Data from a prospective study of the features of systemic lupus erythematosus in patients of Kyrgyzstan (Eurasian RENAISSANCE Register)

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Objective: *to study and analyze the clinical and laboratory manifestations, course, and outcome of systemic lupus erythematosus (SLE) in patients living in Kyrgyzstan.*

Patients and methods. *The prospective study included 150 young patients aged 34 [26, 44] years in a Kyrgyz cohort (KC) with SLE, the disease of which was 3.0 [0.7; 10] years. All clinical, laboratory, and instrumental data of patients, health-related quality of life (HRQOL) indicators, and treatment regimens were recorded in the international research base, such as British Lupus Integrated Prospective System (BLIPS). SLE activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). At the end of the observation, the investigators assessed the following indicators: the number of exacerbations of SLE by the SELENA Flare Index (SFI); the onset of complete or drug-induced remission; the number of deaths; and the development of irreversible organ damages (IOD) according to the damage index (DI).*

Results and discussion. *When seeing the physician for the first time, the KC included more patients with high (n=61 (40.66%)) and very high (n=40 (26.67%)) disease activity. Most (n=60 (40%)) patients were observed to have a subacute type of the course of the disease. At the first visit, the most common manifestations of SLE were damages to the skin (n=99 (72.67%)), serous membranes (n=91 (60.67%)), and lupus nephritis (n=79 (52.67%)). IODs were identified in 15.33% of the patients and were absent in 84.67%. IODs were more often due to the administration of glucocorticoids (GCs) in 43.48% of cases. However, GC therapy was not a predictor of organ damages (relative risk, 0.91; p>0.05). In the KC, the significant predictors of adverse outcomes were old-age onset SLE and its high activity, acute course, and frequent exacerbations.*

Conclusion. *The KC patients had high and very high clinical and laboratory activities (40.6 and 26.6%, respectively), mainly those of acute and subacute SLE (32 and 40%, respectively), obvious immunological disorders. There was a preponderance of damages to the skin (73%), serous membranes (61%), and kidney (53%) among the clinical manifestations of SLE. IODs were found in 15.33% of patients at their study inclusion. These were more frequently represented by GC-induced changes. However, the ongoing GC therapy in the KC patients was not a predictor of organ damages. The significant predictors of an adverse outcome in our patients were old-age onset SLE and its high activity, acute course, and frequent exacerbations.*

Keywords: *systemic lupus erythematosus; Kyrgyz cohort; activity; irreversible organ damages; exacerbation; outcome.*

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Systemic lupus erythematosus (SLE) remains one of the most mysterious and unpredictable diseases of the 21st century.

It is known that the course, outcomes and frequency of development of irreversible organ damage (IOD) in SLE can be affected by ethnic and demographic characteristics of patients. In different ethnic groups, differences in clinical manifestations, degree of activity, and severity of organ damage not only form the features or a subtype of SLE, but can affect the level of survival and mortality, which is significantly higher than in general population [1,2]. In recent years, in order to comparatively study the course, outcome and treatment programs for patients with SLE of different ethnic populations, international registers have been created that were active in North and South America, as well as in Europe back in the 70s of the past century [3]. The data obtained from these registers are of great importance for clinical practice, development and implementation of basic scientific research, as they allow to characterize the subtypes of the disease, causes of IOD, and optimize the methods of early diagnosis and prediction of SLE outcomes [4–7]. In this regard, in 2012, an inter-ethnic register of patients with SLE, the Eurasian Cohort (RENAISSANCE) was created, in which the leading rheumatological centers of the Russian Federation (V.A. Nasonova Research Institute of Rheumatology and the Department of Rheumatology of the Pacific State Medical University), Kazakhstan (Department of

Rheumatology of the Kazakh National Medical university named after S.D. Asfendiyarova) and Kyrgyzstan (Academician M. Mirrahimov National Center for Cardiology and Therapy) take part. The article presents data from a prospective study of the features of SLE in patients from Kyrgyzstan.

The purpose of the study was to analyze the clinical and laboratory manifestations, course and outcomes of SLE in patients living in Kyrgyzstan.

Material and methods

A prospective study included 150 patients with a confirmed diagnosis of SLE (according to the criteria of ACR (1997) [8] and SLICC (2012) [9]) of the Kyrgyz cohort (KC) hospitalized to the clinic of Academician M. Mirrakhimov National Center for Cardiology and Therapy from January 2012 to December 2018. The patients were followed up for 1–3 years. All clinical, laboratory and instrumental data of the patients, health-related quality of life (HRQoL) indicators and treatment regimens were recorded in the international research database – British Lupus Integrated Prospective System (BLIPS). The disease onset variant was verified according to V.A. NasonovaXs classification (1972): acute, subacute or chronic. SLE activity was evaluated using the SLEDAI 2K index (0 – no activity; 1–5 low; 6–10 medium; 11–19 high; and more than 20 points – very high activity) [10].

Outcomes of the disease were evaluated at the end of the follow-up period: number of exacerbations of SLE according to the Selena flare index (SFI) (mild, moderate and severe); the onset of remission (complete or medication-induced); death; development of IOD according to the damage index (DI), developed by the International Organization for Cooperation of SLE Clinics (Systemic Lupus International Collaborating Clinics – SLICC). The absence of damage was evaluated as 0 (no damage), low DI – 1 point, medium DI – from 2 to 4 points, high DI – more than 4 points [11]. SLE remission was defined as medication-induced in the absence of clinical and immunological activity (SLEDAI index 2K – 0 points) while taking hydroxychloroquine 200 to 400 mg/day and / or glucocorticoids (GC) 5 mg/day or less (in terms of prednisolone) for at least 6 months; and as complete in the absence of clinical and immunological activity (SLEDAI 2K index – 0 points) without GC or immunosuppressants from 6 months to 5 years (van Vollenhollen R., 2017; Zen M., 2015).

All patients underwent standard clinical and laboratory examination. Mandatory instrumental studies included electrocardiography (ECG), echocardiography with visualization of the pericardium, valvular apparatus of the heart, systolic blood pressure. Adhesive pericarditis was diagnosed as an echo-negative space behind the posterior wall of the left ventricle (LV) from 1 to 5 mm during both systole and diastole, and exudative pericarditis as an echo-negative space of more than 5 mm detected behind the posterior wall of the LV in the diastole. Pulmonary arterial hypertension (PAH) was verified by echocardiography if the systolic pressure in the pulmonary artery exceeded 30 mm Hg. As a screening immunological study, we used the linear immunological assay (immunoblot) of LIA-Max 17 with the determination of antibodies to double-stranded DNA (anti-ds-DNAs), Sm antigen with D1 polypeptide, and indirect immunofluorescence (IIF) of antinuclear antibodies (ANA) to various components of the nucleus on Hep – 2 cell line with high dilution of blood serum of patients with a titer> 1: 160. In order to assess the immunological activity of the disease, anti-ds-DNAs were determined by enzyme-linked immunosorbent assay (ELISA) and a decrease in the C3-, C4-components of the complement – by immunonephelometric assay (INA). Laboratory signs of antiphospholipid syndrome (APS) included the presence of lupus anticoagulant (LA), false-positive Wasserman reaction, levels of antibodies to cardiolipin (aCL) IgG, IgM isotypes, antibodies to β2-glycoprotein I (anti-β2 GP I) IgG, IgM isotypes (ELISA). In order to assess neuropsychiatric manifestations of SLE, classification criteria of the American College of Rheumatology (ACR) (1999) were used [12]. Neuropsychiatric disorders were diagnosed by a psychotherapist using the classification of mental disorders and behavioral disorders according to ICD – 10.

Due to impossibility of histological study of the kidneys with determination of the morphological type of lupus nephritis (LN) in the republic, we used the clinical classification of LN variants proposed by I.E. Tareeva: fast-progressing LN (FPLN), nephritis with nephrotic syndrome, active LN with severe urinary syndrome, latent LN (nephritis with minimal urinary syndrome) [13]. To determine the degree of a decrease in the glomerular filtration rate (GFR) and severity of proteinuria, we used the KDIGO (2013) classification of chronic kidney disease (CKD). According to this classification there are 6 stages of CKD [14]. GFR was calculated in mL/min/1,73м^2 : S1 (> 90 mL/min) – normal; S2 (60–89 mL/min) – mildly decreased; S3a (45–59 mL/min) – mildly to moderately decreased; S3b (30–44 mL/min) – moderately to significantly decreased; S4 (15–29 mL/min) – sharply decreased; S5 (< 15 mL/min) – terminal renal failure. Assessment of urine protein level was made according to the following criteria: A1 (<150 mg/day) – normal or mild proteinuria; A2 (150–300 mg/day) – significant proteinuria; A3 (>500 mg/day) – high and very high proteinuria.

Statistical processing of the results was carried out using the SPSS 23 program (IBM, USA). The type of distribution of quantitative variables was analyzed using the Lillefors normality criterion. Variables with parametric distribution are presented as M ± SD. Variables with nonparametric distribution are presented as a median with interquartile range [25%; 75% percentiles]. Independent groups were compared using the Mann–Whitney and Kolmogorov–Smirnov criteria, and dependent groups – using the Kruskal–Wallis method. To determine the effect of indicators on the outcome, the method of multiple logistic regression was used with the calculation of the odds ratio (OR) and the confidence interval (CI) of 95%. The significance of differences between the groups was determined using a nonparametric Z-criterion. The differences were considered significant at $p < 0.05$.

Results

Female patients (144 out of 150) of young age (median – 34 [26; 44]), with secondary and secondary vocational education (n =108), mainly of Kyrgyz nationality (n = 134) predominated in the KC (Table 1).

The period from SLE onset to the verification of the diagnosis in the KC ranged from 3 months to 2.5 years, the duration of the disease on the first visit was from 7 months to 10 years, the duration of the follow-up from the initial to the final visit ranged from 1 to 3 years.

At the point of inclusion in the study, 54 of 150 patients (35%) were incapable of work, most patients had high (n =61; 40.66%) and very high disease activity (n = 40; 26.67%). During the initial hospitalization only 3 (2%) patients in the KC had medication-induced clinical and immunological remission. In

the majority of patients, the subacute variant of the disease course was observed (n = 60; 40%); the acute variant was noted in 48 (32%) patients, and chronic variant in 42 (28%) patients.

On the initial visit more than half of the patients had LN (n=79, 53%) and a significant number of patients had skin lesions (n = 99, 73%); serositis was observed in 91 (61%) patients, and alopecia in 88 (59%) patients. In 81 (54%) patients these changes were accompanied by constitutional disorders, which were represented by febrile fever in 72 (89%) cases (Fig. 1). Non-erosive arthritis was revealed in 76 (51%) patients, most often with the involvement of the wrist and small joints of the hands (n = 42, 55%)

In 91 (61%) of 150 Kyrgyz patients with serous lesions pericarditis prevailed: it was observed in 69 patients (76%), more often adhesive (49 patients [71%] of 69) and less frequently – exudative (20 patients [29%] of 69).

Renal damage was observed in more than half of the patients – 79 (53%) of 150, of whom 49 (62%) had active LN. The nervous system was affected in 33 patients (26%); in half of these cases (n=18, 54%]) the central nervous system (CNS) was involved, and in 15 patients (45%) – the peripheral nervous system (PNS). The CNS damage was mainly manifested in diffuse neuropsychiatric symptoms in the form of psychosis with visual and auditory hallucinations (n =9, 50%).

Hematological disorders were observed in 59 (39.33%) Kyrgyz patients out of 150, lymphopenia being the most common – in 40 (67.81%) of 59 patients, with lymphocyte fluctuations in the peripheral blood from 0.3x109/ L to 0.98x109/ L (average 0.72 ± 0.17).

Respiratory damage was observed in 17 (11.33%) Kyrgyz patients, of whom 6 (35.92%) were diagnosed with acute lupus pneumonitis characterized by unproductive cough, severe hypoxemia, shortness of breath, and in half of the cases – with signs of severe respiratory failure (n =3). There were 11 patients with pulmonary arterial hypertension (PAH) with an increase in systolic pressure in the pulmonary artery over 50 mm Hg (according to the Echo-CG data), the average values of which were 71.09 ± 14.54 mm Hg (from 55 to 94 mm Hg). In 6 (54.54%) of 11 patients, secondary PAH was observed: in 3 patients with lupus pneumonitis and in 3 patients with interstitial lung lesions.

Table 1. Demographic characteristics of patients in the KC (n = 150).

Indicator	n(%)
Race, Kyrgyz/ Asian / Europeoid	134 (89.33)/12 (8)/4 (2.67)
Gender: women / men,	144 (96)/6 (4)
Social status: Education: higher / secondary / secondary vocational	42(28)/20(1.33)/88 (58.67) 54 (35)
Disabled: not working / working	42 (77.78)/12 (22.22) 96 (64)
Patients without disability: non-working / working	70 (72.92)/26 (27.08)
Marital status: family presence / absence of family / divorced / widowed	110(73.33)/31(20.67)/ 7(4.67)/2 (1.33)

Table 2. Clinical characteristics of patients in the Kyrgyz cohort during the initial examination

Parameters	N
Patient's age on 1st visit (years), Me [25; 75 percentiles]	34 [26; 44]
The time of appearance of the first signs of SLE before the diagnosis was verified (years), Me [25; 75 percentiles]	1.0 [0.3; 2.5]
Duration of SLE on 1st visit (years), Me [25; 75 percentiles]	3.0 [0.7; 10]
Variants of SLE course, n (%): acute subacute chronic	48 (32) 60 (40) 42 (28)
SLE activity according to the SLEDAI – 2K index (points) on 1st visit, n (%): remission (0) low (1–5) moderate (6–10) high (11–19) very high (20 or more)	3 (2) 15 (10) 31 (20.67) 61 (40.66) 40 (26.67)

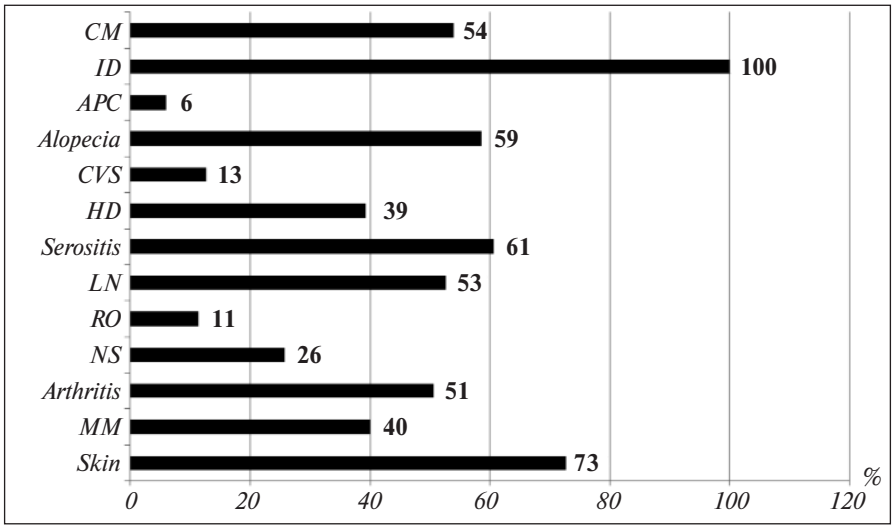

Fig. 1. *The frequency of clinical manifestations in KC patients (n=150), %. CM – constitutional manifestations; ID – immunological disorders; CVS – cardiovascular system; HD – hematological disorders; SM – serous membranes, RD – respiratory organs, NS – nervous system, MM – mucous membranes*

Table 3. Immunological disorders in the Kyrgyz cohort (n = 150).

Immunological indicators	n (%)
Determination of the level of anti-ds-DNA (ELISA)	**n=145**
Increased level Normal values	135 (93.10) 10 (6.90)
Analysis of C3 and C4 components of complement (ELISA)	**n=71**
Complement deficiency Normal values	69 (97.18) 2 (2.82)
Determination of antibodies to Sm-D1 antigen (immunoblot)	**n=97**
Antibodies to Sm-D1 antigen (+)	59 (60.82)
	38 (39.18)
a-CL (IEA)	**n=30**
Positive for a-CL IgG and IgM isotypes Positive anti-β2-gp IgG and IgM isotypes LA	7 (50) 4 (28.57) 2 (14.29)
ANF (IIF ANA)	**n=70**
ANF (+) ANF (-)	66 (94.29) 4 (5.71)

LA - lupus anticoagulant; ANF – antinuclear factor; ANA -antinuclear antibodies; IIF- indirect immunofluorescence; IEA – immunoenzymatic assay

Table 4. Characteristics of exacerbations of SLE (192 episodes in 84 patients)

Parameters	KC n (%)
Mild exacerbation	**103 (54)**
1. Mucocutaneous syndrome	81 (79)
2. Constitutional manifestations	22 (21)
Moderate exacerbation	**48 (25)**
1. Arthritis	16 (33)
2. Serositis	18 (37)
3. LN with minimal urinary syndrome	14 (29)
4. Myositis	0 (0%)
Severe exacerbation	**41 (21)**
1. LH with active urinary syndrome	28 (68)
2. Neuro-lupus	4 (9)
3. Hematological disorders	4 (9)
4.Cardiovascular disorders	5 (12)

Table 5. Causes of exacerbation of SLE in the Kyrgyz cohort at the final examination point (192 episodes in 84 patients)

The cause of exacerbations of SLE	KC n (%)
Self-discontinuation of therapy	44 (52.38%)
Planned discontinuation of therapy (GC)	0 (0%)
GC dose reduction	0 (0%)
Inadequate effect of therapy	0 (0%)
Active SLE	35 (41.67%)
Lack of medicine	1 (1.19%)
Unknown reasons	4 (4.76%)

The frequency of damage to the cardiovascular system (CVS) was insignificant; it was present only in 19 (12.67%) patients out of 150. Most often, diffuse myocarditis was detected (n = 11); 8 of these patients had decreased contractile function of the left ventricle (LV), and 2 patients developed ventricular extrasystole of high grades (Lown III and IVA). In one case, a female patient of 17 years old showed signs of coronariitis with typical anginal pain and subendocardial ischemia of the anterior-septal, lateral and lower walls of the left ventricle.

APS was diagnosed in 9 (6%) of 150 Kyrgyz patients with SLE. It was mainly manifested in venous thrombosis of the lower extremities (6). Pregnancy pathology was observed in 3 women in the form of spontaneous miscarriages at the early stages of gestation.

All 150 patients (100%) showed immunological abnormalities. As can be seen from Table 3, the overwhelming majority of patients had a high immunological activity of SLE, manifested in an increase in anti-ds-DNAs in 135 (93.10%) of 145 examined patients and hypocompletemia in 69 (97.18%) of 71 examined patients. The frequency of ANF positivity (using IIF method on the HEp-2 cell line) was 94%.

During the period of dynamic monitoring (median – 2.2 [1; 3] years) in 84 (56%) of 150 KC patients, 192 exacerbations of the disease from various organs and systems were recorded. The frequency of "outbreaks" of SLE per patient ranged from 1 to 4 cases (2.82 ± 2.21) during a 3-year period of observation. According to the SFI index, mild exacerbation of SLE was observed in 103 out of 192 cases and was manifested in mild mucocutaneous syndrome (n = 81) accompanied by febrile fever (n = 22), Table 4. Moderate exacerbation of the disease was noted in 48 (25%) cases out of 192, manifested in serositis (n = 18), arthritis (n = 16) and LN with minimal urinary syndrome (n =14).

Severe exacerbations of the disease in the KC were recorded in 41 (21%) cases, and mostly included active LN – 28 (68%) cases, less often hematological disorders – 5 (12%) cases, lupus pneumonitis – 4 (9%) cases and neuro-lupus – 4 (9%) cases. Thus, against the background of self-discontinuation of GC and cytostatic therapy, 4 patients had exacerbations of the disease with the CNS involvement which in 2 cases were manifested in generalized seizures, in one case – in visual hallucinations, and in one more case – in dyscirculatory encephalopathy with ataxic syndrome and anxiety disorder in the form of panic attacks. Exacerbation of LN with CKD S1A2 was observed in 6 patients, with CKD S1A3 in 6, with CKD S2A3 in 6, with CKD S3aA3 in 3, CKD S3bA3 in 2, and with nephrotic syndrome in 5 patients.

As can be seen from Table 5, episodes of SLE exacerbations were observed in 84 KC patients against the background of self-discontinuation of GC; in 44 patients – with self-discontinuation

of cytostatic therapy (52.38%), and in 35 patients they were due to activation of the pathological process (41.67%).

On the final visit, there was a significant (almost two-fold) decrease in the disease activity according to the SLEDAI 2K index: from 15.29 ± 8.06 to 7.79 ± 5.57, p <0.01).

The dynamics showed a high percentage of medication-induced clinical and immunological remission (SLEDAI 2K index – 0 points): it was noted in 41 (27.33%) patients. Only one patient in the KC had complete remission (lasting about 2.5 years). Half of patients with medication-induced remission – 20 (48.78%) out of 41 – received GC in a daily dose of 5 mg or less, in combination with hydroxychloroquine 200 to 400 mg/ day.

In addition to the analysis of the episodes of SLE exacerbation, organ damage was assessed according to the DAI / SLICC scale. On the initial examination most patients – 127 (84.67%) had no IOD, and 23 (15.33%) patients were diagnosed with IOD.

Low DAI values were observed in 14 (60.87%), medium values – in 9 (39.13%) out of 150 patients. No patients had high DAI values which was probably due to the short duration of the disease (median – 3 [0.7; 10] years). In 10 (43.48%) patients with IOD on the initial visit, the changes were due to the administration of GC. Five patients had changes in the musculoskeletal system in the form of aseptic necrosis of the femoral heads (n = 2) and steroid spondylopathy (n =3). The presence of steroid cataract was revealed in 3, and steroid diabetes in 2 patients. Changes in the respiratory system were found in 7 (30.43%) of 23 patients, pulmonary fibrosis – in 3 patients, and PAH – in 4 patients. Changes in the CNS were the next in frequency and were observed in 6 (26.09%) patients in the form of ischemic stroke (n = 4; 66.67%) and cognitive disorders (n = 2; 33.33%).

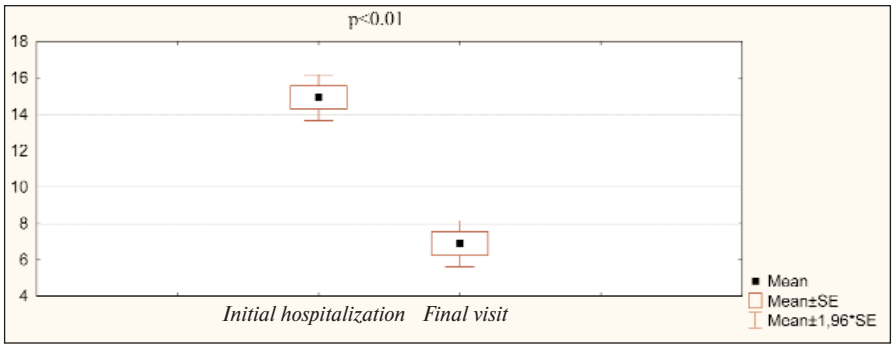

Fig. 2. *Changes in SLEDAI-2K*

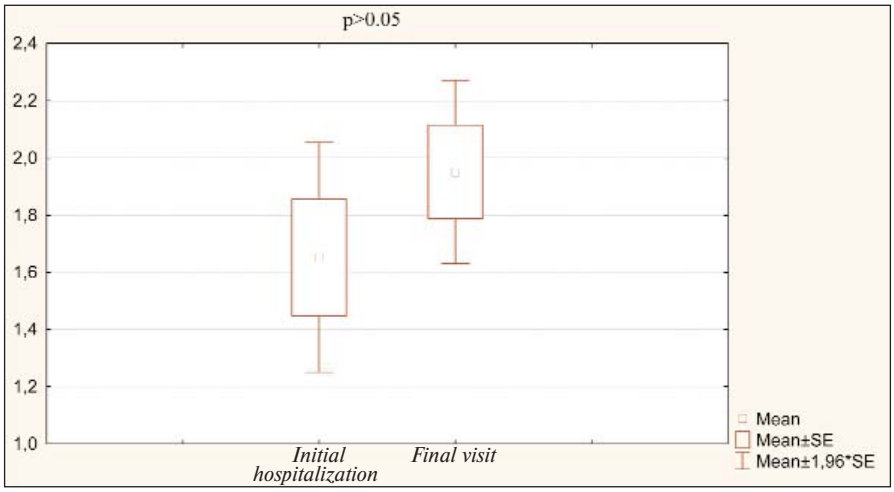

Fig. 3. *Changes in SLICC DI scores during observation*

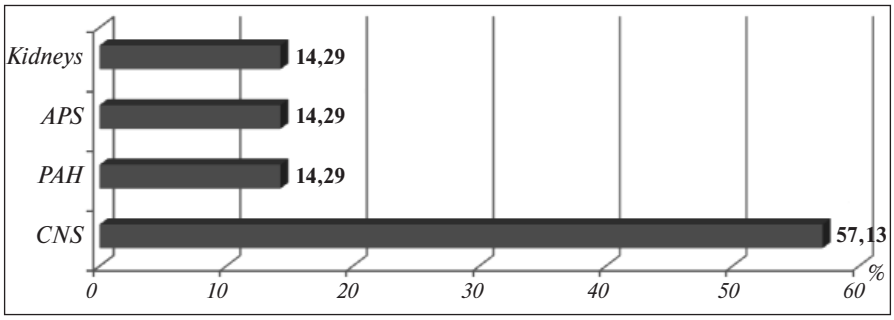

Fig. 4. *Structure of deaths (n=7), %*
Note: *APS – antiphospholipid syndrome; PAH – pulmonary arterial hypertension; CNS – central nervous system*

Dynamic observation (from 1 to 3 years) of the KC of patients revealed a statistically insignificant progression of IOD (p> 0.05), in the absence of high DAI values, although there was an increase in DAI score from 1.65 ± 0.98 to 1.95 ± 1.04 points (p> 0.05) (Figure 3).

On the final visit, there were already 43 (28.67%) patients with IOD (20 more compared with the initial visit).

In most cases (24 patients [55.81%]) IOD developed on the background of taking GC; in half of these cases the musculoskeletal system was involved (n =12; 50%): compression fractures of the vertebral bodies (n = 7; 58.33%)) and aseptic necrosis of the femoral heads (n = 5; 41.67%). The development of steroid cataract was observed in 9 (37.5%) and steroid diabetes in 3 (12.5%) of 24 patients.

Changes in the respiratory system took the second place: they were observed in 9 (20.93%) patients: pulmonary fibrosis – in 5, and PAH – in 4 patients. The next most common lesions included damage to the CNS (n = 6; 13.95%): ischemic stroke in 4 patients and cognitive disorders in 2 patients. Renal damage was detected in 4 (9.3%) patients, of whom 3 had a decrease in GFR and 1 patient developed terminal chronic renal insufficiency (as a result of severe LN).

During the follow-up there were 7 fatal cases (4.7%) out of 150 participants of the study. These were mainly young women (median age – 36 [26; 46] years), with the disease duration of 2 to

11 years (median – 7.5 [2; 11]), who died on average 1.23 ± 1.15 years after the initial observation.

Most deaths were caused by damage to the CNS: ischemic stroke in 2 patients, hemorrhagic stroke in 1 patient, and recurrent transverse myelitis with lower paraparesis and dysfunction of pelvic organs, with signs of severe organic dementia and dyscirculatory encephalopathy in 1 patient. One patient with terminal chronic renal failure died from uremic pulmonary edema due to a severe course of LN. One lethal case of a 37-year-old woman was associated with severe cardiopulmonary insufficiency in the presence of chronic decompensated pulmonary heart (cor pulmonale) due to PAH; she was previously diagnosed with overlap syndrome (SLE in combination with Stevens Johnson syndrome [SJS]). The last patient, a 26-year-old woman, died from secondary renal damage with the development of acute renal damage (ischemic kidney) on the background of APS, which also manifested itself as severe thrombocytopenia, thromboembolism of small branches of the pulmonary artery with the development of high PAH with severe respiratory failure.

The percentage of fatal cases was less than 5% (in the KC – 4.7%), which would affect the reliability of the statistical analysis, that is why, in order to determine the predictors of adverse SLE outcomes, we took an increase in DI (Δ DI) by 1 point or more as the endpoint of the observation. The frequency of such cases was more than 10% (in the KC – 28.7%) on the final visit.

Significant predictors of adverse outcomes (development of IOD) in the KC were high disease activity (according to the SLEDAI 2K index), acute course and age of patients at the onset of the disease (the older the patient, the greater the likelihood of developing IOD), as well as frequent exacerbations of SLE. At the same time, the ongoing GC therapy (on average, 7.4 g/day per patient) in this duration of the follow-up period was not a predictor of an adverse outcome.

Discussion

According to a series of numerous studies conducted in recent decades, there are some differences between the epidemiological, demographic, genetic, clinical, and socioeconomic factors in patients with SLE with different racial and ethnic backgrounds [15–17].

A number of studies provide convincing data on the worst survival of SLE patients in developing countries, which is associated with insufficient educational level of the population, refusal from recommended therapy, and low level of medical care [18–20]. For example, in the Afro-American population, the prevalence of SLE is 3 times greater, with the development of the disease at an earlier age and higher mortality compared with Caucasians [21–25]. According to another study, Afro-American SLE patients had a higher risk of progression of chronic renal failure compared with Caucasian people, as they more often showed diffuse proliferative glomerulonephritis, with severe uremia, hypocompletemia, thrombocytopenia, renal anemia, and arterial hypertension [26].

In the majority of Iranian patients, clinical manifestations of SLE were characterized by arthritis (83.2%), skin syndrome (81.1%), GN (66.4%) and LN (66.4%), less frequently by damage to the CNS (23.4%)) and the lungs (21.5%), with high immunological activity (increased anti-ds-DNA – in 82.3%, ANA – in 86.4%). The frequency of kidney damage in the Iranian cohort was significantly higher compared with the European cohort, while GN was recorded with the same frequency, and, therefore, the influence of genetic and climatic factors on the formation of the ethnic subtype of SLE in this cohort of patients was not excluded [16].

In the Spanish cohort study TRELESSERY, including 4024 SLE patients, 90% were women, young people (35.4 ± 15.1 years), with the mean disease duration of 11.5 years (from 0.6 to 19 years). In this cohort, the most common clinical manifestations of SLE were hematological disorders (79.8%), arthritis (77.9%), skin lesions (acute in 55.2% and chronic in 21.0%), oral ulcers (46.1%) and lupus glomerulonephritis class IV (32.1%). Immunological disorders in the Spanish cohort were found only in 85.8%, and ANA in 99.1% of patients [27].

In our cohort study, including predominantly patients of Asian race, specific features of clinical and laboratory manifestations and variants of the course of SLE were revealed. Thus, in our study patients with high disease activity (67%) and acute course (32%) prevailed. Among clinical manifestations of SLE, lesions of skin (72.67%), serous membranes (60.67%), and kidneys (52.67%) predominated. In addition, the overwhelming majority of patients of the KC had high immunological activity (an increase in anti-ds-DNA in 93.10%, and a deficiency of C3 and C4 complement components in 97.18%) with a high frequency of ANF positivity (94%).

Among SLE patients from South Korea, mainly GN (93%), arthritis (66%) and LN (50%) were recorded, with a high frequency of immunological disorders (93%) [28].

SLE patients from North Africa, in particular, Tunisia, had a higher prevalence of lupus dermatitis (photosensitization in 67.6%, zygomatic rash in 68.7%), LN (49.5%) and immunological disorders (44.8%) which were predominantly represented by positive antibodies to Sm antigen [29].

According to the results of a large multicenter study conducted in Canada, LN prevailed in most Afro-Caribbean patients and Asians. Patients from Asia were younger, had high SLE activity, which required long-term therapy with GC and cyclophosphamide, leading to damage, which along with low social income were predictors of an unfavorable outcome of the disease [30].

It is known that the age at the onset and duration of SLE have a significant impact on the development of damage and frequency of various complications [31,32]. In our study, the duration of SLE (from the onset of the first symptoms) directly affected the degree of accumulation of damage associated with both the disease itself and the therapy. In our study the duration of SLE on the initial visit was rather short (about 3 years). So, the absence of organ damage was observed in 84.67% of patients, and IOD was revealed only in 15.33% of patients. The observed changes were predominantly due to the administration of GC (43.48%), less frequently – to the respiratory system damage (30.43%) and to the central nervous system damage (26.09%).

High risk of IOD development with GC therapy can be associated with the duration of GC use and the cumulative dose [33.34]. Thus, the use of GC in a dose of more than 7.5 mg/day significantly increases the risk of developing steroid cataract (RR = 2.41; $p < 0.05$), osteoporotic fractures (RR = 2.16; $p < 0.05$) and cardiovascular damage (RR = 1.54; $p < 0.05$) compared with a lower dose [35]. In our study, prolonged administration of GC in the KC patients caused changes in the musculoskeletal system in 50% of cases in the form of aseptic necrosis of the femoral heads (20%) and steroid spondylopathy (30%); steroid cataracts (30%) and steroid diabetes (20%) were diagnosed lees frequently. However, the ongoing GC therapy in the KC patients was not a predictor of organ damage (RR = 0.91; $p > 0.05$).

According to some cohort studies, predictors of development of new IOD are older age of patients at the time of SLE onset, high disease activity, involvement of the kidneys and the CNS, and long-term cytotoxic treatment. IOD more often occurs in the Afro-American patient population than in the European population [36–40]. In other studies, some authors attribute these differences to the influence of genetic and climatic factors, others – to low socioeconomic conditions, and, to a lesser extent, to race and ethnicity [18,19].

Conclusion

Thus, the KC patients were characterized by the presence of high clinical and laboratory disease activity (67.33% and 21.09%, respectively, $p < 0.05$), acute SLE course (32% and 25%, respectively, $p < 0.05$), and pronounced immunological disorders (93,10% and 78.91%, respectively, $p < 0.05$). In the KC, among the clinical manifestations of SLE, lesions of the skin (72.67%), serous membranes (60.67%), and kidneys (52.67%) prevailed. The absence of IOD was noted in 84.67%, and IOD presence – in 15.33% of patients. IOD in the KC, was predominantly due to the administration of GC (43.48% and 53.95%, respectively). However, the ongoing GC therapy in the KC patients was not a predictor of IOD ($RR = 0.91$; $p > 0.05$). In the KC significant predictors of adverse outcomes were older age of patients at the onset of the disease, high disease activity, acute course, and frequent exacerbations of SLE.

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