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The proportion of coronary heart disease in development of chronic heart failure by retrospective analysis of three-year registry of hospitalization cases in tertiary healthcare institutions of Kyrgyz Republic

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Abstract

In this retrospective study, we analyzed epidemiological aspects and etiological structure of heart failure in tertiary cardiac hospitals of republic, namely National Center of Cardiology and SRI of Heart Surgery and Organs Transplantation in three-year follow-up from 2016 to 2018. Among all underlying disorders, the proportion of coronary heart disease predominated in heart failure conditions: 31.8% and 84.3% in I-II class and III-IV class groups classified according to New-York Heart Association, respectively.

Key words: heart failure, chronic heart failure, coronary artery disease, arterial hypertension, underlying disease, prevalence, functional class, morbidity, hospitalization case, retrospective study

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Introduction

Heart failure may result as a consequence of vast majority of cardiovascular conditions: any myocardial damages, rhythm disturbances and conduction defects, valvular heart disorders, pericardial diseases and etc. Almost all cardiovascular diseases or systemic conditions with cardiac involvement lead to heart failure (1, 2).

The definition of chronic heart failure (CHF) as proposed by heart failure guidelines of 2010 states that: ``Heart failure is a syndrome developed by malfunction of intracardiac filling and/or contractile mechanisms due to imbalance between vasoconstrictors and vasodilators, accompanied by inadequate perfusion of tissues and clinically manifested by typical symptoms: breathlessness, fatigue, palpitations and fluid retentions (edematous syndrome)`` (1).

Heart failure is characterized by high morbidity and mortality, reduced quality of life and substantial financial burden (3). The newly diagnosed events of heart failure constitutes more than half a million per year and it is estimated that 772000 newly diagnosed events will be supplemented by 2040 (3). In addition to clinically manifested heart failure, approximately 74 millions of people stay with risk factors, or diagnosed by stage A of heart failure (3). According to prevalence of cardiovascular diseases, heart failure occupies third place in United States. It's estimated that, in US five millions of people are suffering from heart failure and by 2040 prevalence of syndrome reaches to ten million (4).

According to 2016 European guidelines for management of acute and chronic heart failure, coronary heart disease (CHD) prevailed as etiologic factor of CHF, which is evidenced by investigations of developed North American countries (8, 9).

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As stated by researchers, underlying diseases of CHF varied by geographic regions. Most of the patients presented with both cardiovascular diseases and non-cardiac comorbidities (9). Hypertension and CHD remain as chief factors of heart failure development and progression in whole population. These two factors possess additive/synergic effect by enhancing the left ventricular remodeling and heart failure progression. The relative burden of heart failure due to these factors may depend on age, gender and race. Generally, considering the heart failure as the complication of only one of the two aforementioned diseases is inappropriate. Nevertheless, prevention of hypertension and ischemic heart disease plays a great role in heart failure prophylaxis in XXI century. Evidence states that, CHD (epicardial or microvascular; clinically manifested or subclinical) may lead to decreasing of myocardial perfusion (both acute and chronic) and subsequent myocardial damage and gradual deterioration of myocardial function (3).

Heart failure guideline of German primary medical care necessitates the importance of education and disease acceptance by patients for optimal compliance. Thus, educational programs concerning disease management and potential involvement of family in patient care play major role (5). Most of the patients with CHD do not fit to secondary prophylactic standards of guidelines due to cigarette smoking, unhealthy diet, and lack of physical activity, high body weight, obesity and high prevalence of diabetes. Risk factor control remains inadequate despite the high medicines consumption, which is significantly differed by centers in secondary prevention practice. Only less than half of patients with CHD enrolled in preventive and rehabilitation programs. All patients with coronary and vascular diseases necessitate contemporary programs of prophylactic cardiology properly adapted to medical and cultural conditions of each country in order to achieve better lifestyle, improvement of risk factor control and rationalizing the cardioprotective medications (6). Inadequate knowledge of patients about their disease is one of the challenges in implication of guidelines and preventive tasks.

In US, prevalence of heart failure varied by ethnicity, socioeconomic class and geography. The lower the socioeconomic status the higher rates of heart failure observed in case the cardiovascular risk factors controlled (7). About 80% of global cardiovascular diseases accounts to middle-income and low-income subjects (7).

We aimed to retrospectively analyze all hospital cases of chronic heart failure over three years in tertiary hospitals of Kyrgyz Republic and establish proportion of coronary heart disease and its characteristics.

Methods

We retrospectively studied and analyzed 38082 medical histories of adult patients regardless of age and sex hospitalized between 2016 and 2018 in cardiac departments of tertiary healthcare institutions of Bishkek: National center of cardiology and internal medicine (NCCIM), Scientific-research institute of heart surgery and organs transplantation, respectively (SRIHSOT).

For classification of heart failure in adults, we used CHF Classification system of New York Heart Association proposed in 1964 (10):

Statistical analysis: We used descriptive statistics to represent data.

	New York Heart Association classification (10)
Functional class (FC)	**Limitations of physical activity and clinical manifestations**
I	No limitations of physical activity. Ordinary physical exertion does not cause to weakness, dyspnea and palpitations.
II	Slight limitation of physical activity. At rest any pathological symptoms are absent. Ordinary physical activity is accompanied by weakness, fatigue, palpitations, breathlessness and other symptoms.
III	Marked limitation of physical activity. Only resting state supplies comfort for patient, but the slightest physical exertions lead to fatigue, palpitations, dyspnea and other symptoms.
IV	Impossibility to perform any physical activity without feeling of discomfort. Heart failure symptoms present at rest and pronounced by any physical exertion.

Results and Discussion

We retrospectively analyzed all hospital cases of CHF over three years in tertiary hospitals of Kyrgyz Republic and found that proportion of CHD prevailed as main underlying disease of heart failure by 71.89%.

A total number of hospitalized patients with CHF of various functional classes for 2016-2018 constituted 38082 patients (Table 1).

According to analysis, the main etiological factor of CHF I-II FC (Table 2) was CHD, predominantly in female patients. Far inferiorly to ischemic etiology, second and third places were occupied by arterial hypertension (AH) and diabetes mellitus (DM), respectively. At the same time proportion of

Table 1. Total number of hospitalized patients with CHF for 2016-2018

	2016	2017	2018	Total
NCCIM	11458	11539	11480	34477
SRIHSOT	1211	1196	1198	3605
Total:	12669	12735	12678	38082
CHF – chronic heart failure				

valvular pathology constituted only 0.85% with intra-group predominance of rheumatic origin (78% of cases). The interesting point from the analysis we concluded the rarity of other etiological conditions as, rhythm and conduction abnormalities, myocardial diseases, anemia, acute cerebrovascular syndromes, complications due to oncology and other diseases.

Table 2. The main underlying diseases of chronic heart failure in adult patients with I-II NYHA FC

Etiological conditions of chronic heart failure	All		Males	Females
	Absolute number	%	Absolute number	Absolute number
CHD	6482	31.85	2743	3739
AH	908	4.46	439	469
Adult congenital heart diseases	57	0.25	28	29
Cardiac valvular pathology of various etiology[1]	174	0.85	33	141
Cardiomyopathies of various etiology[2]	118	0.57	66	52
DM	791	3.88	422	369
Other disease	11817	58		
Total	20347			
*NCCIM data was used [1] congenital etiology was excluded, [2]ischemic factor was excluded AH – arterial hypertension, CHD – coronary heart disease, DM – diabetes mellitus, FC – functional class				

The main etiological disorders of CHF in adults with III-IV classes are highlighted in Table 3. As in groups of patients with I-II classes of CHF, but with markedly exceeding in percentage, in 84.34% of cases, causative condition was CHD. Valvular heart diseases (4.79%) gained the second place. When we looked into this group, rheumatic origin constituted approximately 60% and proportion of ischemic, degenerative origins became increased. Significant role is issued to adult congenital heart defects (ACHD) of both operated and non-operated categories and cardiomyopathies of various etiologies.

Table 4. The number of hospitalizations of CHD patients

	2016	2017	2018
All hospitalizations	12669	12735	12678
Number of hospitalizations due to CHD: **Number** **Percentage**	6492 52%	6813 54%	6865 55%
CHD – coronary heart disease			

The hospitalizations due to CHD make more than half of all hospital cases in cardiac hospitals of country. Nevertheless, ischemic causes tend to decrease, constant progression exists.

The main proportion of hospitalized (considering only tertiary-level hospitals) patients are residents of Bishkek city and Chuy oblast (oblast-administrative unit of Kyrgyz Republic, analogue of the region), where the percentage of emergent hospitalizations constitutes 32% in contrast to whole country, where it shows 12% (including the hospitalized patients of Chuy oblast) (Table 5).

Table 5. Distribution of hospitalized patients with coronary heart disease according to oblasts of country

Oblast	2016	2017	2018	All	
				Number	%
Bishkek	2038	2117	2082	6237	33.00
Chuy	1745	1884	1812	5441	28.83
Osh	261	304	307	872	4.62
Djalal-Abad	419	434	445	1298	6.87
Issyk-Kul	691	697	722	2110	11.18
Naryn	452	467	467	1386	7.34
Talas	274	276	304	854	4.52
Batken	212	234	226	672	3.56
*NCCIM data was used					

Table 6 highlights distribution of NYHA functional class groups of patients according to age. The significant difference between age groups was not detected in I-II FC and III-IV FC. Nevertheless, pathology in age group of 51-70 years prevailed in both CHF groups with 24.4% and 38.1%, respectively.

Table 6. The age distribution of hospitalized CHD patients according to CHF FC groups

Age (years)/ NYHA FC of CHF	I – II			Total		III – IV			Total	
	2016	2017	2018	N	%	2016	2017	2018	N	%
18 – 40	56	77	60	127	0.66	44	32	37	37	0.59
41 – 50	277	307	258	842	4.43	264	300	266	266	4.37
51 – 60	823	824	782	2429	12.80	1198	1153	1083	1083	18.10
61 – 70	681	740	782	2203	11.61	1369	1457	1523	1523	22.92
71 – 80	206	259	250	715	3.76	923	982	988	988	15.25
81 – 90	34	38	35	107	0.56	214	229	287	287	3.84
Elder than 90	-	3	21	24	0.12	3	11	12	12	0.13
Footnote: NCCIM data was used CHD – coronary heart disease, CHF – chronic heart failure, FC – functional class										

The distribution of CHD patients according to sex (Table 7) was obtained as follows: in I-II FC, female gender was predominated by 19.83%, whereas in III-IV FC male gender reliably prevailed.

Table 7. The gender distribution of hospitalized CHD patients according to NYHA FC groups

CHF FC	2016		2017		2018		Absolute number		%	
	male	female	male	female	male	female	male	female	male	female
I – II	890	1187	986	1263	878	1291	2754	3741	14.60	19.83
III – IV	2319	1696	2374	1790	2421	1775	7114	5251	37.71	27.84
CHD – coronary heart disease, FC – functional class										

According to Russian database, AH and CHD as underlying conditions of CHF development prevailed among etiological factors by 95.5% and 69.7%, respectively (1). Combination of these etiological factors is seen in most patients (1).

In Kyrgyz population, the leading cause of heart failure is CHD and its combination with AH makes up 71.89%, moreover percentage of combination has direct proportionality with functional class of CHF. Coronary heart disease stays as the global burden of our regions with 52-54% of all hospitalized conditions. According to age and sex predilections, middle age individuals and male sex is predominated: 37.715% in contrast to 27.84% of females. Due to geographic patterns (mountain area) of our republic, availability of qualified medical care for populations of remote regions severely limited and it's explained by scarcity of emergency admissions from oblasts (only 12%), and the most of them from nearby regions (Chuy and Issyk-Kul oblasts). In addition, the residents of regions represent lower percentage of planned admissions, probably associated with non-appeal for medical care. Ischemic heart disease brings severe economic damage to country by affecting the most able-bodied population and increasing of invalidation due to heart failure.

Conclusion

In studied population, the leading cause of heart failure is CHD, more often detected in middle ages and male patients. It is most often combined with arterial hypertension. Hospitalizations are mostly from urban areas and nearby regions.

Conflict of interest: None to declare

Authorship: T.Z.K., I.A.A., A.S.D., K.Sh.J., D.A.A. equally contributed to study and preparation of manuscript

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References

1. Mareev VYu, Fomin IB, Ageev FT, Begrambekova Yu, Vasuk YuA, Garganeeva AA, et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. Kardiologiia 2018; 58: 8-158.
2. Mareev VY, Ageev FT, Arutyunov GP, Korolev AV, Revishvili ASh. National recommendations of ARSSC and HFS for the diagnostics and treatment of CHF (third revision) (Approved by the HFS Conference December 15, 2009). Journal Serdechnaya Nedostatochnost 2010; 11; 3-62.
3. Velagaleti R, Ramachandran V. Heart failure in the twenty-first century: is it a coronary artery disease or hypertension problem? Cardiol Clin 2007; 25: 487-95;
4. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115: e69-171.
5. Morbach C, Wagner M, Gunter S, Malsch C, Oezkur M, Wood d, et al. Heart failure in patients with coronary heart disease: Prevalence, characteristics and guideline implementation - Results from the German EuroAspire IV cohort. BMC Cardiovasc Disord 2017; 17: 108.
6. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016; 23: 636-48.
7. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016; 13: 368-78.
8. Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. Int J Cardiol 2001; 80: 213-9.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 Guidelines for diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
10. Criteria Committee. New York Heart Association Inc. Diseases of the Heart and Great Vessels. Nomenclature and criteria for diagnosis, 6th edition. Boston, Massachusetts: Little Brown & Co; 1964. p.114.

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The structure of cardiac surgery and interventions in heart failure management in the Kyrgyz Republic: A retrospective analysis

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Abstract

In this study, we retrospectively analyzed the cardiac surgical and interventional care of patients with chronic heart failure hospitalized in Scientific-Research Institute of Heart Surgery and Organs Transplantation (SRIHSOT) and Osh Interregional United Clinical Hospital (OIUCH).

Key words: heart failure, cardiac surgical care, intervention, extent of operation, follow-up

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Introduction

As known, heart failure (HF) is characterized by high morbidity, mortality, and exertion of substantial economic and social burden (1, 2).

Heart failure is defined by the European Society of Cardiology (ESC) as a clinical syndrome characterized by symptoms such as shortness of breath, persistent coughing or wheezing, ankle swelling and fatigue that may be accompanied by the following signs: jugular venous pressure, pulmonary crackles, increased heart rate and peripheral edema (3). 2016 Guidelines classified HF into HF with reduced, mid-range and preserved ejection fraction based on contractile function of left ventricle (3).

Practically, any cardiovascular disease or any non-cardiac conditions with heart involvement can be complicated by heart failure development. Hence, etiological causes of heart failure are versatile: coronary heart disease, arterial hypertension, myocardial damage, cardiomyopathies, valvular heart diseases, congenital heart disease, cardiac damage in diabetes, autoimmune disorders, adverse effects of cancer treatment etc. (4, 5).

Although heart failure is observed at any age and regardless of gender, race and ethnicity of patients, some age, gender and race predispositions coexist (6,7).

According to literature review, prevalence of heart failure is steadily increasing (8).

Despite the continuous development and updating of protocols and guidelines on optimal diagnostic workup and treatment, management of heart failure remains overwhelming and challenging, especially in developing countries (3, 9).

In the management of heart failure, along with medical therapy, surgical and interventional care also plays an important role according to indications (10, 11).

In this retrospective study, we aimed to analyze the structure of surgical and interventional management of heart failure in Kyrgyz Republic in three-year follow-up, between 2016 and 2018.

Methods

A total of 6825 patients hospitalized in Scientific-Research Institute of Heart Surgery and Organs Transplantation (SRIHSOT) and Osh Interregional United Clinical Hospital (OIUCH) healthcare institutions were enrolled into our study

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in periods of 2016-2018 follow-up. Age range varied from 12 days to 87 years. Mean age 64.36 years. Male gender slightly predominated by 52.7%. All operated patients presented clinically with II-III functional class heart failure according to New-York Heart Association (NYHA).

Data regarding surgery/intervention for underlying condition of heart failure were supplied by both hospitals.

Statistical analysis: We used descriptive statistics to represent data.

Results

Total number of operations and interventions, treatment modalities, proportion of procedures in whole hospital cases is highlighted in tables and diagrams. Table 1 shows total number of hospitalization in two clinics for three-year period.

Table 1. Number of hospitalized cases

Hospitals/years	2016	2017	2018	All
OIUCH	782	768	745	2295
SRIHSOT	1203	1580	1747	4430
All	1985	2348	2492	6825
OIUCH - Osh Interregional United Clinical Hospital, SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation				

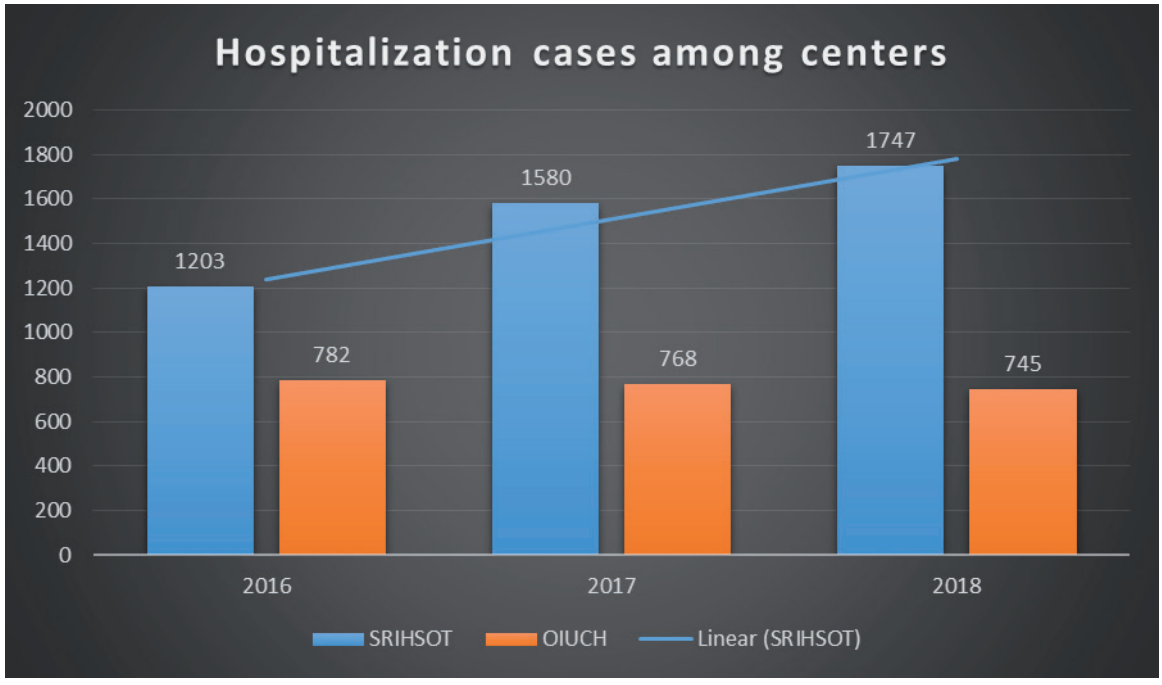

Figure 1. Hospitalization cases among centers

OIUCH - Osh Interregional United Clinical Hospital, SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation

As seen from Table 1 and Figure 1 hospitalization cases steadily increased in cardiac surgery center in contrast to interregional hospital where constant state is noticed. Improvement of surgical care and organizational facility of cardiac surgery center can be considered. In addition, due to responsibility of SRIHSOT for all cardiac surgery conditions, since it is a tertiary hospital, the hospital cases increased. On the other hand, interregional hospital accepts the versatile conditions, including vast majority of non-cardiac diseases, so limited bed number for admission of patients.

Table 2 and Figure 2 inform about extent of surgical and interventional procedures of cases.

Table 2. Amount of surgical and interventional procedures

	2016		2017		2018		All
	Surgery	Intervention	Surgery	Intervention	Surgery	Intervention	
OIUCH	0	92	0	113	0	160	365
SRIHSOT	815	365	1167	368	1250	414	4513
All	**815**	**457**	**1167**	**481**	**1250**	**574**	**4878**
OIUCH - Osh Interregional United Clinical Hospital, SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation							

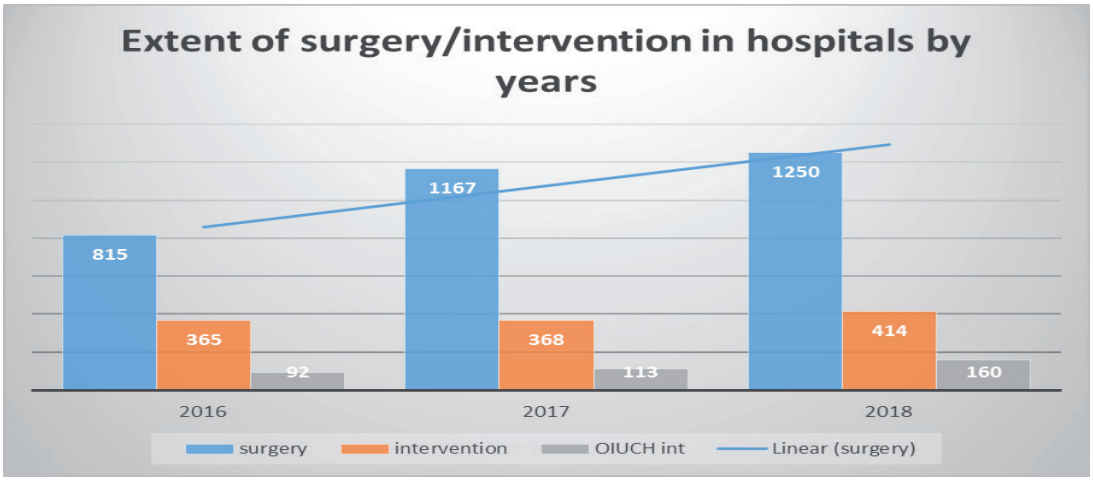

Figure 2. Extent of surgery/intervention in hospitals by year

OIUCH - Osh Interregional United Clinical Hospital, SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation

As seen from Table 2 and Figure 2 surgery cases proportionally to hospitalization increased by time, whereas intervention remained almost in plateau. Osh Interregional hospital represents a slight increase in interventions from 2016 to 2018. It may be associated with improvement in technical and personnel arrangements, optimization of financial costs, increasing of patient education in regions.

Table 3 and Table 4 depict structure of surgical and interventional care of aforementioned hospitals. Due to lack of surgical care in OIUCH, patient data presented separately and accompanied by diagrams for comparison.

Table 3. Hospitalization case structure of SRIHSOT

#	Hospitalization cases	2016			2017			2018			All
		T	S	I	T	S	I	T	S	I	
1	Coronary heart disease[1]	417	144	273	622	324	298	660	402	258	1699
2	Valvular heart disease[2]	217	217	0	380	380	0	315	315	0	912
3	Congenital heart disease[3]	454	454	0	466	463	3	562	532	30	1482
4	Bradyarrhythmias[4]	92	0	92	67	0	67	96	0	96	255
5	Tachyarrhythmias[5]	0	0	0	0	0	0	15	0	30	30
6	ICU cases[6]	0	0	0	12	0	0	0	0	0	12
7	Other disorders[7]	23	0	0	0	0	0	99	0	0	122
8	Total surgery/intervention cases	1180	815	365	1468	1167	301	1648	1234	414	4296

9	Non-surgery and non-intervention cases	23	0	0	12	0	0	99	0	0	134
10	Total	1203	815	365	1480	1167	301	1747	1234	414	4430

I-interventions, ICU – intensive care unit, S-surgeries, T- total patient numbers, OIUCH - Osh Interregional United Clinical Hospital, SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation
[1] Coronary heart disease included both chronic and acute coronary syndromes, surgery assumes coronary bypass surgery (CABG) and intervention by means of percutaneous coronary intervention
[2] Valvular heart diseases included only acquired valve defects, surgery stands for valve repair/replacement
[3] Various hemodynamic and anatomic correction of congenital heart disease was mentioned
[4] Pacemaker implantation was used to treat bradyarrhythmias
[5] EPS and RFA was handled in tachyarrhythmias
[6] ICU cases did not included neither surgery nor intervention. Some patients were hospitalized only for stabilization, some were lost before operation
[7] Other disorders included non-operable conditions or for investigations

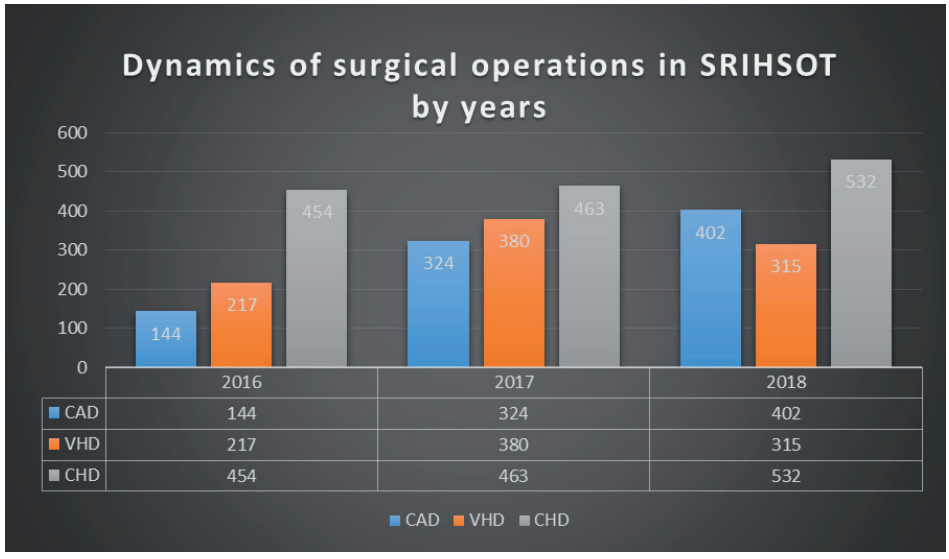

Figure 3. Dynamics of surgical operations in SRIHSOT by years

SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation

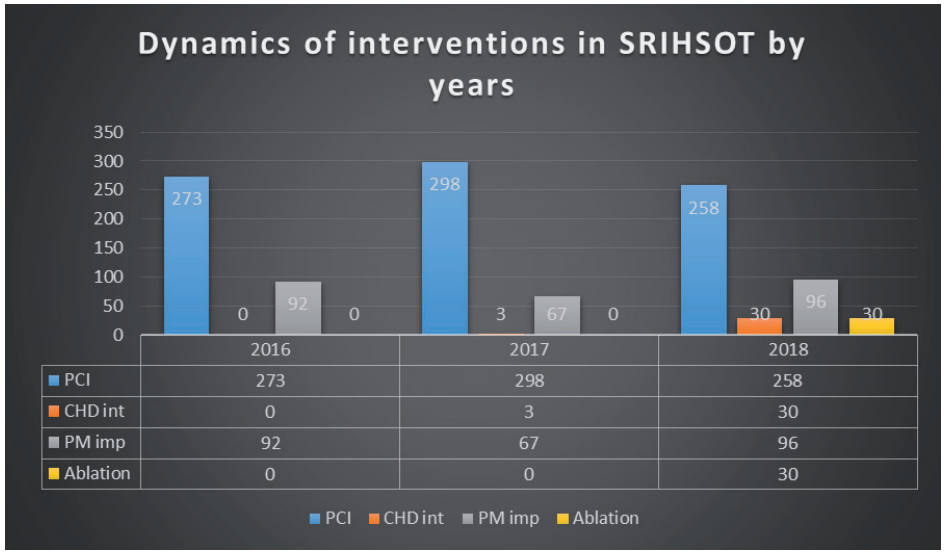

Figure 4. Dynamics of interventions in SRIHSOT by years

SRIHSOT - Scientific-Research Institute of Heart Surgery and Organs Transplantation

Table 4. Hospitalization case structure of OIUCH center

#	Hospitalization cases	2016		2017		2018		All
		T	I	T	I	T	I	
1	Coronary heart disease[1]	649	86	643	107	592	156	1884
2	Valvular heart disease[2]	29	0	33	0	28	0	90
3	Congenital heart disease[3]	7	5	8	4	8	3	23
4	Infectious myocarditis	9	0	3	0	9	0	21
5	Cardiomyopathies[4]	19	0	16	0	23	0	58
6	Essential hypertension	9	0	3	0	2	0	14
7	Other disorders[5]	8	1	9	2	7	1	24
8	All hospitalizations due to CV disorders	730		715		669		2114
9	Non-cardiac conditions with heart failure	52	0	53	0	76	0	181
10	Total	782	92	768	113	745	160	2295

T-total patient numbers, I-interventions
[1] Coronary heart disease included both chronic and acute coronary syndromes, PCI was performed in interventions
[2] Included only acquired heart defects, predominantly rheumatic etiology
[3] Included any forms of congenital heart diseases, both in pediatric and adult congenital heart disease
[4] All forms of cardiomyopathies including peripartum cardiomyopathy
[5] Other interventional cardiology procedures
OIUCH - Osh Interregional United Clinical Hospital

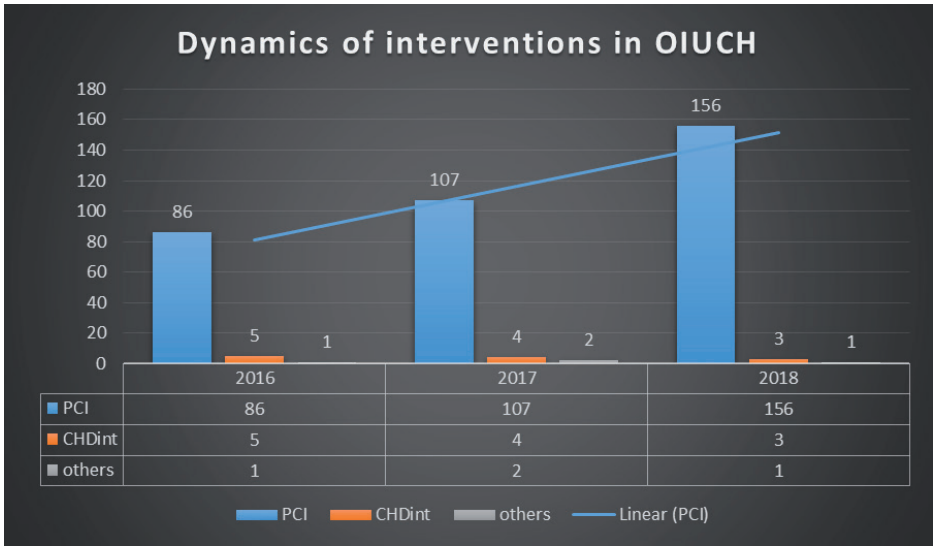

Figure 5. Dynamics of interventions in OIUCH

OIUCH - Osh Interregional United Clinical Hospital

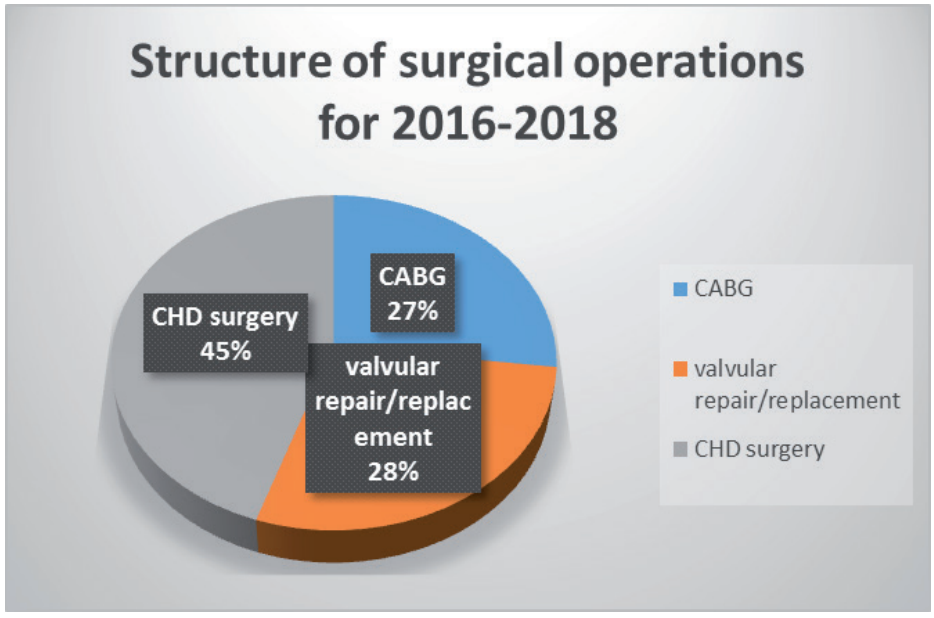

Figure 6. Structure of surgical operations for 2016-2018

CABG – coronary bypass surgery, CHD – congenital heart disease

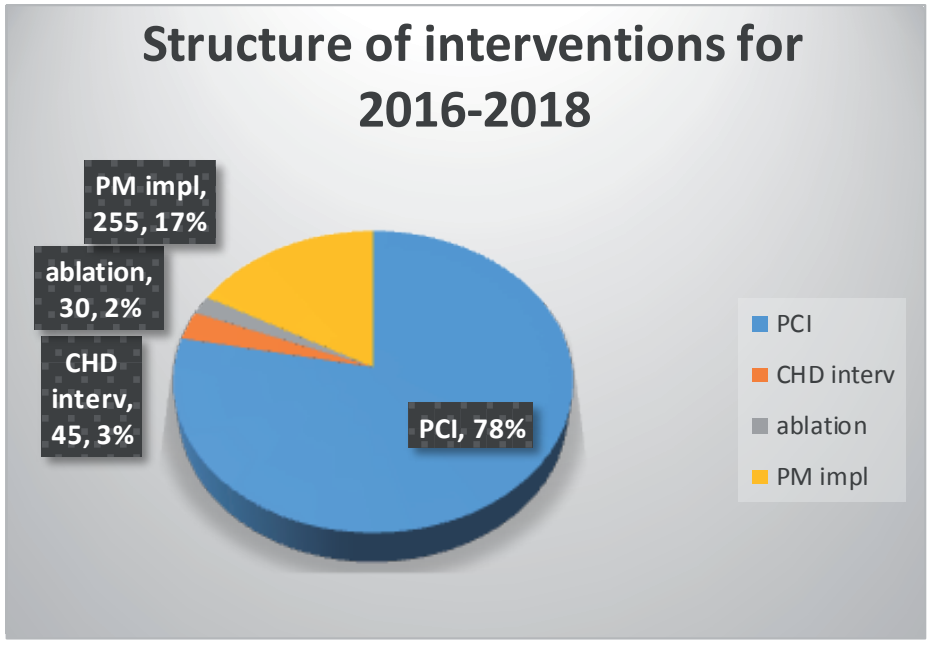

Figure 7. Structure of interventions for 2016-2018

CHD – congenital heart disease, PCI – percutaneous coronary intervention, PM - pacemaker

Cardiac surgery center presented high surgical availability, by means of procedural ratio to whole hospitalizations in 2016-2018: 98%, 99% and 100% respectively. Osh Interregional Hospital interventional rates were as follows: 11.7%, 14.7% and 21.4% by years.

As seen from tables of hospitalization cases of SRIHSOT, coronary heart disease as underlying condition of heart failure prevailed in both clinics: 1699 (38.3%) and 1884 (82%) of all cases.

The second major etiological factors of heart failure in SRIHSOT are congenital heart diseases. Roughly, 80% of hospitalized patients had NYHA II class of heart failure. As seen from tables and diagrams, congenital heart diseases surgery predominated when surgical cases were compared

(45% of all surgery cases for three years) and is represented by steady increase: 454, 463, and 532.

The third place in etiological factors of heart failure was presented by acquired valvular heart diseases. Only in SRIHSOT, these patients underwent operation. Dynamics of surgery shows some fluctuations in time periods: 217, 380 and 315, respectively.

According to OIUCH data, cardiomyopathies and myocarditis registered in 58 and 21 cases, respectively, whereas in SRIHSOT they have not been mentioned. Nevertheless, these conditions have not been subjected to surgery or intervention.

Discussion

The date of birth of cardiac surgery in Kyrgyzstan is considered May 19, 1959. On this very day, in the Department of General Surgery of the Republican Clinical Hospital of the Ministry of Health of the Kyrgyz SSR, in the city of Frunze, professor, academician Akhunbaev Isa Konoevich performed the first heart operation in Central Asia and Kyrgyzstan - digital mitral commissurotomy. From that date, cardiac surgery is directed into clinical practice and development (12).

Heart failure plays a major role in patient selection for surgical treatment in most cardiac patients (13, 14). In addition, surgery evidently decreases progression or fatal outcomes of heart failure. In the STICH-trial, the addition of coronary bypass surgery for medical therapy decreased events of sudden death and pump failure (15).

One of the main challenges for cardiac surgeons is to prevent perioperational, more precisely, postoperative heart failure development (16).

Availability and extent of procedures varied by centers, and it can be associated with healthcare status of hospitals. Cardiac surgery center presented high surgical availability, by means of procedural ratio to whole hospitalizations in 2016-2018: 98%, 99% and 100% respectively. Osh Interregional Hospital interventional rates are as follows: 11.7%, 14.7% and 21.4% by years.

If we compare surgery and intervention in SRIHSOT, rate of coronary bypass surgery was increased gradually and subsequently predominated over percutaneous coronary interventions: 144 vs. 273, 324 vs. 298 and 402 vs. 258, respectively. It can be explained by improvement of cardiac care from 2017th, since the development of state programs concerning optimal management of acute coronary syndromes and treatment of coronary heart disease, improvement of therapeutic management based on contemporary guidelines, as well as increasing in quantity of private cardiac centers with angiographic and surgical facilities. Similar condition also noticed by OIUCH center, where number of interventions increased by years: 86, 107 and 156, respectively.

SRIHSOT is the single tertiary reference center for surgical management of congenital heart diseases. Therefore, we can assume general statistics of whole republic operable congenital defects from database of this center. OIUCH data showed only 23 cases of CHD, and 12 (52%) of them underwent intervention. On the other hand, interventional management of amenable congenital defects encountered with challenges. Firstly, it can be considered due to personal issues, so it urgently necessitates increase in qualified pediatric cardiologists. We do not have enough data regarding to types of achieved congenital heart disease procedures and extent of operations/interventions. In further investigations, this point must be taken into account.

In the group of valvular heart diseases, no interventional procedures were performed neither in SRIHSOT nor in OIUCH. In addition, these cases necessitate performance of interventional cardiologists, though transcutaneous aortic valve implantation and endovascular techniques must be carried out into practice.

We realize the activation of interventional management of rhythm and conduction disturbances by 2018. It can be associated with development of arrhythmia care in Republic recent years by implementation of electrophysiological studies and radiofrequency ablations.

Conclusion

In our study, we analyzed structure of surgical and interventional procedures performed in patients with II-III NYHA classes. Availability and extent of procedures either surgery or intervention varied by centers, thus, cardiac surgery center had a big difference from interregional hospital.

Generally, procedures handled in both hospitals are steadily increasing. As in therapeutic cases, coronary heart disease predominated among all underlying disorders of heart failure. Hopefully, precise investigations concerning surgical and interventional management of heart failure, including survival analysis of these patients will be conducted in further studies.

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References

1. Van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016; 18: 242–52.
2. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev 2017; 3: 7-11.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
4. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM. et al. Heart failure etiology and response to milrinone in decompensated heart failure: Results of the OPTIME-CHF study. J Am Coll Cardiol 2003; 41: 997-1003.
5. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease etiology and risk factors to heart failure with preserved or reduced ejection fraction: insights from the National Heart, Lung and Blood Institute. Circulation 2009; 119: 3070-7.
6. O'Neal WT, Sandesara P, Hammadah M, Venkatesh S, Samman-Tahhan A, Kelli HM, et al. Gender differences in the Risk of Adverse Outcomes in Patients with Atrial Fibrillation and Heart Failure with Preserved ejection fraction. Am J Cardiol 2017; 119: 1785-90.
7. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender- and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 1994; 24: 1700-7.
8. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. Int J Cardiol 2017; 236: 283-9.
9. Malamba-Lez D, Ngoy-Nkulu D, Steels P, Tshala-Katumbay D, Mullens W. Heart failure etiologies and challenges to care in the developing world: an observational study in the Democratic Republic of Congo. J Card Fail 2018; 24: 854-9.
10. Agnetti G, Piepoli MF, Siniscalchi G, Nicolini F..New insights in the diagnosis and treatment of heart failure. Biomed Res Int 2015; 2015: 265260.
11. Roy SD, Siva ST, Alankrita T, Dushyant R, Mohamed AO, Paramdeep P. Recent trends in surgical management of heart failure in the United States. J Card Fail 2017; 23: S122.
12. Prokhorov AM. Akhunbaev Isa Konoevich. Bol'shaya Sovetskaya Encyclopedia. 30 vol. 3rd ed. Moscow. Sovetskaya Encyclopedia. 1969-1978.
13. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017; 38: 2739–91.
14. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, et al. Chronic heart failure in congenital heart disease. A Scientific Statement from the American Heart Association. Circulation 2016; 133: 770-801.
15. Carson P, Wertheimer J, Miller A, O'Connor MC, Pina IL, Selzman C, et al. STICH trial. Surgical treatment for Ischemic Heart Failure. JACC Heart Fail 2013; 1: 400-8.
16. Smilowitz RN, Berger JS. Perioperative management to reduce cardiovascular events. Circulation 2016; 133: 1125-30.

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Survival analysis of renal patients underwent transplantation in Kyrgyz Republic and various countries by 10 years follow-up

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Abstract

In our study we conducted survival analysis of 204 patients visited Scientific-Research Institute of Heart Surgery and Organs transplantation and who underwent renal transplantation in Kyrgyzstan and other Eurasian countries between 2005 and 2016 years (age range: 9-71 years, mean: 38.21 (12.74) years, median: 34.0 (0.89) years; gender: 142 male (69.6%)).

During follow-up period, mortality event was observed in 16 (7.84%) patients. Survival function probabilities of patients and rational risk factors of survival functions were evaluated by Kaplan-Meier and Cox regression analyses, respectively. According to Kaplan-Meier results survival probabilities calculated for 1st year: 0.96 (0.014), for 3rd year: 0.94 (0.018), for 5th year: 0.86 (0.04), for 7th year: 0.75 (0.10). Among age groups 28-39 age ranges prevailed by 11 patients. Nevertheless, that difference did not show statistical significance: p=0.322. The intensity of transplantation also analyzed according to years, which revealed increasing in numbers of operations by time. For instance, when in 2006 only two cases were registered in our center, but numbers of transplanted patients reached up to 48 in 2015. The association of mortality states and years of transplantation found significantly by Kaplan-Meier test (Breslow p<0.001). The survival analysis was compared according to countries and revealed significant results (Breslow p<0.05). From other factors influencing mortality, sex did not show strong impact on survival by Kaplan-Meier analysis, but significant association was found by Cox regression analysis.

Key words: renal transplantation, survival function, cumulative survival, mortality, follow-up, Kaplan-Meier analysis, Cox regression analysis, event, censored value

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Introduction

The graft transplantation has been used in kidney failure as reliable and effective treatment option since 1936 (1). Studies show the increase in survival rate by transplantation in comparison to hemodialysis (2-4). On the background of technological modernizations, surgical achievements, survival improvements the transplantation was further motivated by healthcare institutions. Intensive demands, appropriate donor challenges and other factors led to the development of high-income economic sector in transplantational management (5). This situation is expressed with the concept of transplantation tourism. The approximate cost of kidney transplantation is $18,000 in India, $32,000 in Nigeria (the most active center), $78,000 in the UK and $117,000 in the US (6). If the transplantation was achieved by several countries in 1960s, now it is performed by vast majority of centers. It is stated that this number is around 80 (7, 8). The Transplant Society and the International Society of Nephrology state, that despite the Istanbul Declaration, which was approved by more than 110 professional and governmental organizations in 2008 for the prevention of crime in transplantation and the prevention of illegal programs, is still not known to what extent the situation is controlled (9).

Nevertheless, nowadays, despite the well-developed surgical techniques, preoperational and postoperational workup, donor-recipient relationships significantly affect the survival (7, 8). From that standpoint, posttransplantational survival performance differs by countries and medical centers (2). Shortly, countries and transplantation centers demonstrates variation of survival estimations and risk ratios (2, 7, 8).

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In this study, we investigated posttransplantational survival analysis of patients who underwent renal transplantation in Kyrgyzstan and other Eurasian, predominantly neighboring countries. Besides the general analysis of survival after renal transplantation, analysis by transplantation years and differences among countries was also included in our study.

Methods

A total of 204 patients operated in various 8 countries were included to our study: 142 (69.6%) males, 62 (30.4%) females. Mean age was 38.0 (0.89) years, median 34.0 (12.7) years. Conservative treatment at 1st year after transplantation was started in corresponding country where the patient was operated. After the 1st year of procedure, treatment and follow-up was continued by our clinic. We excluded from analysis rejections and complications, mortality cases during the 1st year of follow-up. Differences of survival by operated countries, by transplantation years, by age and gender groups are investigated in this study.

Statistical analysis: Demographic properties of study population were depicted by descriptive techniques of SPSS version 22 program (IBM SPSS 22, New York, USA). Distribution and homogeneity of variations were calculated by Kolmogorov-Smirnov and Shapiro-Wilk tests, which identified nonparametric distribution ($p<0.001$). Survival estimates according to years were analyzed by Kaplan-Meier analysis. Factors such as, age, gender, transplantation years, operating countries, affecting survival parameters were investigated by log-rank test, Breslow and Tarone-Ware techniques. Differences between countries were calculated by post hoc test. Cox regression analysis was applied for rational risk factors of age, gender, country and transplantation years. Mortality probabilities under these factors were calculated by logistic regression analysis.

Results

As seen from Table 1, out of 204 patients 16 (7.8%) died, whereas other 188 are surviving and by statistical description, they belong to censored state.

Table 1. Descriptive parameters of study population

Variables	Numbers and statistical expressions	
Status	Dead -16 (7.8%)	
	Alive -188 (91.7%)	
	Valid percent – 92.2%	
Age	Range -9-71years	Std error-0.892
	Mean-38.9 years	SD-12.739
	Median-34.00	Variance-165.819
Gender	Male – 142 (69.6%)	
	Female – 62 (30.4%)	

Kaplan-Meier calculations depicted general survival as followings: for 1st year 0.961 (0.014), for 3rd: 0.94 (0.018), for 5th: 0.861 (0.042), for 7th: 0.753 (0.107) (Fig. 1).Mortality rate was 7.8%. Age and gender factors on survival functions were distinctly calculated by Kaplan-Meier analysis and both of them did not show statistical significance.

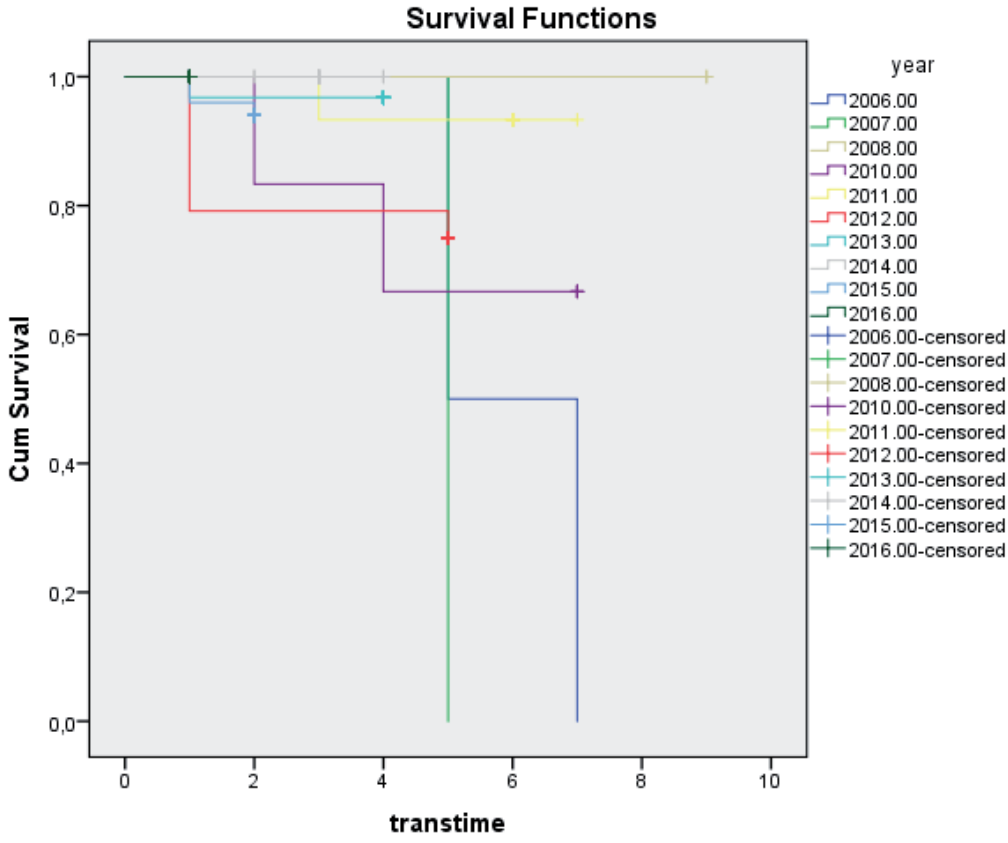

Figure 1. Survival functions

Table 2. Patient numbers undergone transplantation according to years

Years	2006	2007	2008	2010	2011	2012	2013	2014	2015	2016
Patients, %	2.1	1.05	2.1	6.29	15.7	24.11	31.15	36.17	50.24	37.18
Mortality	2	1	0	2	1	6	1	0	3	0

As seen from Table 2, beginning with 2006 the number of transplanted patients was increasing. Mortality number rationally to patient number was also increasing. Especially in 2012, mortality extremely increased in contrast to other years. Patient survival affected by transplantation year indicated statistical significance (Log-rank $p<0.001$, Breslow $p<0.05$, Tarone-Ware $p<0.05$).Hazard function analysis revealed increase of mortality risk from 5th year to 6th and 7th years in contrast to 4th year (Fig. 2).

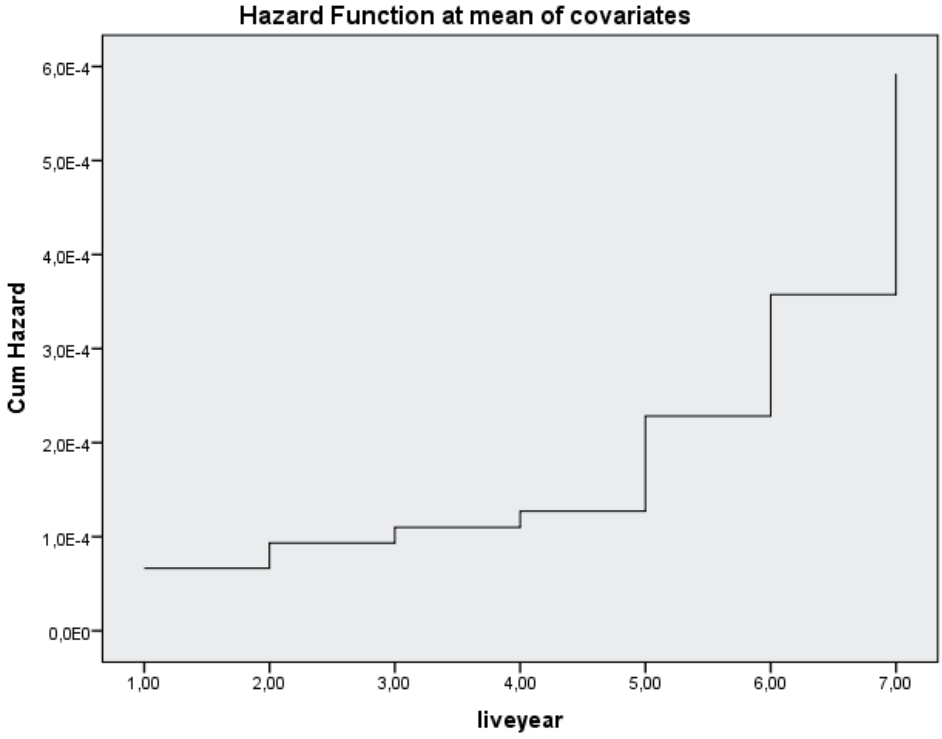

Figure 2. Hazard function analysis

Table 3. Distribution of patients by transplanted countries

	Countries	Frequency of transplantation	Percent	Mortality events	Event- free (alive)	Mortality percent
1	China	6	2.94	2	4	33
2	India	7	3.43	-	7	0
3	Kazakhstan	13	6.37	-	13	0
4	Kyrgyzstan	24	11.76	5	19	21
5	Pakistan	26	12.7	5	21	19
6	Russia	11	5.39	1	10	9
7	Tajikistan	8	3.92	1	7	12
8	Turkey	109	53.43	2	107	2

As seen from Table 3, transplanted patient numbers varied by countries. Mortality conditions of countries are analyzed by Kaplan-Meier and Breslow test revealed significant difference ($p<0.05$) whereas Log rank and Tarone-Ware tests did not give strong results. Post hoc test was used for defining of difference between countries and proved significant difference among China, Pakistan, Kyrgyzstan and Tajikistan.

Table 4. Estimates of cumulative survival according to transplanted countries

Country	Loss year	Cumulative pro Est	Std error
China	5 6 10	0.83 0.66 0.66	0.15 0.19 0.19
India	3	0.1	0.1
Kazakhstan	3	0.1	0.1
Kyrgyzstan	1 5 6	0.87 0.65 0.65	0.06 0.19 0.19
Tajikistan	1 5	0.87 0.87	0.11 0.11
Pakistan	1 2 3 5	0.96 0.88 0.84 0.78	0.03 0.06 0.07 0.87
Russia	5 7	0.85 0.85	0.13 0.13
Turkey	1 4 7	0.99 0.96 0.96	0.009 0.032 0.032

The Table 4 reflects admission of patients to different countries in different years for renal transplantation. According to that point, survival estimates of patients were presented in different countries by different time periods.

Relationships of considered independent factors of mortality were analyzed by Cox regression test.

In summary, age was found as a significant factor affecting mortality (B: 0.080; SE: 0.040; Exp B: 0.923; CI 0.853-100, $p<0.05$) Thus, age by 1.08 decreases mortality. Sex had a strong relation to mortality (B:-2.738; SE: 0.876; Exp: 0.065; CI: 0.012-0.360, $p<0.05$) Male sex was found as a factor by 15 times decreasing the mortality. From other factors affecting the mortality in our model, transplant years did not show strong relations statistically. By our model, four countries (China, Pakistan, Kyrgyzstan, Tajikistan) were found with significant risk results by time periods in mortality. Mortality risk was increased by 84 times in Pakistan (B:4.430; SE:1.274; ExpB:83.953 ; CI:6.909-1020.064 $p<0.01$;); by 15 times in Kyrgyzstan (B: 2.767, SE:1.123; ExpB:15.905; CI:1.759-143.791, $p<0.05$;); 128 times in Tajikistan (B4.854;SE:1.798; ExpB:128.246; CI:3.782-4348.269, $p<0.01$;).

Mortality rates under the circumstances of considered predictor variables (odds ratios) were evaluated by logistic regression analysis. According to obtained results, age decreased mortality rate by 1.16 times (B:-0.149; SE: 0.060; ExpB: 0.862; CI: 0.767-0.969, $p<0.001$), whereas, male gender decreased mortality by 47.6 times significantly ($p<0.001$; B-3.849; SE: 1.337; ExpB: 0.021; CI: 0.002-0.293). Years of transplantation were not found as strong factors. Oppositely, when countries compared, Pakistan ($p<0.01$); Kyrgyzstan ($p<0.01$) and Tajikistan ($p<0.01$), presented with 670; 175 and 1494-fold increase in mortality.

Discussion

Currently, renal transplantation is preferred over hemodialysis as a treatment option for renal failure due to high positive outcomes in terms of survival (3, 4). Hence, intensive studies are continuing on renal transplantation practices and factors affecting survival after transplantation.

Not only preoperative and postoperative medical predictors, but donors, operating centers and countries, age, gender, ethnical and other factors also included in these studies (2, 11-16).

If we mention about impact of sex and age on survival, despite the insignificant results of Kaplan-Meier analysis, both Cox regression and logistic regression analyses identified them as statistically strong factors in our research. Compared to Neri's study, where mortality increased by over 60 years old (15), mortality in our study was not observed in 17 patients elder the 60 years. The high mortality frequency was registered as 11 patients (68.75%) in 28-39 age group. This result is similar to the study on survival after transplantation in Canada and United States (2). Both Cox and logistic regression tests revealed strong association of decreased of mortality rate

and male gender. Nevertheless, according to Nyberg and associates, gender did not implied effective role on mortality (14). Contrarily, Chen et al. stated the significant difference of survival in gender comparison (13). This point can be explained by some social grounds rather than medical reasons and it also requires further evidence-based investigations.

In the initial years, if renal transplantation was performed by certain countries, in time, procedure spread to much more countries and medical centers on the background of improved surgeries and positive outcomes. According to some thoughts, expansion of financial aspects of transplantational management is alarming (6).

One of other factors of current problem is the increasing the number of candidates for transplantation regarding to propagation of procedure on the level of countries. Number of patients visiting our clinic is steadily increasing as seen from Table 3. The main purpose of our study directed to analyze the presence of difference in patient loss by transplantation years and operating countries. Where the Kaplan-Meier analysis showed transplantation years as significant factors (Breslow $p<0.05$), both regression tests did not give meaningful results. When the analysis of operating country conducted, both Kaplan-Meier and regression tests demonstrated significant mortality factors in case of three countries (Pakistan, Kyrgyzstan and Tajikistan). The result can be associated with various factors. Thus, it can be explained by versatility of factors on survival of transplanted patients both in preoperative and postoperative periods. Several studies devoted to post-transplant survival comparisons in numerous countries around the world. In a study, survival conditions between the USA and Canada, significant differences were found between the two countries after the first year of transplantation (2). Factors influencing the frequency of mortality in this age group may also be subject for debates. In a study of survival differences of 622 patients at different transplantation centers in different countries in Europe, multivariate analysis between countries and centers showed that the risk of mortality increased four-fold for low to moderate risk patients and 1.6-fold for the medium to high risk group (12). Including the pre-transplantation workup and management, detailed studies are required in order to investigate the patient loss in these countries.

On the other hand, the cumulative survival rate of patients receiving post-transplantation treatment in our center is high at 1 and 5 years, considering survival in other countries (16).

Conclusion

To sum up, despite the high frequency of mortality, which is considered due to preoperative and intraoperative issues, Kyrgyzstan is presented by high survival rate for 10 years by 92.8% in posttransplanted patients. In this case, it may be effective management for the patients to return our center after the transplantation where they underwent, as well as the dynamic follow-up in well-being natural conditions. This point must be approved by evidence. Notwithstanding, mortality challenges in aforementioned countries necessitates further investigations of procedural facilities and methods to find out exact factors.

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References

1. Watson CJE, Dark JH. Organ transplantation: historical perspective and current practice. Br J Anaesth 2012; 108 (Suppl 1); i29–i42.
2. Kim SK, Schaubel DE, Fenton SS, Leichtman AB, Port FK. Mortality after kidney transplantation: A comparison between the United States and Canada. Am J Transplant 2006; 6: 109–14.
3. Kramer A, Pippias M, Noordzij M, Vianda SS, Afentakis N, Ambuhl PM, et al. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. Clin Kidney J 2018; 11(1); 108–122.
4. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341: 1725-173.
5. Rizvi SA, Anwar Naqvi SA. Renal replacement therapy in Pakistan. Saudi J Kidney Dis Transpl 1996; 7: 404-8.
6. Okafor UH. Transplant tourism among kidney transplant patients in Eastern Nigeria. BMC Nephrol 2017; 18: 215.
7. Garcia GG, Harden PN, Chapman JR. The global role of kidney transplantation. Kidney Int 2012; 81: 425–7.
8. Rizvi SA, Naqvi SA, Hussain Z, Hashmi A, Akhtar F, Hussain M, et al. Renal transplantation in developing countries. Kidney Int Suppl 2003; 83: S96-S100.
9. Sever MS, Kazancioglu R, Yildiz A, Turkmen A, Ecder T, Kayacan SM, et al. Outcome of living unrelated (commercial) renal transplantation. Kidney Int 2001; 60: 1477-83.
10. Akoh JA. Renal transplantation in developing countries. Saudi J Kidney Dis Transpl 2011; 22; 637-50.
11. Wong JS, Port FK, Hulbert-Shearon TE, Carroll CE, Wolfe RA, Aogodoa LY, et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int 1999; 55: 2515-23.
12. Khan IH, Campbell MK, Cantarovich D, Catto GR, Delcroix C, Edward N, et al. Survival on renal replacement therapy in Europe: is there a 'centre effect'? Nephrol Dial Transplant 1996; 11: 300-7.
13. Chen PD, Tsai MK, Lee CY, Yang CY, Hu RH, Lee PH, et al. Gender differences in renal transplant graft survival. J Formos Med Assoc 2013; 112: 783-8.

14. Nyberg G, Bohme I, Norden G. Gender difference in a kidney transplant population. Nephrol Dial Transplant 1997; 12: 559-63.

15. Neri F, Furian L, Cavallin F, Ravaioli M, Silvestre C, Donato P, et al. How does age affect the outcome of kidney transplantation in elderly recipients? Clin Transplant 2017; 31(10): doi: 10.1111/ctr.13036

16. Wang JH, Skeans MA, Israni AK. Current status of kidney transplant outcomes: dying to survive. Adv Chronic Kidney Dis 2016; 23: 281-6.

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The TACE's role in the management of primary liver cancer

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Abstract

Objective: Identify the most effective and safe method of transcatheter hepatic artery chemoembolization (TACE) in patients with primary liver cancer.

Methods: Overall, 139 patients, who underwent 558 TACE procedures were included in the study. Gender in the group of patients was distributed approximately equally and amounted to 72 men (52%) and 67 women (48%), the average age was 57.8 (9.9) years (range from 23 to 92 years). In most patients, the underlying disease for the development of hepatocellular carcinoma was cirrhosis of the liver in the outcome of hepatitis C or B. Characteristics of liver tumors were examined by magnetic resonance imaging or computed tomography and ultrasound. For verification of the diagnosis, a percutaneous liver biopsy was performed under ultrasound guidance, and the level of alpha-fetoprotein was also determined. All patients were considered unresectable due to cirrhosis and / or local spread of the tumor. Chemoembolization was performed by following scheme: one procedure in 2 months, not less than 3 procedures.

Doxorubicin was used for chemotherapy. As a carrier of chemotherapy, Lipiodol (Guerbet, France) or saturable Hepaspheres (Merit Medical, USA) were used. Each patient received from 3 to 13 procedures.

Results: Postembolization syndrome occurred in all cases, but was effectively treated. One patient died due to acute liver failure with the borderline stage of the disease according to the BCLC classification (EASL 2012) and the multinodular form of HCC. There were no serious complications in the treatment process. In two patients in the area of the puncture of the femoral artery, pseudoaneurysm was formed, which was eliminated by compression under ultrasound guidance. About 10% of patients developed subacute cholecystitis in the postoperative period and were associated with non-targeted chemoembolization in the cystic artery. In all patients, the symptoms of cholecystitis at the time of discharge were relieved conservatively.

Survival median – 19 months. Dynamics of tumors was assessed by RECIST criteria. In the group of patients with hepatocellular carcinoma after first 3 TACEs partial response and stabilization were observed in 83%, progression in 17%. In 18 cases (13%), histologically proved tumor necrosis after TACE was achieved, without progression during follow-up. Three patients after reducing of tumor size was resected, 32 patients continue treatment.

Conclusion: Transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma shows high efficacy, low mortality and the development of postoperative complications in patients with concomitant liver cirrhosis and locally advanced tumor lesion.

Key words: Chemoembolization of hepatic artery, hepatocellular carcinoma

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Introduction

The "gold" standard in the treatment of patients with hepatic malignancies are liver resection, as well as systemic chemotherapy aimed at eliminating or reducing the extent of the hepatic pathological process and achieving an operable state (1-3). Surgical treatment of hepatocellular carcinoma (HCC) is associated with long-term survival (3-6). However, radical management is possible only in 5-15% of patients in case of confirmed diagnosis of HCC (7-9).

Radical treatment in poor hepatic function, bilobar spreading of the process, extrahepatic metastasis with HCC is possible only in 10-30% of cases (6, 10). Postoperative mortality is less than 3% in patients without cirrhosis and 7–25% in patients with cirrhosis (3). Relapse of the primary tumor within 3-5 years after liver resection is observed in 70-90% of patients, of which repeated resection can be performed in less than 10% (4).

Systemic chemotherapy and radiation for hepatic neoplasia are ineffective, even when using combinations of several drugs (4, 11-13). Attempts to find more effective, minimally invasive methods of therapy motivated the development of intravascular interventions under fluoroscopic control.

Modern therapeutic endovascular interventions for unresectable HCC include hepatic arterial infusion of chemicals, transcatheter arterial chemoembolization of saturable microspheres (TACE), hepatic artery oil chemoembolization and radioembolization (14-21). At present, with HCC, TACE is more often used with the use of drug-saturated microparticles with high absorbing ability and long, slow, dosed release of chemotherapy, which allows delivering drugs to the tumor node in high concentration and ensuring their long-term effect directly on the affected area without systemic toxic effect (22-25). The saturation of the microspheres with a cytostatic is performed immediately before their administration. The compound remains stable longer than the oil emboli: the half-life of the dose from the liver is from 6 to 72 days. The most commonly used cytostatics are doxorubicin, epirubicin and other drugs. Monitoring the effectiveness of treatment is carried out using regular ultrasound (US), multi-detector computed tomography (MDCT) and magnetic-resonance imaging (MRI), as well as monitoring the level of alpha-fetoprotein (AFP). TACE cycles are repeated every 2-3 months.

The nature of the blood supply to primary liver cancer affects the effectiveness of TACE. The HCC is characterized by pronounced hypervascularization of the lesion with a large number of chaotic, histologically altered vessels with multiple arteriovenous shunts (26).

According to Shpak et al. (23), in the hypervascular type of HCC, the arterial type of blood supply predominates, with potent visualization of the tumor vessels and reaching a maximum concentration of contrast medium in the range from the late arterial to late portal phase with its subsequent leaching (27, 28).

Randomized study of Lammer et al. (29) was devoted to compare the efficacy of drug-eluting bead TACE (DEB-TACE) and conventional TACE (cTACE) with doxorubicin. The results of treatment of a large group (n=212) of patients with HCC were studied. A complete response, a partial response, and stabilization were observed more often in the DEB-TACE group (27%, 52%, and 63%, respectively) than in the group with cTACE (22%, 44%, and 52%, respectively). DEB-TACE showed significantly fewer complications (especially due to systemic toxicity of doxorubicin), in comparison with conventional HEPA (28).

Malenstein et al. (27), in turn, showed greater efficacy of the conventional TACE technique compared to DEB-TACE (HepaSphereTM saturated with doxorubicin) in the treatment of unresectable HCC. The response to treatment of 30 patients according to RECIST criteria in the DEB-TACE and cTACE groups was observed in 77% and 92% of cases, progression in 23% and 8%, respectively (the difference was not statistically significant).

Thus, to date, sufficient experience has been accumulated on the use of various endovascular approaches in the treatment of malignant liver lesions. Endovascular chemoembolization of the hepatic arteries is an option for the treatment of patients with inoperable tumors of the liver due to its high efficiency and relative safety, allowing to achieve stabilization or regression of the process. The long-term effect of chemoembolization is due to the implementation of three main treatment mechanisms: the creation of a locally high concentration of the drug with its selective administration, the long-term presence of the chemotherapy drug in the focus, and the induction of ischemic tumor necrosis. The use of microspheres is slightly more effective than classical oil chemoembolization; however, further accumulation of experience is required to determine the indications for each method.

Purpose of the study was to determine the efficacy and safety of TACE in patients with hepatocellular carcinoma.

Methods

The study included 139 patients who underwent 558 hepatic chemoembolization procedures. According to the results of MRI or MDCT, as well as ultrasound, the characteristics of foci in the liver were studied. Chemoembolization was carried out according to the scheme: one procedure in 2 months, but no less than three procedures. Upon receipt of a positive response to treatment, the intervals between TACE increased to 3-6 months. At the beginning of TACE, all patients were found to be unresectable. The chemotherapy with doxorubicin was used, during one procedure; 25 to 100 mg of the drug was administered. Saturated hepatospheres (Merit Medical, USA) or Lipiodol (Guerbet, France) were used as a chemotherapy

drug carrier. Depending on the carrier used, the group of patients was divided into two subgroups.

The study group consisted of 139 patients with HCC, of which 72 men and 67 women, the average age was 57.8 (9.9) years (range from 23 to 92 years). An angiographic feature of patients in this group was the presence of hypervascularization of tumor nodes along the entire perimeter (Fig. 1). Hepaspheres were used as carriers in 97 patients (70%), Lipiodol in 42 (30%) patients. Each patient underwent from 3 to 13 procedures.

In order to understand the distribution of the chemotherapeutic agent carrier in the tumor tissue, the inert black metal, 40 to 60 microns in size, in the form of a suspension with a contrast medium, was intraoperatively injected via a syringe into the liver tissue fragment with HCC, and removed immediately after venous vascular isolation, in the form of a suspension with a contrast agent. We visually assessed the nature of the color change in different areas of the tumor depending on the maximum accumulation of microparticles. Light microscopy using the ImageScope automated morphometric program determined the distribution of microspheres in the tumor tissue.

Results and discussion

During the current hospitalization, 1 death was recorded due to acute liver failure in a patient with a terminal stage of the disease according to the BCLC classification (EASL 2012) and a multinodular form of HCC. There were no serious complications during the treatment. Two patients in the area of the puncture formed a false aneurysm, which was eliminated by compression under ultrasound control. Postembolization syndrome, noted in all patients, was relieved pharmacologically. Approximately 10% of patients showed signs of subacute cholecystitis in the postoperative period and were associated with improper administration of chemoemboli into the artery. In all patients, signs of cholecystitis at the time of discharge were relieved conservatively.

The dynamics of disease was evaluated according to the RECIST criteria. Median survival was 19 months.

In the subgroup with Lipiodol, after three courses, a partial response and stabilization were observed in 60%, progression in 40%, and in the subgroup with hepaspheres in 83% and 17%, respectively (Fig. 2). In 18 (13%) patients, tumor necrosis after TACE was histologically confirmed, with the lack of disease progression during dynamic observation. After reducing the size of the lesion, three patients underwent liver resection, 32 patients continuing treatment.

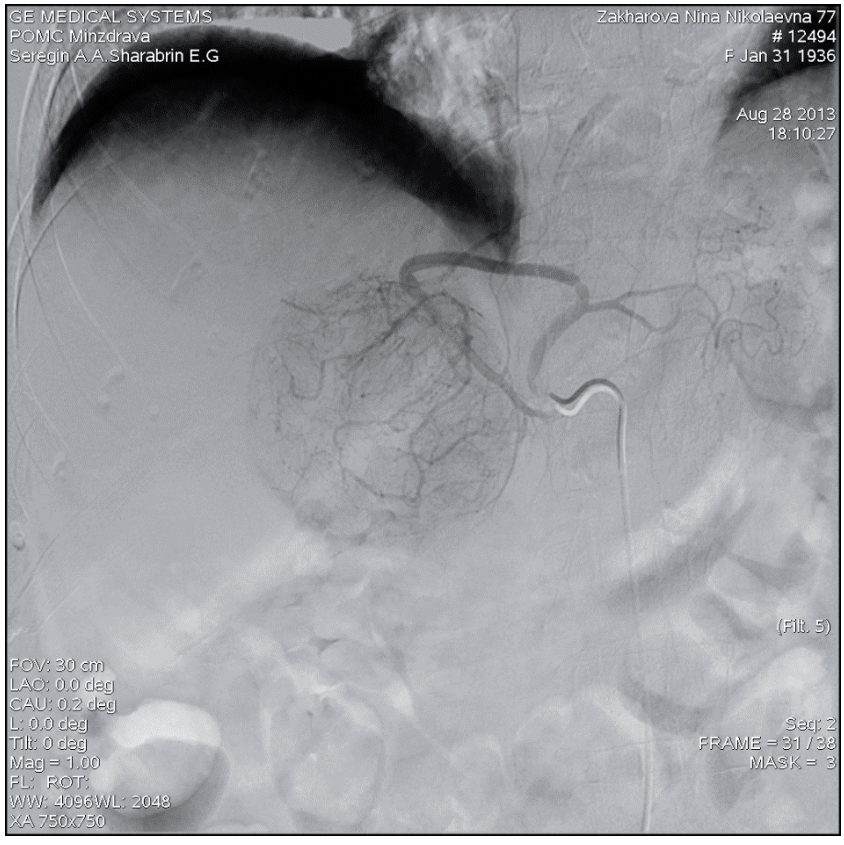


Figure 1. Angiogram of aberrant left hepatic artery from the left gastric artery of a 76 years old patient Z. with hepatocellular carcinoma. A hypervascular node is visualized in the left lobe of the liver.

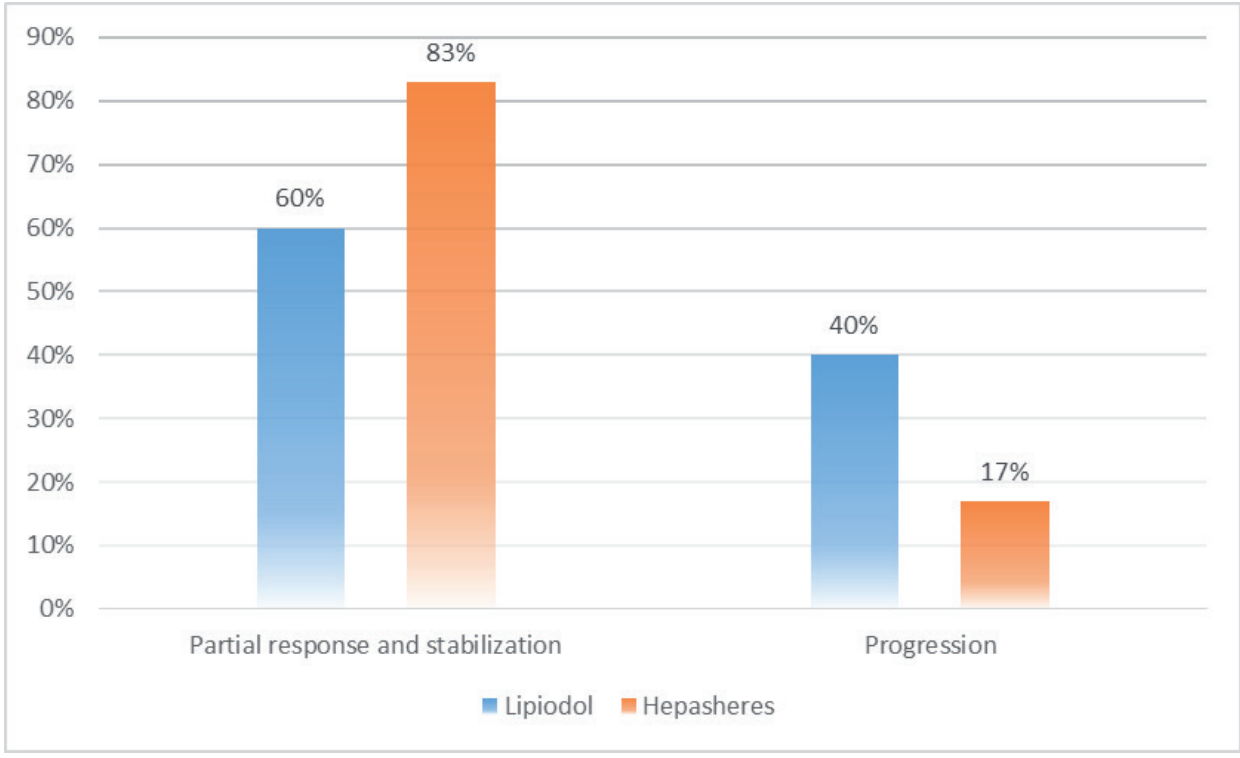


Figure 2. TACE results in the study group (hepatocellular carcinoma). The partial response and stabilization of the process in the subgroup with hepaspheres is higher than in the subgroup with Lipiodol.

TACE - transcatheter hepatic artery chemoembolization

Morphological study

During intra-arterial infusion of a suspension of microparticles (hepaspheres), it was noted that in the hepatocellular carcinoma the microparticles were distributed evenly in the central and peripheral zones of the tumor (Fig. 3).

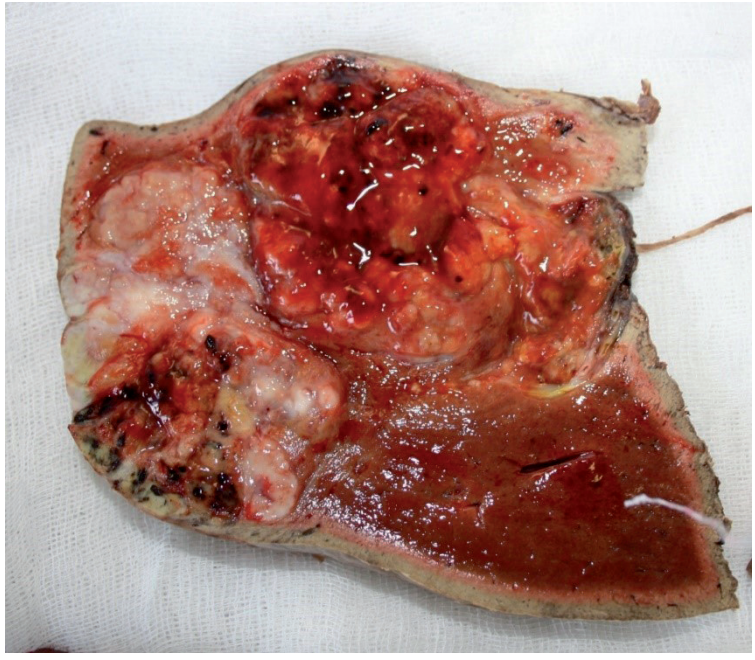
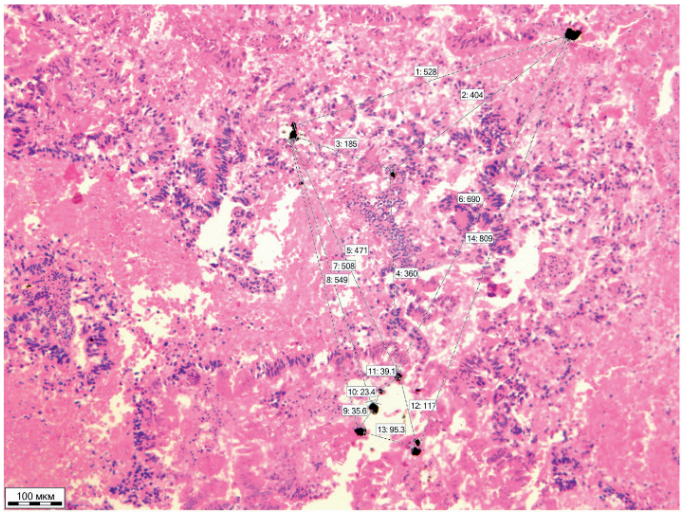
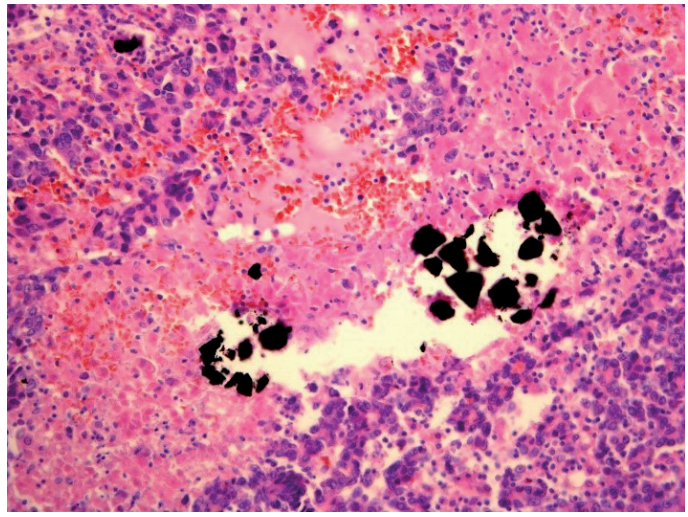


Figure 3. Macrospecimen. Uniform distribution of microparticles in the tissue of hepatocellular carcinoma in the form of multiple black foci in the central and peripheral zones of the tumor.

It was found that the distance between the microparticles was from 23.4 to 809 μm (Fig. 4).



A)



B)

Figure 4. The micropreparation. Uniform distribution of labeled microparticles in the tissue of hepatocellular carcinoma: a) x100 magnification; b) x200 magnification. Hematoxylin and eosin stain.

Conclusion

Hepaspheres have shown great effectiveness in the treatment of hepatocellular carcinoma, a partial response and stabilization of the process were obtained in 83% of patients during the first six months. Disease progression was observed in 17% of patients.

Chemoembolization with Lipiodol showed good penetration of the drug into the tumor tissue; however, in this subgroup of patients, only 60% of patients received a partial response and stabilization of the process and a higher rate of disease progression during the first six months of treatment.

The study showed the need to use more courses of chemoembolization of the hepatic artery with the predominant use of drug-saturated hepaspheres in the treatment of hepatocellular carcinoma.

Chemoembolization of the hepatic artery in the treatment of hepatocellular carcinoma is the method of choice for unresectable tumors with cirrhosis. TACE has shown high efficiency and safety of the method, with minimal risks of complications.

Conflict of interest: None to declare

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References

1. Cunningham C, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and Cetuximab plus Irinotecan in Irinotecan–refractory metastatic colorectal cancer. N Engl J Med 2004; 351: 337–45.
2. Virshke ER. Endovascular technologies in the treatment of patients with malignant tumors of liver and pancreas. PhD thesis of a doctor of medicine. Moscow 2009; 42p.
3. Dzhuraev MD, Nematov ON. Short-term results of preoperative chemoembolization of hepatic artery in patients with hepatocellular carcinoma caused by cirrhosis. Siberian Oncology Journal 2011; 3: 70-3.
4. Tarazov PG. Endovascular interventions in treatment of primary liver cancer). Practical Oncology 2008; 9: 209-15.
5. Plechev VV, Mufazalov FF, Shestakov AI, Ishmetov VSh, Loginov MO, Utenskaya ID. Efficacy of treatment by chemoembolization in hepatocellular carcinoma and distant metastases into the liver. Meditsinskiy Vestnik Bashkortostana 2012; 7: 80-3.
6. Patyutko Yul. Surgical treatment of hepatic malignancies. Moscow.: Prakticheskaya Meditsina; 2005. 234p.
7. Garin AM, Bazin IC. The most prevailed ten malignant tumors). Moscow: KMK; 2006. 266p.
8. Shpanhenberg HC, Timme R. Hepatocellular carcinoma. Meditsinskiy Sovet 2011; 9-10: 112-5.
9. Gritsaenko AI, Mukhamedyanov LF, Pogadaev VV, Ishtukov RR. Case of treatment of unresectable hepatocellular carcinoma of the liver through the hepatic artery chemoembolization microspheres. Creativnaya Onkologia i Hirurgia 2014; 2: 9-14.
10. Kosyrev VYu. Radiofrequency thermoablation in combined treatment of malignant tumors (indications, methodology, results of treatment). PhD thesis for doctor of medicine. Moscow 2011. 42p.

11. Arybzhanov DT, Ormanov NK, Kulakeev OK, Zhumataev ZZ, Abdurahmanov BA, Besedin BV. Diagnostics and treatment of tumor lesions of liver in South Kazakhstan. Meditsinskaya Vizualizatsiya 2011; 1; 28.

12. Nartailakov MA, Mukhamedyanov IF, Gritsaenko AI. Chemo-infusion into the hepatic artery in the complex treatment of metastatic liver cancer. Materials of the III International Scientific and Practical Conference "High Technologies in Medicine". 2010; 1: 83.

13. Ormanov NK, Arybjanov DT, Besedin BV, Abdurahmanov BA. Results of chemoembolization in the treatment of primary liver cancer in South Kazakhstan. Diagnosticheskaya Interventsionnaya Radiologia 2011; 5: 29-30.

14.Nicolini A, Crespi S, Martinetti L. Drug delivery embolization systems: A physician's perspective. Expert Opin Drug Deliv 2011; 8: 1071-84.

15. Sun Z, Li G, Ai X, Luo B, Wen Y, Zhao Z, et al. Hepatic and biliary damage after transarterial chemoembolization for malignant hepatic tumors: Incidence, diagnosis, treatment, outcome and mechanism. Crit Rev Oncol Hematol 2011; 79: 164-74.

16. Welker MW, Trojan J. Anti-angiogenesis in hepatocellular carcinoma treatment: Current evidence and future perspectives. World J Gastroenterol 2011; 17: 3075-81.

17. Wong R, Frenette C. Updates in the management of hepatocellular carcinoma. Gastroenterol Hepatol (N Y) 2011; 7: 16–24.

18. Konno T, Maeda H, Yokoyama I, Iwai K, Ogata K, Tashiro S, et al. Use of a lipid lymphographic agent, lipiodol, as a carrier of high molecular weight antitumor agent for hepatocellular carcinoma. Gan To Kagaku Ryoho 1982; 9: 2005-15.

19. Konno T, Tashiro S, Maeda H, Iwai K, Ogata K, Mochinaga M, et al. Intra-arterial injection of an oily antineoplastic agent in hepatic cancer. Gan To Kagaku Ryoho 1983; 10: 351-7.

20. Bonartsev AP, Iordansky AL, Bonartseva GA. Biodegradation and biomedical use of bacterial poly (3-hydroxybutyrate). Novoe v Polimerah I Polimernyh Kompozitah. 2010; 1: 36-48.

21. Liapi E, Geschwind JF. Transcatheter arterial chemoembolization for liver cancer: is it time to distinguish conventional from drug-eluting chemoembolization? Cardiovasc Intervent Radiol 2011; 34: 37-49.

22. Felix R, Langer R, Langer M. Bildgebende diagnostik bei lebererkrankungen. Springer, Berlin. Heidelberg, New York; 1993. 23-66.

23. Shpak SA, Momot NV, Tanasichuk-Gazhieva NV. Features of multislice computed tomography in the differential diagnosis of primary malignant tumors of the liver. Novoutrennyaya 2010; 2: 98-105.

24. Lelyuk VG, Lelyuk SE. The state of hemodynamics with focal lesions of the liver (literature review and analysis of their own observations). SonoAce-Ultrasound 2000; 6.

25. Gadaleta CD, Ranieri G. Transarterial chemoembolization as a therapy for liver tumors: New clinical developments and suggestions for combination with angiogenesis inhibitors. Crit Rev Oncol Hematol 2011; 80: 40-53.

26. Malagari K, Chatzimichael K, Alexopoulou E, Kelekis A. Hall B, Dourakis S, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: Results of an openlabel study of 62 patients. Cardiovasc Intervent Radiol 2008; 31: 269-80.

27. van Malenstein H., Maleux G., Vandecaveye V, Heye S, Laleman W, van Pelt J, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011; 34: 368-76.

28. Balakhnin PV, Kanevich MD, Manihas GM. Chemoembolization of primary and metastatic liver tumors with drug-saturated hepatospheres: the role of plane-detection computed tomography as a method for evaluating treatment effectiveness according to EASL and RECIST criteria. Diagnosticheskaya Interventsionnaya Radiologia 2011; 5: 13-4.

29. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intevent Radiol 2010; 33: 41-52.