DOI 10.4149/BLL_2024_88

Bratisl Med J 2024; 125 (9):
564–571

CLINICAL STUDY

Arterial hypertension after liver transplantation

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ABSTRACT

One of the most prevalent influenceable risk factors for poor cardiovascular outcome is arterial hypertension. This is a prospective analysis of liver transplant recipients in which 24-hour blood pressure (BP) measurement was performed. The primary aim was to identify post-LT (liver transplantation) patients without a history of arterial hypertension who meet the criteria for arterial hypertension using 24-hour BP monitoring. Secondary objectives were to determine how many patients with known treated arterial hypertension had suboptimal BP control.

The group included 88 patients (men, 52.3%, history of arterial hypertension group: n=56, no history of arterial hypertension group: n=32) with an average age at the time of measurement of 62.4 years±11. The average time since LT at the time of measurement was 45.2 months. De novo arterial hypertension using 24-hour BP monitoring was diagnosed in 28%. Hypertonic changes in the fundus oculi were confirmed as predictor for suboptimally controlled hypertension [OR 5,1265, p=0.0279]. On the other hand, male sex [OR 3.1840, p=0.0311], together with age [OR 1.3347, p=0.0153] and waist circumference [OR 4.3490, p=0.0418] predicted the need of intensification of antihypertensive treatment.

Male sex, age and waist circumference should increase the index of suspicion and lead to zoom-in on a possibility of poorly controlled blood pressure. Where automated blood pressure monitoring is unavailable, regular examination of the fundus could serve as an available surrogate marker of suboptimally controlled arterial hypertension *(Tab.6, Fig. 1, Ref. 36)*. Text in PDF www.elis.sk

KEY WORDS: liver transplantation, arterial hypertension, automated blood pressure monitoring.

Abbreviations: ACEi – angiotensin-converting enzyme inhibitors, BMI – body mass index, BP – blood pressure, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, CyA – Cyclosporine A, eGFR – estimated glomerular filtration rate, LT – Liver transplantation, MMF – mycophenolate mofetil, TAC – tacrolimus

Introduction

After a pioneering work of Starzl in the sixties and ever since its first approval by the National Institute of Health in the eighties, worldwide liver transplantations (LT) have been saving and prolonging lives of dozens of thousands of patients each year (1, 2). Although five-year post-LT survival rate is the designated quality measure, prevailing aspirations of transplant centers are higher, with more and more patients surviving twenty plus years (3). This unprecedented success comes at the cost, however: post-LT cohort has been attacked by the global plague of non-communicable diseases, with cardiovascular diseases becoming one of the leading causes of post-LT morbidity and mortality (4). Cardiovascular mortality ranges around 20% five years after LT (2, 4, 5, 6). In this line, further improvement of the long-term post-transplant survival has remained unmet need of the last decade (7).

The development of cardiovascular complications in patients after LT occurs significantly more often compared to the general population, primarily as a result of the superposition of immunosuppression, which promotes the development of arterial hypertension, hyperlipoproteinemia and diabetes mellitus (8, 9, 10). One of the most prevalent influenceable risk factors for poor cardiovascular outcome is arterial hypertension (11, 12, 13).

Arterial hypertension is defined by systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg (14). In the case of liver transplant patients, it occurs in more than 30–50%, second only to the heart transplant population (13, 15, 16). Moreover, the fact that its frequent and typical phenotype is high prevalence of nocturnal arterial hypertension and non-dipping also contributes to the adverse consequences of hypertension after organ transplantation (17).

The etiopathogenesis of arterial hypertension after LT is multifactorial and includes a group of mechanisms shared with the general population, hemodynamic changes associated with liver failure before LT and the use of immunosuppressive drugs, primarily calcineurin inhibitors (10, 18, 19).

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The mechanism of the pathogenic effect of CNIs is primarily based on vasoconstriction. Vasoconstriction is caused by excessive secretion of endothelin-1 and thromboxane and decreased production of prostacyclin, which leads to increased activity of the sympathetic nervous system. In addition to these mechanisms, calcineurin inhibitors, namely cyclosporine and tacrolimus, act on sodium retention (13, 18, 19). Of importance, the effects of tacrolimus and cyclosporine on the increase in blood pressure differ (20). By acting on the renin-angiotensin-aldosterone system, glucocorticoids, also used as part of immunosuppressive therapy, increase blood pressure (BP) (19, 21).

As is generally known, arterial hypertension leads to endothelial damage, atherosclerosis, hypertensive nephropathy with the development of chronic kidney disease and remodeling of the left ventricle. Good BP control is therefore crucial in preventing cardiovascular complications after LT and essential to ensure long-term graft and patient survival (19). However, good long-term BP control after LT faces several pitfalls: both patients and physicians have a natural tendency to focus on liver function; higher pressures measured in the post-transplant clinic are often underestimated as a consequence of the white coat syndrome, especially if the patient also measures the pressures at home and they do not show such high values (19) tend to direct the management of hypertension, and the doctor when contacted is afraid to change the antihypertensive treatment because of the "liver" and drug interactions of immunosuppressants (19, 22). Suboptimal management may result (22), so this domain is of great interest.

In the treatment of arterial hypertension after LT, it is important to focus on influencing lifestyle (ie, low sodium diet, stop smoking, weight reduction). In our, as well as in other sets of patients after LT, the results of lifestyle treatment are still unmet need (23). Therefore, if it is not possible to achieve the BP target values (130/80 mmHg) with this change, medical treatment is necessary (24). The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers is clearly indicated in the case of detected microalbuminuria (or proteinuria), however, in general, the treatment of arterial hypertension after LT is consistent with the general population with regard to the patient's comorbidities (25).

The primary aim of our work was to identify post-LT patients without a history of arterial hypertension who meet the criteria for arterial hypertension using 24-hour BP monitoring. Secondary objectives were to determine how many patients with known treated arterial hypertension had suboptimal BP control according to automated blood pressure monitoring; and find out which organs are most often affected by arterial hypertension in this population of patients (both in the group of patients with known arterial hypertension and in patients without a history of arterial hypertension) and to identify those patients who are most at risk in untreated (or poorly treated) arterial hypertension.

Materials and methods

This is a prospective follow-up of patients after LT in the years regularly checked in the hepatology clinic at the Transplant Center Banská Bystrica (01/2021–06/2021), in which 24-hour BP measurement was performed. All patients who agreed and signed the consent form, and who were checked between 01/2021–06/2021 at the outpatient clinic of Transplant center Banská Bystrica were included in the study. The file included patients older than 18 years without and with a history of arterial hypertension – defined as office systolic and diastolic BP more than 140 mmHg and/or 90 mmHg (based on this data, the patients were subsequently divided into subgroups). For each patient, at the time of BP measurement, the following were recorded: age, sex, time (in months) since LT, underlying etiology of liver cirrhosis (others were included in the group: Caroli's disease, Echinococcosis, glycogenosis, carcinoid, polycystic liver disease, waist circumference, body mass index (BMI), immunosuppressive treatment used, and antihypertensive treatment was recorded in patients with known arterial hypertension. As part of the follow-up, we evaluated a change or adjustment of treatment after measuring BP, treatment was adjusted (increase in the dose of an already used preparation/addition of a preparation), or initiation of antihypertensive treatment (in the group of patients without a history of hypertension at the time of BP measurement). All patients underwent an echocardiographic examination (performed by one doctor) with the assessment of the following parameters: Left ventricular hypertrophy, left ventricular ejection fraction and the presence of left ventricular diastolic dysfunction. Left ventricular hypertrophy was defined as diameter of interventricular septum more than 12 mm or/and as an increased left ventricular mass index (LVMI) to greater than 95 g/m in women and increased LVMI to greater than 115 g/m in men.

Left ventricular dysfunction was defined using PW doppler (E/A ration and TDI parameters) based on Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography, 2016.

None of the patients included in the study was diagnosed with left ventricular hypertrophy or left ventricular diastolic dysfunction before liver transplantation.

The patients also underwent an ophthalmological examination focusing on the presence of de novo changes in the fundus oculi.

Immunosuppression: The mean level of calcineurin inhibitor (tacrolimus – TAC, cyclosporin A – CyA) was determined from the last 3 values before BP measurement, the recorded dose of corticosteroids (prednisolone) and mycophenolate mofetil (MMF) is the current dose at the time of BP measurement.

Laboratory parameters: at the time of BP measurement, creatinine value was recorded with determination of estimated glomerular filtration rate (eGFR) according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), fasting blood glucose, cholesterol and triacylglycerol levels, and quantitative proteinuria in urine (under standard conditions of 24-hour collection urine).

24-hour monitoring of BP: All patients had a 24-hour BP measurement under standard conditions (2 measurements/hour). The average measurement time, average number of measurements/24 hours, average systolic and diastolic BP - for the entire measurement, average systolic and diastolic BP – during the day and during the night, and finally the maximum and minimum systolic and diastolic BP were evaluated.

The monitored parameters and file characteristics are shown in Table 1.

Statistical analysis

We used a certified statistical programme, MedCalc version 13.1.2. (VAT registration no. BE 0809 344 640, Member of International Association of Statistical Computing, Ostend, Belgium), to perform statistical analyses. Continuous data were compared using the Student's t-test or the Wilcoxon rank-sum test as appropriate. The χ^2 test and Fisher's exact test were used for categorical variables.

Univariate and multivariate logistic regressions were used to assess monitored parameters in order to predict the risk of increased doses or change of antihypertensive treatment. Statistically significant parameters assessed in the univariate analysis were entered to the multivariate model. Statistically significant parameters were also further analysed by means of probit regression. We considered a $p< 0.05$ to be statistically significant.

Ethical approval

All procedures involving human participants have been approved according to the ethical standards of the institutional research committee, including the 1964 Helsinki Declaration and its later amendments of comparable ethical standards. Informed consent for included participants was checked and approved by FD Roosevelt Faculty Hospital's ethical committees.

and all signed informed consents have been archived for at least 20 years after research was completed.

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Results

The group included 88 patients (men, 52.3%) with an average age at the time of measurement of 62.4 years±11. The average time since LT at the time of measurement was 45.2 months. The dominant etiology of liver cirrhosis before LT was alcohol associated liver disease in 42% (Fig. 1).

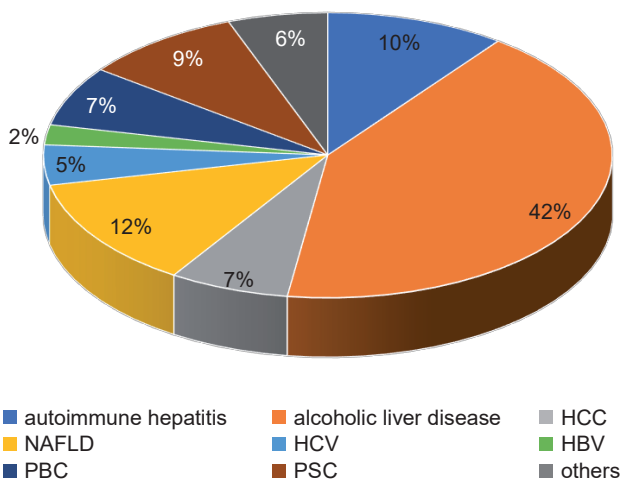

Fig. 1. The underlying etiology of liver cirrhosis at the time of liver transplantation.

We further divided the group into two groups according to the history of arterial hypertension – those with already diagnosed

Tab. 1. Set characteristics.

Set characteristics (n=88)	
Average age at the time of measurement (years)	62.4±11
Gender – men (%)	52.3
Time since transplantation (months) at the time of measurement	45.2±31
Waist circumference (cm)	97.6±12.8
BMI (kg/m^2)	28.1±4.6
Corticosteroids in treatment (%)	20.5
Dose of corticosteroids/day (mg)	7.9±3.8
Tacrolimus in treatment (%)	89.8
Mean TAC level (ng/ml)	5.7±2.1
Cyclosporin A in treatment (%)	10.2
Mean CyA level (ng/ml)	139±40
MMF in treatment (%)	96.6
Average dose of MMF/day (mg)	1038±495
History of arterial hypertension (%)	63.6
ACEi/sartan in treatment (%)	26.1
Ca blocker in treatment (%)	20.5
Beta blocker in treatment (%)	58
Diuretic in treatment (%)	10.2
Other antihypertensive drug in treatment (%)	4.5
Creatinine (µmol/l)	94.5±34.8
Proteinuria (g/day)	0.7±0.3
eGFR CKD-EPI (ml/min)	76.2±23.4
Fasting blood glucose (mmol/l)	6.5±2.4
Cholesterol (mmol/l)	5±1.1
Triacylglycerols (mmol/l)	1.6±0.9
Left ventricular hypertrophy (%)	4.5
LV ejection fraction (%)	61±9.7
Diastolic dysfunction	42
Hypertonic changes in the fundus oculi (%)	43.2
24-hour monitoring of blood pressure	
Duration of Holter measurements (hours)	23.2±4.2
Average number of measurements	46.8±21
Mean sBP (mmHg)	133±18
Mean dBP (mmHg)	80±13
Mean sBP during the day (mmHg)	134±19
Mean dBP during the day (mmHg)	82±14
Mean sBP during the night (mmHg)	128±21
Mean dBP during the night (mmHg)	74±12
Maximum sBP (mmHg)	172±28
Maximum dBP (mmHg)	114±25
Minimum sBP (mmHg)	100±18
Minimum dBP (mmHg)	54±13
Mean HR/min	73±8.1
Maximum HR/min	104±22
Minimum HR/min	54±13
Medication use adjustment (%)	4.5
Added antihypertensive drugs (%)	47.7

BMI – body mass index; TAC – tacrolimus; CyA – cyclosporin A; MMF – mycophenolate mofetil; ACEi – angiotensin-converting enzyme inhibitors; Ca – blocker – calcium channel blocker; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; LV – left ventricle; sTK – systolic blood pressure; dTK – diastolic blood pressure; HR – heart rate

and treated arterial hypertension (n=56) and patients without diagnosed arterial hypertension at the time of 24-hour monitoring of BP (n=32). Surprisingly, patients without arterial hypertension were significantly older, had a significantly smaller waist circumference (with equal representation of men and women) and significantly lower BMI values. At the same time, we found a significantly higher average value of cyclosporine A in this group (which may be distorted by the small number of patients treated with cyclosporine – a total of 9 patients, 5 in the group with arterial hypertension and 4 patients in the group without arterial hypertension). As part of the treatment of arterial hypertension, logically, patients without arterial hypertension did not have any medication, except for three patients (9.4%) who were treated with a beta-blocker for another indication (tachycardia). Patients without a history of arterial hypertension had significantly better renal parameters (expressed by creatinine, proteinuria and eGFR), were significantly less frequently diagnosed left ventricular hypertrophy during echocardiographic examination, as well as hypertonic changes in the fundus oculi.

Within the 24-hour BP measurement, we found that patients without a history of arterial hypertension had significantly lower systolic BP (overall, during the day and also during the night). We did not confirm a statistically significant difference in diastolic BP. At the same time, we recorded a significantly higher heart rate in the mentioned cohort of patients (probably due to the absence of a beta blocker in regular medication, in contrast to the group of patients with arterial hypertension). In the group of patients without a history of arterial hypertension, antihypertensive was added in 9 patients (28%), while in patients with arterial hypertension it was added in 58.9% of patients. A comparison of the monitored groups is shown in Table 2.

In the next analysis, we focused on the occurrence of risk factors in the group of patients with arterial hypertension with insufficiently controlled hypertension, confirmed by 24-hour BP monitoring with the need for adjustment or change of antihypertensive treatment. Significant parameters from univariate analysis (Tab. 3) were subsequently analyzed in multivariate analysis, where we found that an independent risk factor for insufficiently controlled arterial hypertension (expressed by the need to change/increase antihypertensive treatment) in the group

Tab. 2. Comparison of patients with a history of arterial hypertension and without a history of arterial hypertension.

	History of AH n=56	No history of AH n=32	p
Average age at the time of measurement (years)	60.1±9.6	66.2±12.4	**0.0118**
Gender – men (%)	58.9	40.6	0.1002
Time since transplantation (months) at the time of measurement	48±31	40.2±30.8	0.2593
Waist circumference (cm)	100.4±11.7	92.4±13.3	**0.0043**
BMI (kg/m^2)	29.1±4.4	26.4±4.4	**0.0069**
Corticosteroids in treatment (%)	16.1	28.1	0.1820
Dose of corticosteroids/day (mg)	8.6±4.9	7.2±2.3	0.1320
Tacrolimus in treatment (%)	91.1	87.5	0.5937
Mean TAC level (ng/ml)	5.8±2.1	5.5±2.2	0.5280
Cyclosporin A in treatment (%)	8.9	12.5	0.5937
Mean CyA level (ng/ml)	115±18	144.9±37.4	**<0.0001**
MMF in treatment (%)	98.2	93.8	0.2760
Average dose of MMF/day (mg)	1031±476	1050±535	0.8637
ACEi/sartan in treatment (%)	41.1	0	**<0.0001**
Ca blocker in treatment (%)	32.1	0	**0.0004**
Beta blocker in treatment (%)	85.7	9.4	0.1251
Diuretic in treatment (%)	16.1	0	**0.0172**
Other antihypertensive drug in treatment (%)	7.1	0	0.1251
Creatinine (µmol/l)	102.5±39.4	80.6±18.5	**0.0040**
Proteinuria (g/day)	0.88±0.4	0.14±0.09	**<0.0001**
eGFR CKD-EPI (ml/min)	70.2±23.9	85.8±18.5	**<0.0001**
Fasting blood glucose (mmol/l)	6.7±2.4	6.1±2.5	0.2696
Cholesterol (mmol/l)	5.1±1.1	4.9±1	0.3991
Triacylglycerols (mmol/l)	1.8±0.9	1.3±0.9	**0.0141**
Left ventricular hypertrophy (%)	7.1	0	0.1251
LV ejection fraction (%)	61.9±6.3	60.7±13.9	0.5800
Diastolic dysfunction	41.1	43.8	0.8062
Hypertonic changes in the fundus oculi (%)	51.8	28.1	**0.0318**
24-hour monitoring of blood pressure			
Duration of Holter measurements (hours)	23±5.3	23.4±0.8	0.6732
Average number of measurements	43.3±21	52.9±19.8	**0.0382**
Mean sBP (mmHg)	136.3±20.4	126.6±12.5	**0.0168**
Mean dBP (mmHg)	81.4±14	77.7±9.1	0.1837
Mean sBP during the day (mmHg)	137.3±20.8	128.7±12.4	**0.0361**
Mean dBP during the day (mmHg)	83±15.7	79.8±9.8	0.3006
Mean sBP during the night (mmHg)	133.4±22.6	119.8±13.9	**0.0028**
Mean dBP during the night (mmHg)	75.7±12.8	71.1±9.1	0.0771
Maximum sBP (mmHg)	175.8±32.1	166.4±20.1	0.1385
Maximum dBP (mmHg)	115.7±26.7	111.4±21.1	0.4366
Minimum sBP (mmHg)	101.7±19.6	96.9±15.9	0.2412
Minimum dBP (mmHg)	54.9±13.4	52.2±13.4	0.3658
Mean HR/min	70.5±7.6	75.8±8	**0.0027**
Maximum HR/min	102.4±25.5	106.4±16.5	0.4281
Minimum HR/min	55.9±7.2	57.1±7.1	0.4518
Medication use adjustment (%)	7.1	0	0.1251
Added antihypertensive drugs (%)	58.9	28	**0.0055**

AH – arterial hypertension; BMI – body mass index; TAC – tacrolimus; CyA – cyclosporin A; MMF – mycophenolate mofetil; ACEi – angiotensin-converting enzyme inhibitors; Ca – blocker – calcium channel blocker; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; LV – left ventricle; sTK – systolic blood pressure; dTK – diastolic blood pressure; HR – heart rate

of patients with arterial hypertension was hypertonic changes in the ocular fundus (Tab. 4).

Based on 24-hour BP measurement, in the previously untreated group without arterial hypertension, we detected hitherto "unrecognized" hypertension in 28% of patients, in whom we subsequently started antihypertensive therapy. We also focused on identifying risk factors in this cohort of patients. Similar to the first case, we subjected the data to univariate analysis with the end point of starting arterial hypertension treatment. Significant variables were evaluated in multivariate analysis (Tabs 5 and 6). We found that an independent risk factor for "unrecognized" arterial hypertension after LT was male sex, waist circumference and hypertonic changes in the fundus oculi.

Tab. 3. Univariate analysis – log regression, end point modified antihypertensive treatment (patients with a history of arterial hypertension).

	Odds ratio	95% CI	p
Average age at the time of measurement (years)	1.0043	0.9491–1.0627	0.8823
Gender – men	1.5385	0.5136–4.6082	0.4413
Time since transplantation (months) at the time of measurement	1.0001	0.9995–1.0007	0.8308
Waist circumference (cm)	1.0767	1.0138–1.1435	**0.0074**
BMI (kg/m^2)	1.2301	1.0556–1.4335	**0.0033**
Corticosteroids in treatment	1.2414	0.2755–5.5945	0.7766
Dose of corticosteroids/day (mg)	0.9766	0.8439–1.1301	0.7521
Tacrolimus in treatment	2.7500	0.4200–8.0066	0.2853
Mean TAC level (ng/ml)	0.9930	0.7496–1.3154	0.9611
Cyclosporin A in treatment	0.3636	0.0555–2.3810	0.2853
Mean CyA level (ng/ml)	1.0433	0.9274–1.1736	0.4579
MMF in treatment	1.7138	0.8752–8.2454	0.1581
Average dose of MMF/day (mg)	1.0002	0.9990–1.0014	0.7045
ACEi/sartan in treatment	0.8889	0.2967–2.6635	0.8335
Ca blocker in treatment	0.9565	0.3007–3.0432	0.9400
Beta blocker in treatment	1.0000	0.2131–4.6930	1.0000
Diuretic in treatment	2.3750	0.4444–12.6924	0.2859
Other antihypertensive drug in treatment	2.1866	0.8909–9.7842	0.9982
Creatinine (μmol/l)	1.0035	0.9882–1.0191	0.6409
Proteinuria (g/day)	2.5305	0.0975–4.3651	0.1812
eGFR CKD-EPI (ml/min)	1.1681	0.2959–4.6108	0.8243
Fasting blood glucose (mmol/l)	2.0518	1.0998–3.8278	**0.0021**
Cholesterol (mmol/l)	0.6312	0.3763–1.0588	0.0699
Triacylglycerols (mmol/l)	1.3369	0.6832–2.6162	0.3837
Left ventricular hypertrophy	1.7143	0.1643–7.8872	0.6408
LV ejection fraction (%)	0.9155	0.8205–1.0216	0.0971
Diastolic dysfunction	1.0714	0.2394–4.7946	0.9282
Hypertonic changes in the fundus oculi	5.2708	1.4664–18.9449	**0.0083**

BMI – body mass index; TAC – tacrolimus; CyA – cyclosporin A; MMF – mycophenolate mofetil; ACEi – angiotensin-converting enzyme inhibitors; Ca – blocker – calcium channel blocker; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; LV – left ventricle; sTK – systolic blood pressure; dTK – diastolic blood pressure; HR – heart rate

Tab. 4. Multivariate analysis – log regression, end point modified antihypertensive treatment (patients with a history of arterial hypertension).

	Odds ratio	95% CI	p
Waist circumference (cm)	0.9974	0.9067–1.0972	0.9577
BMI (kg/m2)	1.1800	0.9224–1.5095	0.1878
Fasting blood glucose (mmol/l)	1.4807	0.7387–2.9679	0.2686
Hypertonic changes in the fundus oculi	5.1265	1.1941–22.0087	**0.0279**

BMI – body mass index

Discussion

Hypertension is an important cardiovascular risk factor that influences patient survival after organ (not only liver) transplantation. In our patient group, we looked at objective 24-hour BP measurement in post-LT patients with and without a history of arterial hypertension. Patients after LT are regularly monitored in transplant centers or, according to the customs of individual workplaces, they are also checked in regional hepatology clinics. Despite the fact that this is a group of patients under regular medical supervision, more than half of the patients with known arterial hypertension required the addition of an antihypertensive drug to their chronic medication and another almost 8% increased the dose of the drug already used in the treatment of arterial hypertension.

The authors Hryniewiecka et al identified, using automated blood pressure monitoring, up to 87.5% of patients one month after LT with insufficiently controlled arterial hypertension. When using clinical blood pressure monitoring it was 78.12% in the same group (p=NS). Compared to our analysis, significantly fewer patients were included in the follow-up (n=33), but the authors – similarly to our results – pointed to a high prevalence of arterial hypertension after LT and a relatively high percentage of patients with insufficiently controlled BP despite regular follow-up in the transplant center (26). Another analysis performed in a set of 270 patients after LT (average follow-up 43 months after LT) also confirmed a high prevalence of arterial hypertension after LT (53%), while before LT A arterial hypertension was present in only 15% of the monitored patients ($P < 0.001$). The authors also identified so-called transient hypertension in the first month after LT, present in approximately 15% of patients (27).

BP values obtained through automated blood pressure monitoring correlate with organ damage in patients with arterial hypertension more closely than BP values measured in a standard medical facility. They are more sensitive in predicting CV prognosis (coronary events, NCMP). Dominant BP values at night are considered a stronger predictor. The incidence of CV events is higher in patients with lower or no

nocturnal drop in BP compared to patients with a more significant drop. However, extreme dippers already have a higher risk of NCMP. The indication of repeated automated blood pressure monitoring examination is not explicitly established, it acquires practical importance especially for monitoring the effect after potentiation of antihypertensive medication. At the same time, automated blood pressure monitoring is the only generally available method that allows evaluating changes in blood pressure even during sleep (28, 29).

In the studies examining automated blood pressure monitoring data from 10 cohorts over three continents, the authors found that the prevalence of masked hypertension defined using the daytime, 24-h, and/or nighttime periods on automated blood pressure monitoring ranged from 8.8% in Belgium (in the Belgian Population Study) to 30.5% in China (the JingNing Population Study) among individuals with non-elevated clinic BP (30).

In our group, after the initial automated blood pressure monitoring evaluation, we recorded insufficiently controlled hypertension in 35 patients with already existing arterial hypertension (62.5%), in the cohort of patients with hitherto unknown hypertension, we diagnosed arterial hypertension de novo in 9 (28%) patients.

By repeated automated blood pressure monitoring examination, after adequate adjustment of antihypertensive treatment, we confirmed a beneficial effect on the blood pressure values of specific patients – this clearly results in a positive influence on their prognosis, as each reduction of systolic blood pressure by 10 mmHg and diastolic blood pressure by 5 mmHg reduces mortality in the long term for sudden strokes by 40% and for coronary events by 30% (31).

Up to now, standard care for the treatment of arterial hypertension after LT arterial hypertension after liver transplantation has not been established. Because of its pathogenesis, a vasodilator agent may represent the first-choice drug. Calcium channel blocking agents are the preferred class of antihypertensive drugs because of their efficacy at smooth muscle vasodilations (1, 32). In our group, up to 85.7% of patients were treated with a beta-blocker, 41% with ACEi and 32% of patients were taking a calcium blocker. Before LT, patients use BB – carvedilol in connection with portal hypertension and prevention of bleeding from esophageal varices, due to this fact it is probably the drug of continued first choice in the treatment of arterial hypertension after liver transplantation (33, 34).

Tab. 5. Univariate analysis – logistic regression, endpoint adjusted for antihypertensive treatment (patients without a history of arterial hypertension).

	Odds ratio	95% CI	p
Average age at the time of measurement (years)	1.0322	0.9650–1.1040	0.3439
Gender – men	4.5714	0.8814–7.2111	**0.0078**
Time since transplantation (months) at the time of measurement	0.9993	0.9983–1.0003	0.1584
Waist circumference (cm)	1.2093	1.0171–1.4378	**0.0079**
BMI (kg/m^2)	0.9962	0.8342–1.1896	0.9661
Corticosteroids in treatment	2.8800	0.5551–4.9414	0.2096
Dose of corticosteroids/day (mg)	1.1432	0.9236–1.4150	0.2191
Tacrolimus in treatment	0.3333	0.0393–2.8290	0.3201
Mean TAC level (ng/ml)	1.6589	1.0342–2.6610	**0.0166**
Cyclosporin A in treatment	3.0000	0.3535–5.4610	0.3201
Mean CyA level (ng/ml)	0.1505	0.0649–2.8385	0.9977
MMF in treatment	0.3636	0.0203–6.5271	0.4991
Average dose of MMF/day (mg)	1.0002	0.9987–1.0017	0.7842
Creatinine (μmol/l)	1.0483	0.9993–1.0997	**0.0375**
Proteinuria (g/day)	0.6767	0.4795–1.4808	0.9662
eGFR CKD-EPI (ml/min)	0.1915	0.0133–2.7541	0.2030
Fasting blood glucose (mmol/l)	1.1007	0.8269–1.4649	0.5176
Cholesterol (mmol/l)	1.4856	0.6400–3.4485	0.3490
Triacylglycerols (mmol/l)	1.5517	0.6845–3.5175	0.2765
Left ventricular hypertrophy	1.7343	0.4316–7.7882	0.8640
LV ejection fraction (%)	1.0328	0.9698–1.1000	0.3014
Diastolic dysfunction	1.0370	0.1725–6.2329	0.9683
Hypertonic changes in the fundus oculi	2.6000	0.4620–4.6307	**0.0393**

BMI – body mass index; TAC – tacrolimus; CyA – cyclosporin A; MMF – mycophenolate mofetil; ACEi – angiotensin-converting enzyme inhibitors; Ca-blocker – calcium channel blocker; QPU– quantitative proteinuria; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; LV – left ventricle

Tab. 6. Multivariate analysis – logistic regression, end point modified antihypertensive treatment (patients without a history of arterial hypertension).

	Odds ratio	95% CI	p
Gender – men	3.1840	1.4089–6.2433	**0.0311**
Waist circumference (cm)	1.3347	1.0570–1.6854	**0.0153**
Mean TAC level (ng/ml)	1.6471	0.8817–3.0770	0.1176
Creatinine (μmol/l)	1.0471	0.9706–1.1296	0.2340
Hypertonic changes in the fundus oculi	4.3490	1.2459–6.9191	**0.0418**

In our analysis, we found that patients in the group with a history of arterial hypertension had a significantly higher BMI and waist circumference compared to patients without arterial hypertension, which we cannot consider a surprising finding. However, waist circumference and male gender were identified as independent risk factors for "undiagnosed" arterial hypertension – that is, for arterial hypertension that was only confirmed by automated blood pressure monitoring with the need to start antihypertensive treatment. In a recently published analysis of 370 patients after LT, BMI was inversely associated with 15 years patient survival (HR 1.08, 95% CI 1.03–1.14, p=0.001 per kg/m2), independent of age, gender, muscle mass, transplant characteristics, cardiovascular risk factors, kidney- and liver function (35). Weight control after LT is therefore crucial in influencing long-term graft and patient survival.

One of the most important results from our analysis was the identification of hypertonic changes in the fundus as a risk factor (surrogate marker) for insufficiently controlled arterial hypertension, not only in the group of patients with known arterial hypertension, but also in the group of patients who were not diagnosed with arterial hypertension and during clinical blood pressure monitoring arterial hypertension was not recorded during regular check-ups at the transplant center. Automated blood pressure monitoring as a method for diagnosing arterial hypertension in patients after LT appears to be the method of choice, especially in the pediatric patient population, where automated blood pressure monitoring confirmed hypertension in one out of three office hypertensive patients (36). In the population of adult patients it is the opposite, automated blood pressure monitoring might be needed to detect masked hypertension. However, it is not always possible to carry out this examination (for example, at the regional level). A simple and accessible fundus examination could therefore replace automated blood pressure monitoring, at least as part of screening, and could be standardly introduced into protocol examinations in patients after LT.

Conclusion

In the study interval of 45.2 months, we diagnosed de novo arterial hypertension after liver transplantation using automated blood pressure monitoring in 28% of patients.

Automated blood pressure monitoring revealed suboptimally controlled hypertension in 66% of patients, for whom in 7.1% it was enough to adjust the doses of the originally taken drug, and 58.9% of patients required the addition of another antihypertensive drug.

Male sex, together with age and waist circumference should increase the index of suspicion and lead to zoom-in on a possibility of poorly controlled blood pressure. Where automated blood pressure monitoring is unavailable, regular examination of the fundus could serve as a widely available surrogate marker of suboptimally controlled arterial hypertension.

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Received January 1, 2024.
Accepted March 14, 2024.