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Factors associated with long-term cardiovascular survival in atherosclerotic ischemic kidney disease

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Abstract

Objective. To find clinical predictors of long-term cardiovascular survival in patients with ischemic kidney disease (IKD) caused by atherosclerotic renal arteries lesions. **Design and methods.** In 1999–2012, 185 patients (118 males; aged 35–79 years) with the diagnosed significant atherosclerotic lesions of renal arteries (stenosis ≥ 50 %) were included in an open, single-center observation prospective study. Among them 123 subjects underwent renal revascularization (RR): open surgery in 61 cases, percutaneous angioplasty of renal arteries and stent implantation — in 62 patients. The mean follow-up was 33 months (95 % confidence interval 29–37 months). The estimated outcomes included hypertension dynamics, renal function and cardiovascular mortality. Kaplan-Meyer curves and Cox proportional hazards regression model were used for survival analysis and associated factors assessment. **Results.** Cumulative cardiovascular survival in IKD patients after renal revascularization was significantly higher. Regression analysis showed that the independent predictors of long-term cardiovascular mortality included renal revascularization, cerebrovascular disease and lower limbs ischemia. Relative risks of cardiovascular death were 0,25 in case of renal revascularization; 4,0 and 3,7 in the presence of cerebrovascular disease and lower limb ischemia, respectively. Independent predictors of long-term cardiovascular mortality after RR were lack of hypertension improvement (OR 8,7); post-surgery estimated glomerular filtration rate ≤ 45 ml/min/1,73 m^2 (OR 5,6); baseline proteinuria ≥ 1 g/day (OR 8,7); and peripheral artery disease with the lower limb ischemia (OR 46). **Conclusions.** Renal revascularization is associated with the higher long-term cardiovascular survival. An improvement of cardiovascular prognosis in IKD patients after surgery should be expected when antihypertensive and renoprotective efficacy of RR is achieved and concomitant lower limb ischemia is cured.

Key words: ischemic kidney disease, renal revascularization, cardiovascular survival, risk factors

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Резюме

Цель исследования — поиск клинических предикторов отдаленной сердечно-сосудистой (СС) выживаемости у пациентов с ишемической болезнью почек (ИБП), вызванной атеросклеротическими окклюзионными поражениями почечных артерий (ПА). **Материалы и методы.** В открытое одноцентровое обсервационное проспективное исследование было включено 185 больных (118 — мужчины; возраст 35–79 лет), у которых в период с 1999 по 2012 годы были выявлены гемодинамически значимые (стеноз ≥ 50 %) атеросклеротические поражения ПА. У 123 больных была выполнена реваскуляризация почек (РП), в том числе в 61 случае выполнены открытые РП, у 62 больных — чрескожная ангиопластика ПА со стентированием. В ходе проспективного наблюдения (средний срок — 33 месяца, 95-процентный доверительный интервал 29–37 месяцев), регистрировались динамика артериальной гипертензии (АГ), функция почек и смерть от СС причин. Для анализа выживаемости и ассоциированных факторов применяли метод Каплана-Мейера и регрессионную модель пропорциональных рисков. **Результаты.** Кумулятивная СС выживаемость в группе больных ИБП, подвергнутых открытой или эндоваскулярной РП, была выше, чем у пациентов, не подвергшихся оперативному лечению. При регрессионном моделировании установлено, что РП, наличие цереброваскулярной болезни (ЦВБ) и ишемии нижних конечностей (ИНК) являются независимыми предикторами СС смерти в отдаленном периоде. Снижение относительного риска (ОР) СС смерти при выполнении РП составило 75 %; ОР возрастал в 4 и 3,7 раза при наличии клинических проявлений ЦВБ и ИНК соответственно. Независимыми факторами, ассоциированными с отдаленной СС смертностью после РП, были отсутствие динамики АГ в отдаленном периоде (ОР 8,7); расчетная скорость клубочковой фильтрации ≤ 45 мл/мин/1,73 м^2 в послеоперационном периоде (ОР 5,6); исходная суточная потеря с мочой ≥ 1 г/сут (ОР 8,7); а также наличие облитерирующего атеросклероза артерий с ИНК (ОР 46). **Заключение.** Выполнение реваскуляризации почек у пациентов с ИБП ассоциировано с существенным улучшением отдаленной СС выживаемости. Улучшение отдаленного прогноза

у оперированных больных можно ожидать при эффективности РП в отношении коррекции артериальной гипертензии и дисфункции почек, а также при устранении ИНК.

Ключевые слова: ишемическая болезнь почек, реваскуляризация почек, сердечно-сосудистая выживаемость, факторы риска

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Introduction

Ischemic renal disease (IRD), caused by atherosclerotic lesions of renal artery (RA), remains a relevant problem due to a high cardiovascular risk and poor survival [1–7]. Novel diagnostics technologies and surgical methods to treat renal ischemia should have led to a substantial improvement in IRD management. However, the results of recent prospective comparative studies are disappointing, as they did not show any significant differences in long-term outcomes, including survival, in groups of conventional therapy and renal revascularization (RR) [6, 8, 9]. These "paradoxical" data point to the need for further research and analysis of prospective studies in order to assess post-RR outcomes.

The main purpose of our study was to analyze the predictors of long-term cardiovascular survival in a representative group of IRD patients.

Design and methods

In an open, prospective, single-center, observational study, we included 185 patients who had known hemodynamically significant (≥ 50% stenosis by angiography) atherosclerotic lesions of the RA, diagnosed between 1999 and 2012. Among them, there were 118 men and 67 women aged from 35 to 79 years (mean age — 60 ± 9 years). Unilateral RA lesions were detected in 114 (62%) subjects, bilateral — in 71 (38%). All of them were hypertensive, and drug-resistant hypertension (HTN) was diagnosed in 63% cases. 112 patients (61%) demonstrated renal dysfunction (RD) with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 $m^{2.}$ Stage III chronic kidney disease was diagnosed in 80 (72%), IV — in 27 (24%) and V — 5 patients (4%) [10, 11].

All IRD patients were divided into 2 groups. Group 1 included patients undergoing RR (n = 123). An isolated intervention (open or endovascular RR) in the absence of indications for vascular reconstructions of other vessels was performed in 103 cases; 20 patients underwent combined interventions on RA, kidneys and/or abdominal aorta, its branches and iliac arteries due to aneurysms and occlusions. Group 2 (control) included 62 patients with IRD who had not undergone RR: 19 subjects had only relative indications for RR [moderate HTN controlled by one or two antihypertensive drugs in the absence of severe RD], they underwent reconstruction of lower extremity arteries (LA) due to the progressive manifestations of chronic ischemia (ILA). In 43 cases, IRD surgery was not performed due to patient's denial from RR or combined surgery on the LA.

Among 123 patients who underwent RR (groups 1 and 2), including 76 open RR (74 bypass RA surgery, 1 transaortic endarterectomy of RA, and 1 PA implantation) and 7 nephrectomies (in combination with revascularization contralateral kidney) in 61 subjects, and 80 percutaneous angioplasties with PA stenting in 62 patients.

The decision to perform an operation was based on the analysis of the expected effects regarding BP, kidney function, general, cardiovascular and potential intervention-associated risks and was taken *ex consilio* by angiosurgeons and nephrologists after clinical examination and direct angiography were performed. All patients, regardless of the surgery, received detailed recommendations about lifestyle correction, diet and drug therapy in accordance with applicable principles of cardioprotection and renoprotection [10, 12, 13]. The treatment included angiotensin converting enzyme inhibitors or AT1-receptor blockers, angiotensin, statins, and optionally (or to replace the therapy) calcium channel blockers, beta-blockers, saluretics.

At baseline (in operated patients immediately prior to the RR) the following demographic and clinical parameters were registered: gender, age,

Table 1

CLINICAL PARAMETERS IN PATIENTS WITH ATHEROSCLEROTIC LESIONS OF RENAL ARTERIES AND ISCHEMIC RENAL DISEASE AT BASELINE

Parameter	All patients (n = 185)	Group 1 (with RR) (n = 123)	Group 2 (without RR) (n = 62)	P (Group 1 vs. Group 2)
Male, %	64	62	71	0.210
Age, years	60 ± 9	60 ± 9	63 ± 8	0.03
BMI, kg/m^2	26 ± 4	26 ± 4	24 ± 4	0.009
Bilateral RA lesion, %	37	47	18	< 0.001
HTN duration months	122 (46; 222)	128 (45; 249)	120 (59; 213)	0.197
Smoking, %	69	67	72	0.457
Diabetes mellitus, %	9	8	10	0.701
Antihypertensive drugs, n	2.9 ± 1.4	3.3 ± 1.2	2.1 ± 1.4	< 0.001
SBP, mm Hg	161 ± 25	166 ± 25	148 ± 19	< 0.001
DBP, mm Hg	92 ± 13	95 ± 12	84 ± 10	< 0.001
Mean BP mm Hg	117 ± 16	119 ± 15	106 ± 12	< 0.001
CHD, %	40	38	45	0.323
AMI, %	18	18	16	0.703
Myocardial revascularization, %	9	10	5	0.203
CVD, %	26	26	26	0.976
Aortic aneurysm, %	13	15	10	0.299
LLI, %	55	42	82	< 0.001
Cr, mmol / l	0.12 (0.1; 0.16)	0.13 (0.1; 0.16)	0.10 (0.08; 0.15)	0.742
eGFR ml / min / 1.73 m^2	50 ± 23	47 ± 19	55 ± 20	0.02

Note: * — operated patients, immediately prior to the operation; RR — renal revascularization; BMI — body mass index; RA — renal artery; HTN — hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure; CHD — coronary heart disease; AMI — acute myocardial infarction; CVD — cerebrovascular disease (presence of stroke or transient ischemic attacks); LLI — lower limb ischemia; Cr — serum creatinine; eGFR — estimated glomerular filtration rate.

body mass index; hypertension duration; systolic blood pressure (SBP); diastolic blood pressure (DBP); mean blood pressure (BP); need for antihypertensive therapy; presence of diabetes mellitus, verified coronary heart disease (CHD), acute myocardial infarction, previous myocardial revascularization; cerebrovascular disease (CVD), including past stroke or transient ischemic attacks; lower limb ischemia (LLI); serum creatinine (Cr), GFR EPI formula [14]. Descriptive statistics is presented in Table 1.

Mean follow-up period was 33 months, 95% confidence interval (CI) 29–37 months (3 to 132 months). During follow-up, the dynamics in HTN, renal function, and mortality due to cardiovascular causes were registered.

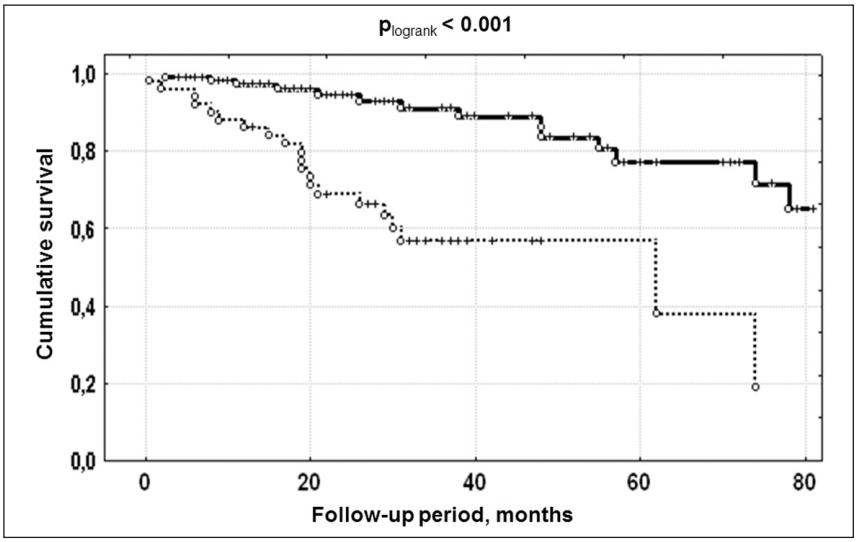
Statistical analysis

For comparative analysis of independent samples Student's t-test, χ^2 test or Mann-Whitney test were used depending on data distribution. Long-term cumulative survival was assessed by Kaplan-Meier analysis, and logrank was calculated. A Cox regression model with stepwise selection of the independent variables was used to verify the independent predictors of post-RR mortality. Cardiovascular fatal cases were considered as complete cases; survivors and deaths from other causes were estimated as censored cases. Data are presented as mean and standard deviation, unless otherwise indicated. The differences were considered statistically significant at $p < 0.05$. Analysis was performed using the statistical software application package "SPSS 14.0" (Chicago, IL, USA).

Results

As expected, cardiovascular survival in the joint group of patients with IRD undergoing endovascular or open RR (group 1) was higher than in non-operated patients (group 2) (Fig. 1). It

Figure 1. Cumulative cardiovascular survival in patients with coronary artery disease after renal revascularization and in non-operated subjects



Note: solid line — renal revascularization; dotted line — without operation; circles — total cases; crosses — censored cases.

Table 2

INDEPENDENT FACTORS ASSOCIATED WITH CARDIOVASCULAR SURVIVAL IN THE JOINT GROUP WITH ISCHEMIC RENAL DISEASE (n = 185) (STEP COX REGRESSION ANALYSIS)*

Parameter	B ± SE	Wald statistics	p	OR	95 % CI, for Exp (B)	
					Lower	Upper
RR	1.40 ± 0.36	14.88	< 0.001	0.25	0.12	0.50
LLI	1.32 ±0.44	9.23	0.002	3.76	1.60	8.83
CVD	1.41 ± 0.33	17.96	< 0.001	4.09	2.13	7.84

Note: * — the independent variables not included in the regression model: gender, age, smoking, baseline mean BP, baseline estimated glomerular filtration rate, presence of diabetes mellitus, unilateral/bilateral involvement of the renal arteries, the presence of an aortic aneurysm, ischemic heart disease, surgery revascularization of the lower limbs arteries; OR — odds ratio, (Exp (B); CI — confidence interval; RR — renal revascularization; LLI — lower limb ischemia; CVD — cerebrovascular disease.

should be noted that operated patients compared to non-operated ones showed higher SBP and DBP, higher mean number of antihypertensive drugs, lower eGFR, other parameters were comparable in both groups (Table 1). Patients who underwent endovascular and open RR, were matching by baseline clinical parameters and survival rates (data are not displayed).

Regression analysis showed that RR, along with CVD and LLI, is an independent predictor of long-term cardiovascular death (Table 2). However, such factors as gender, age, smoking, diabetes mellitus, bilateral RA lesions, mean BP, aortic aneurysm, initial eGFR, surgery LLI were proven to be insignificant in the multivariate model. The relative risk reduction (RR) of cardiovascular death after RR was 75 %; odds ratio (OR) was 4 and 3.7-fold in case of clinical manifestations of CVD and LLI, respectively (Table 2).

Multivariate analysis identified the following independent predictors of long-term cardiovascular mortality: the lack of HTN dynamics at long-term-follow-up (OR 8.7), eGFR ≤ 45 mL/min in the postoperative period (OR 5.6), daily proteinuria at baseline ≥ 1 g/day (OR 8.7), and the presence of atherosclerotic lesions with LLI (OR 46) (Table 3). Figure 2 displays cumulative survival in patients with different values of these indicators.

Discussion

Atherosclerotic IRD is one of the most serious forms of cardiovascular disease associated with a

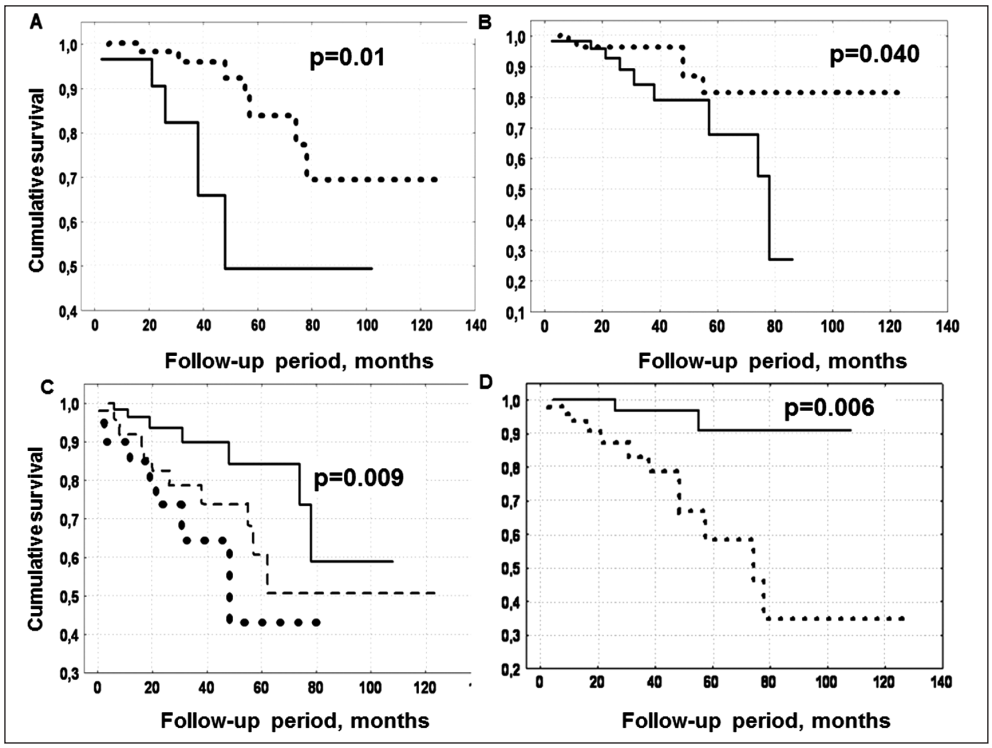
Table 3

INDEPENDENT FACTORS ASSOCIATED WITH REMOTE CARDIOVASCULAR MORTALITY IN OPERATED PATIENTS WITH ATHEROSCLEROTIC ISCHEMIC RENAL DISEASE (n = 123) (STEP-BY-STEP MULTIVARIATE COX REGRESSION ANALYSIS)*

Parameter	B ± SE	Wald statistics	p	OR	95 % CI, for Exp (B)	
					Lower	Upper
No BP changes at long-term follow-up (compared with the group with reduced BP)	2.16 ± 0.84	6.610	0.01	8.60	1.672	45.289
Postoperative GFR ≤ 45 ml/min (compared to GFR > 45 ml/min)	1.72 ± 0.83	4.237	0.04	5.602	1.086	28.900
Initial daily proteinuria ≥ 1 g/day (compared to proteinuria < 1 g/day)	2.16 ± 0.82	6.879	0.009	8.71	1.729	44.077
LLI (compared to the absence of LLI)	3.83 ± 1.38	7.687	0.006	46.388	3.079	78.878

Note: * — the independent variables that are not included in the regression model: smoking, diabetes mellitus, the volume of intraoperative bleeding, male gender, age, estimated of glomerular filtration rate at follow-up, the presence of cerebrovascular disease and ischemic heart disease; OR — odds ratio, Exp (B); CI — confidence interval; BP — blood pressure; eGFR — estimated glomerular filtration rate; LLI — lower limb ischemia.

Figure 2. Cumulative survival in patients with ischemic kidney disease (Kaplan Meier curves) after surgery



Note: A) the dynamics of arterial hypertension (HTN) at long-term follow-up: solid line — no HTN change, dotted line — HTN improved; B) postoperative level of estimated glomerular filtration rate (eGFR): solid line — eGFR ≤ 45 mL/min, dotted line — GFR>45 mL/min); C) the baseline level of daily proteinuria: solid line — 0–0,14 g/day, the dotted line — 0,15–0,99 g/day; dotted line — ≥ 1,0 g/day; D) the presence of atherosclerotic lesions of lower limb arteries before surgery (dotted line — there are atherosclerotic lesions of the arteries of the lower extremities; solid line — no lesions of the arteries of the lower extremities).

poor prognosis [1, 3]. HTN and renal dysfunction, which are the main clinical manifestations of IRD, are powerful factors for cardiovascular disease and atherosclerosis progression, as a result of hemodynamic and metabolic disorders [2–4, 7, 10, 13, 15]. They determine high mortality rate in IRD. In case of unilateral RA stenosis ≥ 60%, 4-year survival was 59% if conservative treatment was administered and no surgery was performed, and with bilateral lesions of similar degree it was 47% [16]. In the present study, patients receiving conservative treatment had 4-year survival below 60% with a further reduction at follow-up.

RR was accompanied by a significant improvement in cardiovascular survival in a remote postoperative period compared to patients who got conservative therapy. Our results seem consequent, although they contradict the negative results of prospective randomized studies assessing RR effectiveness and impact on the long-term prognosis [5, 8, 9]. Endovascular RR was the only operative approach assessed in these comparative studies [8, 9]. At the same time, half of the patients in this group underwent bypass RA surgery, which may provide a better long-term outcome compared to endovascular treatment [17]. However, the assumption of greater efficiency of open operations regarding long-term outcomes compared to endovascular interventions was not confirmed [18]. Therefore, we analyzed survival in the joint group of patients (endovascular + bypass surgery).

Patients' selection for RR is a crucial factor for the interpretation of the results on the effectiveness of RR compared to conservative treatment. In the mentioned studies randomization was based on the decision of the treating physician leading to the exclusion of patients requiring RR [5, 9, 19]. In our study, we a multidisciplinary approach (vascular surgeons, cardiologists and nephrologists participated in the discussion) was applied. We can assume that a careful selection of patients who potentially will benefit most benefit from the RR is the way to improve long-term outcomes [19, 20]. In our opinion, such an approach should be applied in the management of IRD patients.

Long-term follow-up is an advantage of our study. However, the limitations include the lack of randomization for RR implementation RR and, as a result, differences in the severity of IRD and cardiovascular disease in two groups. However, it should be noted that the highest cumulative survival rates was shown in patients undergoing RR, although they had more severe pre-operation manifestations of IRD — HTN and RD and comparable rates of comorbid cardiovascular disease. Moreover, to overcome these limitations a multivariate regression analysis was performed. It demonstrated that RR is associated with a reduced risk of cardiovascular death, regardless of other significant clinical factors.

We also identified independent factors associated with the risk of cardiovascular mortality in long-term postoperative period and we confirmed our assumption that improvement in survival is provided by the positive effect of RR regarding HTN and renal dysfunction. HTN is a standard and easily recognizable indication for RR [3]. However, not only antihypertensive, but also renoprotective effect of RR due to the delay of renal scarring progression and stabilization of renal function. Thus, RD, assessed daily by proteinuria and eGFR, was one of the predictors of adverse cardiovascular outcomes after RR. Both parameters are well-known predictors of total and cardiovascular mortality, as stated in national and international guidelines [10]. On average renal function before and after revascularization does not differ significantly [21]. At the same time, we have observed alternate changes in GFR in the postoperative period. Some patients develop an evident increase or decrease in GFR, in others it remains unchanged [20, 22]. The total rate of RR outcomes qualified as an "improved" or "stabilized" kidney function is 60–70% [23–25], however, the number of patients reaching end-stage renal failure, remains high [26, 27].

A severe reduction in GFR ≤ 45 mL/min/1.73 m^2 in the postoperative period Can be observed in three following situations: 1) a reduction of the baseline high eGFR to < 45 ml/min/1.73 m^2 after revascularization; 2) a very low baseline eGFR with moderate positive dynamics; 3) a low baseline eGFR without positive changes after revascularization. The first scenario may be due to the development of acute kidney injury due to various causes with an incomplete recovery. The last two scenarios are due to late diagnosis and the preoperative development of fibroplastic severe changes in the kidney. These changes are

likely to occur in patients with systemic HTN, are irreversible and can involve both ischemic and contralateral kidneys (in case of unilateral stenosis).

Daily proteinuria exceeding 1 g/day usually has a glomerular etiology. In case of IRD, proteinuria indicates the severity of the global and segmental glomerular sclerosis that is a characteristic morphological feature of chronic renal hypoperfusion [20]. Obviously, it can be considered an additional unfavourable factor of low RR efficiency for the long-term prognosis.

The lack of antihypertensive effect of RR is unsurprisingly associated with poorer survival. We assume that in these cases preoperative persistently elevated BP is associated with fibroplastic changes in ischemic and/or contralateral kidney, and to a less extent with the current organ ischemia. In this regard, the investigation of the role of kidney ischemia for HTN development and organ dysfunction is critical in order to determine the indications for revascularization and to increase its efficiency [20, 27].

In our group, as well as in IRD patients in general, clinical manifestations of extrarenal atherosclerosis were clinically significant. LLI was one of the most frequent, its presence was independently associated with the increased risk of cardiovascular mortality. We have previously shown that a simultaneous or sequential intervention on RA and the lower extremities is associated with a significant improvement in remote cardiovascular survival in IRD patients [28]. The elimination of this risk factor is an evident approach to improve survival in IRD patients.

Conclusions

Revascularization in IRD patients is associated with a substantial improvement in long-term cardiovascular survival. The main predictors of long-term survival after surgery include antihypertensive and renoprotective efficiency of the procedure and LLI elimination. Implementation of approaches to foresee and achieve maximal antihypertensive and renoprotective effects after RR, as well as a timely correction of LLI could lead to a significant improvement in survival in IRD patients.

Conflict of interest
The authors declare no conflict of interest.

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