²)	88.66 ± 18.44	74.66 ± 16.13	91.51 ± 17.51	< 0.001

Over the follow-up period, 24 donors (16.9%) reached the composite endpoint: 21 (14.7%) presented an eGFR below 45 mL/min/1.73 m² at the last evaluation, and 3 (2.2%) died from causes unrelated to donation. The renal component was approximately seven times more frequent than the mortality component. None of the 142 donors presented an eGFR below 15 mL/min/1.73 m² and none required renal replacement therapy.

Donors who reached the endpoint were significantly older (61.48 ± 6.72 vs. 50.68 ± 11.15 years; $p < 0.001$), with higher creatinine (0.98 ± 0.16 vs. 0.83 ± 0.17 mg/dL; $p < 0.001$) and lower eGFR (74.66 ± 16.13 vs. 91.51 ± 17.51 mL/min/1.73 m²; $p < 0.001$). Among the comorbidities, dyslipidemia was significantly more frequent in the endpoint group (58.3% vs. 29.7%; $p = 0.009$), while obesity (25.0% vs. 10.2%; $p = 0.07$) and hypertension (41.7% vs. 25.4%; $p = 0.11$) showed the same trends without reaching significance.

Table II.6.2. Univariate and multivariate logistic regression analysis of the predictors of the composite endpoint.

Variable	OR (univ.)	95% CI (univ.)	p (univ.)	OR (multiv.)	p (multiv.)
Age at donation	1.12	1.06–1.20	< 0.001	1.11	0.01
BMI at donation	1.09	0.97–1.24	0.13	—	—
Obesity	2.94	0.98–8.84	0.05	—	—
Arterial hypertension	2.09	0.84–5.21	0.11	—	—
Dyslipidemia	3.32	1.34–8.18	0.009	—	—
eGFR at donation	0.94	0.91–0.97	< 0.001	0.95	0.07

On univariate analysis, age at donation proved the strongest predictor (OR = 1.12; 95% CI 1.06–1.20; $p < 0.001$), followed by dyslipidemia (OR = 3.32; 95% CI 1.34–8.18; $p = 0.009$) and eGFR at donation (OR = 0.94 per 1 mL/min/1.73 m²; $p < 0.001$). In the multivariate model, **only age at donation remained a significant independent predictor** (adjusted OR = 1.11; 95% CI 1.02–1.21; $p = 0.01$); baseline eGFR showed a borderline trend (OR = 0.95; $p = 0.07$), and none of the metabolic comorbidities retained an independent association. The apparent association between dyslipidemia and the endpoint

was completely attenuated, suggesting substantial confounding by the age variable, donors with dyslipidemia being, on average, almost a decade older.

The mean eGFR decline over the follow-up period was −27.37 ± 17.80 mL/min/1.73 m² (95% CI −30.33 to −24.42; $p < 0.001$), corresponding to a mean annual rate of approximately 3.3 mL/min/1.73 m² per year, a value consistent with the physiological response to unilateral nephrectomy[93]. Only two donors presented an eGFR ≤30 mL/min/1.73 m². The secondary analyses confirmed the central role of age, with a progressively higher proportion of endpoint attainment in the older age groups, and suggested a cumulative effect of comorbidities (approximately 30% in donors with ≥2 comorbidities vs. 13% in those with none), an effect that nevertheless loses significance after adjustment for age.

6.4. Discussion

The central finding is that, over approximately 8.4 years, preoperative metabolic comorbidities did not constitute independent predictors of the composite endpoint. The loss of significance on multivariate analysis is explained by the close correlation of these conditions with age, the only independent predictor[84]. The data are consistent with the observations of Massie et al., who, in 133,824 donors, identified age as one of the strongest risk factors, with an increase in absolute risk at 20 years from 0.29% in donors under 30 years to 1.09% in those over 60 years[84]. The univariate association between dyslipidemia and the endpoint reflects the overall cardiometabolic burden associated with aging, rather than an independent nephrotoxic effect[94]. Obesity did not independently predict adverse outcomes, consistent with large studies[2,95], although the mechanisms of obesity-related glomerulopathy could manifest at longer follow-up durations[31].

Mild, controlled hypertension did not independently predispose to renal deterioration, consistent with the Al Ammary study[83]. Baseline eGFR showed a borderline association, supporting the recommendation to consider baseline renal function an integral component of risk assessment[6]. The mean decline observed is consistent with the compensatory hypertrophy described by Lenihan et al.[93]. The identification of age as the sole predictor raises the question of mechanisms: the physiological loss of nephrons with age[96], the attenuation of the hypertrophic response[97-98] and the intersection of the eGFR decline trajectory with clinical thresholds[99], to which are added the molecular changes of renal aging (inflammaging, cellular senescence)[100-102]. The Grams model,

applied retrospectively, estimates a median 15-year risk of approximately 0.2–0.3% for the cohort's median profile[9]. Compared with American[24,84] and European cohorts[25,103], the results support the safety of donation in carefully selected individuals. The limitations include the retrospective design, the sample size, and the single-center origin, as well as possible residual confounding by unmeasured variables.

6.5. Conclusions of Study 1

(1) Age at donation was the only significant independent predictor of the composite endpoint. (2) Metabolic comorbidities did not significantly influence the outcome after adjustment. (3) Mortality was low (2.2%), and renal function deterioration below 45 mL/min/1.73 m² occurred in 14.7%, with no case of end-stage kidney disease. (4) The mean eGFR decline was −27.37 mL/min/1.73 m². (5) The findings support the paradigm of individualized assessment, well-controlled metabolic conditions not representing an absolute contraindication, provided adequate monitoring.

7. STUDY 2. LONG-TERM PSYCHOSOCIAL AND SOCIOECONOMIC OUTCOMES OF LIVING KIDNEY DONORS

7.1. Introduction

The long-term psychosocial and socioeconomic consequences are less studied than medical safety. Most donors report a quality of life comparable to that of the general population, but a minority experience depression, anxiety, regret, and financial burden[90,104-105]. Eastern European data remain insufficient, and donors who experience a significant decline in renal function could constitute the group at highest risk for regret and stress[106]. The specific hypothesis is that psychosocial outcomes remain favorable, but deterioration of eGFR below 45 mL/min/1.73 m² is associated with refusal to repeat the decision to donate.

7.2. Materials and methods

The study was designed as a cross-sectional retrospective evaluation of the sub-cohort of 136 donors (from the initial cohort of 142, by excluding the 6 who could not be interviewed), with a mean follow-up of 100.97 ± 17.89 months. Data were collected through a structured questionnaire, administered during follow-up visits or by telephone interview. Donors were stratified according to eGFR at the last evaluation, using the threshold of 45 mL/min/1.73 m² (corresponding to chronic kidney disease stage 3b).

Differences were analyzed using the Fisher exact test, given the low frequency of some outcomes.

7.3. Results

The sub-cohort included 136 donors with a mean age of 52.15 ± 11.29 years, with 101 (74.3%) female. The vast majority of donations came from first-degree relatives (130, 95.6%). At donation, 36 donors (26.5%) had hypertension, 44 (32.4%) dyslipidemia, 15 (11.0%) obesity, and 27 (19.9%) were smokers. At the last evaluation, 19 donors (14.0%) developed de novo hypertension, 24 (17.6%) dyslipidemia, and 2 (1.5%) type 2 diabetes mellitus.

Table II.7.2. Psychosocial and socioeconomic outcomes reported by donors at the last evaluation, stratified by eGFR.

Outcome	Whole cohort (n=136)	eGFR ≥ 45 (n=118)	eGFR < 45 (n=18)	p
Impact on social life	2 (1.5)	1 (0.8)	1 (5.6)	0.24
Impact on professional life	2 (1.5)	2 (1.7)	0 (0)	0.75
Negative impact on family life	0 (0)	0 (0)	0 (0)	1.00
Regret about the donation decision	0 (0)	0 (0)	0 (0)	1.00
Refusal to repeat the donation	14 (10.3)	8 (6.8)	6 (33.3)	0.003
Change in body image	2 (1.5)	2 (1.7)	0 (0)	1.00
Depression	7 (5.1)	7 (5.9)	0 (0)	0.59
Anxiety	8 (5.9)	8 (6.8)	0 (0)	0.59
Stress	7 (5.1)	7 (5.9)	0 (0)	0.59
Fear of kidney failure	3 (2.2)	3 (2.5)	0 (0)	1.00
Financial burden	0 (0)	0 (0)	0 (0)	1.00
Change of occupation	0 (0)	0 (0)	0 (0)	1.00

Overall, adverse outcomes were rare. No donor reported regret about the decision to donate, negative impact on family life, financial burden, or change of occupation. Symptoms of depression were reported by 5.1%, anxiety by 5.9%, stress by 5.1%, and fear of kidney failure by 2.2%. However, 14 donors (10.3%) stated that they would not repeat the donation if offered the choice again, despite the absence of explicit regret.

Stratification by eGFR showed that 118 donors (86.8%) maintained an eGFR ≥ 45 mL/min/1.73 m², and 18 (13.2%) reached an eGFR below this threshold. The only outcome with a significant difference was the willingness to repeat the donation: donors with an eGFR < 45 mL/min/1.73 m² were almost five times more likely to state that they would not repeat the donation (33.3% vs. 6.8%; p = 0.003). Apparently paradoxically, the negative psychological symptoms were reported exclusively in the group with preserved renal function, an observation that probably reflects the small size of the group with deteriorated function (n = 18) and a possible compensatory psychological mechanism of retrospective

rationalization, consistent with the literature on cognitive dissonance[107]. Compared with international data, refusal to repeat the donation (10.3%) was slightly higher than the reported range (0–7%), depression (5.1% vs. ~4.2%) and anxiety (5.9% vs. ~5.5%) were similar, and fear of kidney failure was markedly lower (2.2% vs. ~13%)[108-109].

7.4. Discussion

The study provides one of the longest follow-up evaluations of psychosocial outcomes, with a mean period approaching nine years. Social functioning remains unchanged or improves in most donors[110-111], and most return to work within four to six weeks, with return time being a predictor of financial burden[112]. No donor reported a negative impact on family life, consistent with a systematic review in which 83–100% reported unchanged or improved relationships[111].

The central clinical signal is the dissociation between explicit regret (0%) and refusal to repeat the donation (10.3%)[113], the latter being strongly dependent on subsequent renal function (33.3% vs. 6.8%; $p = 0.003$). "Regret," with its moral connotation, represents a more severe judgment than "unwillingness to repeat," which suggests that the question about hypothetical repetition is a more sensitive instrument for detecting latent distress. The psychological symptoms (depression 5.1%, anxiety 5.9%, stress 5.1%) are consistent with Western cohorts[104,109,114]. Their concentration in the group with preserved function may reflect the small size of the group with eGFR < 45 ($n = 18$) and a mechanism of retrospective rationalization, in accordance with cognitive dissonance theory[107].

Fear of kidney failure was markedly lower (2.2%) than in the Rodrigue study (13%)[108], probably due to the reassurance provided by structured follow-up, the demographic profile, and cultural factors; the absolute risk of end-stage kidney disease remains low[24]. The particularities of the Eastern European cohort include the pronounced female predominance (74.3%)[115-117], the almost exclusively intra-familial donations (95.6%)[118] and the absent financial burden (0%), surprising compared with Canadian data[119-121], explained by the coverage of the procedure's costs by the national insurance system. The eGFR threshold of 45 mL/min/1.73 m² functions as a psychological reference point that retrospectively reshapes the evaluation of the decision[122], arguing for communication in the form of trajectories rather than categorical thresholds[123-124]. The most recent EAU-YAU systematic review confirmed very low

regret rates[125]. The central clinical message supports rigorous pre-donation risk stratification, transparent counseling, lifelong renal monitoring, and the integration of structured psychological evaluation, possibly through instruments such as a “donor passport”[6,90,126]. The limitations include the cross-sectional design, the non-validated institutional questionnaire, and the small subgroup with eGFR < 45.

7.5. Conclusions of Study 2

(1) Psychosocial and socioeconomic outcomes were generally favorable, with a low frequency of regret (0%), negative family impact (0%), financial burden (0%), and psychological symptoms (below 7%). (2) 10.3% of donors stated that they would not repeat the donation. (3) Deterioration of eGFR below 45 mL/min/1.73 m² was associated with a significantly higher probability of refusal to repeat the donation (33.3% vs. 6.8%; $p = 0.003$). (4) This association persists in the absence of explicit regret. (5) The findings reinforce the importance of rigorous selection criteria, structured pre-donation counseling, and lifelong renal monitoring.

8. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

8.1. General conclusions of the thesis

Conclusion 1. In the cohort of 142 living donors operated on at the Fundeni Clinical Institute between 2015 and 2019, the demographic and metabolic profile reflects the Eastern European specificity: a mean age of 52.44 years, female predominance (72.5%), almost exclusively intra-familial donations, high prevalence of hypertension (28.2%) and dyslipidemia (34.5%), and lower prevalence of obesity (12.7%) and smoking (21.8%).

Conclusion 2. Over a mean follow-up period of approximately 8.4 years, 16.9% of donors (24 of 142) reached the composite endpoint. Mortality was very low (2.2%), the predominantly expressed component being renal. No donor presented an eGFR < 15 mL/min/1.73 m² and none required renal replacement therapy.

Conclusion 3. Age at the time of donation was the only significant independent predictor of the composite endpoint (adjusted OR = 1.11; 95% CI 1.02–1.21; p = 0.01). Baseline renal function showed a borderline association (p = 0.07), and the metabolic comorbidities lost their association after adjustment for age and baseline renal function.

Conclusion 4. The univariate association between dyslipidemia and the endpoint (OR = 3.32; p = 0.009) is an example of confounding by the age variable, reflecting the overall cardiometabolic burden associated with aging, with implications for the interpretation of published data lacking adequate adjustment.

Conclusion 5. The mean eGFR decline was −27.37 mL/min/1.73 m² (annual rate of approximately 3.3 mL/min/year), a value consistent with the physiological response expected after unilateral nephrectomy.

Conclusion 6. In the sub-cohort of 136 donors evaluated psychosocially, the outcomes were generally favorable, without regret, negative family impact, financial difficulties, or professional change; symptoms of depression (5.1%), anxiety (5.9%), and stress (5.1%) were comparable to the general population and international cohorts.

Conclusion 7. The most frequently reported adverse outcome was the hypothetical refusal to repeat the donation (10.3%), a frequency slightly higher than the 0–7% range reported in systematic reviews, representing the central clinical signal of the psychosocial study.

Conclusion 8. Stratification by renal function revealed a strong association between eGFR deterioration below 45 mL/min/1.73 m² and refusal to repeat the donation (33.3% vs. 6.8%; p = 0.003), suggesting that this threshold functions as a psychological reference point that retrospectively reshapes the evaluation of the decision.

Conclusion 9. The concentration of manifest psychological symptoms exclusively in the group with preserved renal function suggests the possible intervention of retrospective rationalization mechanisms in donors with functional deterioration, in harmony with the literature on cognitive dissonance.

Conclusion 10. Taken together, the results of the two studies support the paradigm of individualized assessment of the living donor, according to the 2017 KDIGO guideline. Mild and well-controlled metabolic comorbidities do not represent absolute contraindications, but the psychological dimension of the outcome must be integrated into counseling and long-term follow-up.

8.2. Personal contributions

Contribution 1 — Characterization of a representative Eastern European cohort. Detailed characterization of a single-center cohort of 142 living donors, with a mean follow-up of approximately 8.4 years (sections 6.3.1 and 7.3.1).

Contribution 2 — Quantification of the long-term composite endpoint. Determination that 16.9% of donors reached the composite endpoint over 100.88 ± 17.75 months (section 6.3.2).

Contribution 3 — Identification of age at donation as the sole independent predictor. Demonstration, through multivariate logistic regression, that age at donation is the only significant independent predictor (adjusted OR = 1.11; p = 0.01) (section 6.3.5).

Contribution 4 — Demonstration of the attenuation of the association between dyslipidemia and the endpoint. Highlighting the confounding role of age, the univariate association (OR = 3.32; p = 0.009) being completely attenuated in the multivariate model (sections 6.3.4–6.3.5 and 6.4).

Contribution 5 — Quantification of the physiological eGFR decline in the Romanian context. Determination of a mean eGFR decline of −27.37 ± 17.80 mL/min/1.73 m² (annual rate of 3.3 mL/min/year) (section 6.3.6).

Contribution 6 — Systematic evaluation of 12 psychosocial and socioeconomic domains. The first systematic evaluation in a Romanian cohort of 12 distinct domains in living donors (section 7.3.2).

Contribution 7 — Identification of the eGFR threshold as a critical psychological reference point. The finding that donors with an eGFR below 45 mL/min/1.73 m² refused hypothetical repetition of the donation in a significantly higher proportion (33.3% vs. 6.8%; p = 0.003) (section 7.3.3).

Contribution 8 — Dissociation between explicit regret and refusal to repeat the donation. Highlighting a psychological phenomenon: despite the complete absence of explicit regret (0%), 10.3% stated that they would not repeat the decision (section 7.4).

Contribution 9 — Placement of the Eastern European cohort in the international context. Systematic comparison with international data, with particularities such as a slightly higher frequency of refusal to repeat and a markedly lower frequency of fear of kidney failure (section 7.3.4).

Contribution 10 — Integrated argument for the individualized assessment paradigm. Synthesis of the results of the two studies in support of the individualized approach according to KDIGO 2017, with emphasis on long-term monitoring of renal function and mental health.

Contribution 11 — Concrete recommendations for local clinical practice. Formulation of a set of recommendations: quantitative pre-donation risk stratification, structured counseling, annual monitoring, and introduction of the question regarding hypothetical repetition of the decision.

Contribution 12 — Scientific dissemination through publications. The results were disseminated through two scientific manuscripts and through the narrative review "Risk Factors and Outcome in Living Kidney Donors," which formed the theoretical foundation of the general part.

8.3. Future research directions

The research opens several directions: (1) prospective multicenter studies and a national registry harmonized with European registries; (2) validation of psychosocial instruments (SF-36, PHQ-9, GAD-7, the Fear of Kidney Failure scale); (3) study of the effect of psychological thresholds through qualitative studies; (4) investigation of GLP-1

receptor agonists among donors with obesity or prediabetes; (5) development of integrated predictive models, both medical and psychosocial; (6) very long-term follow-up (15–20 years) for the characterization of late outcomes. In conclusion, the thesis contributes to consolidating the evidence base regarding the safety and long-term outcome of living-donor kidney transplantation, supporting the paradigm of individualized assessment and an integrated approach combining rigorous selection, structured monitoring, and attention to the psychological dimension of donation.

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