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Research Article

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The Sudden Cardiac Death Continuum. Message 1

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RELEVANCE Many clinical conditions are considered in a sequence of interrelated events of the continuity of the pathological process. This makes it possible to discover its patterns, specific mechanisms of occurrence and development of the disease. However, the continuum of sudden cardiac death (SCD) remains unknown.

AIM OF THE STUDY To clarify the sequence of events of the continuum of the SCD using the example of initially healthy workers of locomotive crews of the Trans-Baikal Railway.

MATERIAL AND METHODS Based on the material of a 6-year prospective observation of a natural group of 7,959 men aged 18–66 years, predictors of microalbuminuria (MAU), creatininemia (CR), reduced glomerular filtration rate (rGFR), retinopathy (RP), and SCD were determined in 22 positions. A 2×2 table, multivariate regression analysis, and survival analysis were used, and the relative risk of risk factors (RF) was estimated, which made it possible to study and construct a continuum of chronic kidney disease from pre-prepared symptomatic blocks: MAU, RP, CR, rGFR using the synthesis method based on the principle of assembling puzzles, to which the SCD block was added according to this principle.

RESULTS The formation of SCD depends on the set of risk factors in each individual case and can occur from any peripheral point of the SCD continuum (from the risk factor). The formation of SCD is determined by the proximity of the predictor to the outcome, its independent effect and (or) interaction with other risk factors. The most dangerous predictor of SCD is excessive alcohol consumption, which causes damage to the heart and (or) kidneys, closing the dysfunctional circle of re-entry cardiorenal continuum and forming cardiorenal syndrome. In the population, those most at risk of SCD are those with an initially low number of nephrons and (or) a congenital defect of the microcirculatory bed.

CONCLUSION Further study of the continuum of sudden cardiac death is needed to determine whether cardiac or renal involvement is primary and whether the risk of sudden cardiac death increases. cardiac death when each predictor is added to the continuum of sudden cardiac death, the effects of risk factor damage, their increasing power with prolonged exposure, the magnitude of tissue damage, and the probability and timing of sudden cardiac death.

Keywords: alcohol, chronic kidney disease, continuum, sudden cardiac death, predictors, cardiorenal syndrome, risk factors

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AH — arterial hypertension
ASP — atherosclerotic plaque
ATSA — atherosclerosis of the aorta
BMI — body mass index
CAI — chronic alcohol intoxication
CI — confidence interval
CKD — chronic kidney disease
CRS — cardiorenal syndrome
CVD — cardiovascular diseases
DM — diabetes mellitus, type 2, mild
EAC — excessive alcohol consumption
ED — endothelial dysfunction
FHCVD — family history of early cardiovascular disease
HUS — hemolytic uremic syndrome
LVMH — left ventricular myocardial hypertrophy
MAU — microalbuminuria
MCB — microcirculatory bed
OR — relative risk
PWV — pulse wave velocity
RCS — renocardial syndrome
RCW — locomotive crew workers
RP — retinopathy
RF — risk factor
sGFR — reduced glomerular filtration rate
SCD — sudden cardiac death
TIM — thickening of intima media
TOD — target organ damage

INTRODUCTION

Modern concepts of many clinical conditions are built in a sequence of interconnected events of the cardiovascular continuum [1] — continuity expressing the holistic nature of the object, homogeneity and interrelation of its parts and conditions [2]. To clarify them, the method of scientific knowledge is used — modeling: the subject of the study is replaced by a model, which is then studied and the studied object is cognized. Structural modeling can be carried out by different approaches: creating information structures (structure) of the object and structural equation modeling (*SEM*). The latter method includes at least a dozen methods and algorithms of the approach: regression equations, iterative methods of maximum likelihood algorithms, iterative correlations and others [3]. The presented work will show the first part of the work performed — the study of sudden cardiac death (SCD) by comparative and multivariate analyses with an assessment of the identified predictors of the relative risk (RR). The physical model of the continuum, supplemented by the time dimension, creates a theoretical-physical construction - a space-time continuum, in which it is possible to determine what is the cause and what is the effect, i.e. the sequence of events and the time of their occurrence. This part of the work will be presented in subsequent publications. This knowledge about SCD, a disease that most often has only a preclinical course, remains unknown to this day. The emergence of new data in this area will allow us to discover patterns and specific mechanisms for the occurrence and latent formation of SCD, determine methods for its prediction, detection, prevention and timely therapy of this disease.

Aim of study: to clarify the chain of events of the VSD using the example of a group of initially healthy workers of locomotive crews of the Trans-Baikal Railway.

MATERIAL AND METHODS

In 2008–2013, 7959 initially healthy men aged 18–66 years (LCW) were examined annually on the Zabaikalsky Railway [4–6], who, in accordance with the order — inclusion criteria [7], did not have cardiovascular diseases (CVD) except for stage 1, stages I or II hypertension. During medical expert commissions, all LCW were identified with risk factors for cardiovascular diseases (RF CVD), target organ damage (TOD) according to the criteria of the Russian Medical Society for Arterial Hypertension, the All-Russian Scientific Society of Cardiologists 2008, 2011 for arterial hypertension (AH) [8, 9]. The order [7] allowed the presence of RF in LCW. This condition did not allow the LCW to always be healthy (Fig. 1–6), and over 6 years of observation they were diagnosed with TOD (Table 1) and CVD, including 15 cases of SCD. The design of the study of the LCW of the Zabaikalsky Railway is shown in Fig. 1. Its results have been published [4–6]. The list of examinations of the LCW of the Zabaikalsky Railway with the approval of the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education ChSMA dated 09.11.2011 No. 30 [6] was performed on certified modern equipment using generally accepted diagnostic methods (Table 1). Since the deceased SCD LCW did not have CVD, SCD was diagnosed according to the WHO definition of 1964, 1979 as “death that occurred instantly or within 1–6 hours from the onset of the first signs of heart disease in a person who had a stable, safe condition” [10] and the results of a forensic medical examination. In all cases, SCD was manifest, in 93% of cases lightning-fast. Holter ECG (electrocardiography) examination of the LCW Zabaikalsky Railway for hypertension, with suspicion of any cardiac pathology, during annual examination of persons aged 40 years and older, did not reveal contraindications for admission to train work under paragraph 29 (rhythm and conduction disorders) of the order [7] of subsequently deceased SCD LCW. In *KrelRisk* 1.1. (Russia) and *Statistica* 6.0. (USA), all cases of SCD were examined by statistical analysis. To determine the relationship between possible predictors (RF, TOD) and SCD, two groups of respondents (those with and without SCD) were compared. Quantitative variables were compared by the Mann-Whitney criterion and Pearson's χ^2, Pearson's χ^2 with Yates's correction — qualitative. Since the last two criteria lose their sensitivity when working with small values (n<10), they were additionally compared using the two-sided Fisher exact test. All criteria were statistically significant, but their preference was determined by the quantitative value (n) of the assessed variable. To

confirm the relationship of the identified variables with SCD, a multivariate stepwise regression analysis was performed with the inclusion of variables and the OR of the established predictors was estimated [11]. To clarify the difference between these risks at all time points for respondents with different characteristics [11] and to determine the triggers that have the most significant and independent effect on the development of SCD, to clarify the increase in the risk of SCD with the addition of each predictor to the latent pathological process, the Cox proportional hazard regression model was used. According to the Kaplan-Meier curves in the survival analysis, the probability and time of SCD formation under the influence of each and every predictor of SCD were established [12]. Graphical assessment of the influence of predictors on the survival function (SF — probability of absence of SCD) and the number of "failures" (probability of SCD occurrence) in dynamics of each trigger as an independent effect and all together allowed us to establish the time of SCD formation, its probability and stages of endothelial dysfunction (ED) progression. Multivariate analysis showed that SCD was preceded by damage to only one target organ — reduced glomerular filtration rate (rGFR) [4–6, 8, 9] (Tables 1–3), that is, heart pathology incompatible with life (dysfunction) was determined by kidney dysfunction (pathology). rGFR □ SCD. This relationship was designated in the diagram in accordance with the multivariate analysis data (Table 3), according to which rGFR was hypothetically defined as an interacting factor. Thus, by the synthesis method, the SCD module was added to the chronic kidney disease (CKD) continuum model, previously assembled in a similar way (Fig. 5). SCD ← sGFR ↔ CR (creatininemia) ↔ RP (retinopathy) ↔ MAU (microalbuminuria). By designating the interdependent relationship of CKD symptoms: sGFR, CR, MAU and RP I–II according to the jigsaw puzzle principle (a way to assemble a puzzle in the form in which it exists), these blocks were connected (Fig. 3A, 5, 6). The decision to clarify the formation of RP I–II came with the results of studying the symptoms of CKD: MAU, CR and sGFR. According to the data obtained, RP I–II was a predictor of MAU and CR symptoms. At the same time, MAU and CR preceded RP I–II [4, 5, 13–17] (Table 3, Fig. 5). In the course of theoretical research (see discussion), it was concluded that the pathological cardiorenal connection was interdependent (Fig. 3B) and occurred as cardiorenal or renocardial syndrome.

Fig. 1. Design of the conducted prospective study

Fig. 2. An example of the influence of environmental factors on the end point, the interaction of factors
Note: RF — risk factor

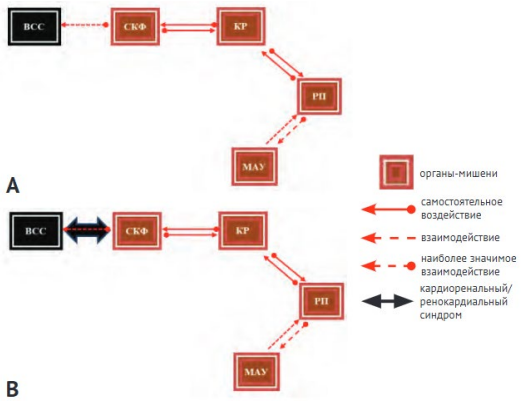


Fig. 3. Scheme of renocardial continuum (A) and cardiorenal syndrome (B)
Notes: SCD - sudden cardiac death; CR - creatininemia; MAU - microalbuminuria; GFR - glomerular filtration rate; RP - retinopathy. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor / confounder interaction

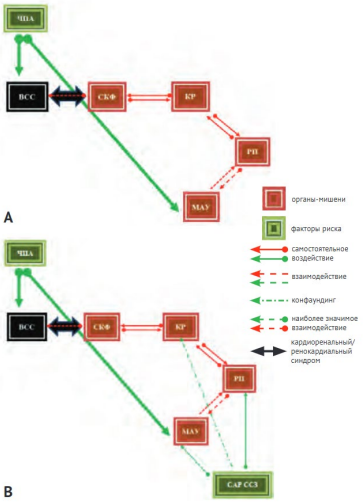
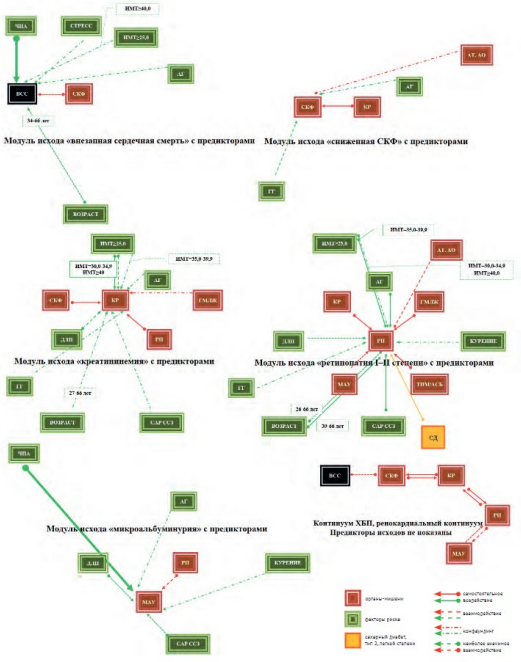


Fig. 4. Risk factors: excessive alcohol consumption (A) and family history of early cardiovascular disease (B) in the cardiorenal continuum

Notes: SCD - sudden cardiac death; CR - creatininemia; MAU - microalbuminuria; FH CVD - family history of early cardiovascular disease; GFR - glomerular filtration rate; RP - retinopathy; EAC- excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor / confounder interaction



ig. 5. Synthesis of the renocardial continuum, CKD and their symptomatic blocks

Notes: AH - arterial hypertension; ASP - atherosclerotic plaque; ATSA - atherosclerosis of the aorta; SCD - sudden cardiac death; LVMH - left ventricular myocardial hypertrophy; DLP - dyslipidemia; BMI - body mass index; CR - creatininemia; MAU - microalbuminuria; FH CVD - family history of early cardiovascular disease; DM - diabetes mellitus, type 2, mild; GFR - glomerular filtration rate; RP - retinopathy; TIM - intima-media thickening; EAC - excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor / confounder interaction

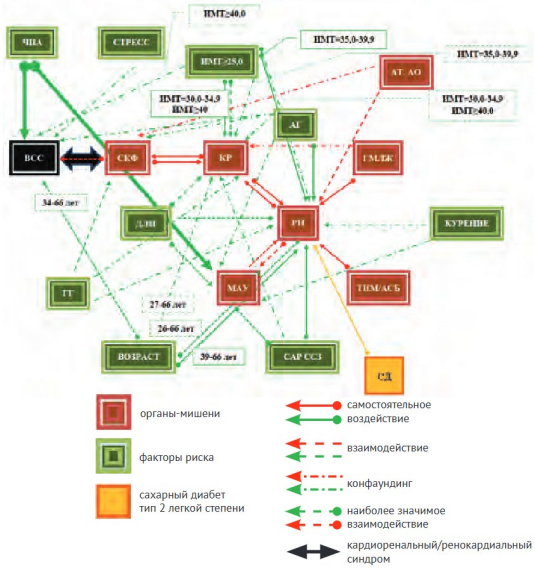


Fig. 6. Continuum of chronic kidney disease and sudden cardiac death. All predictors

Notes: AH - arterial hypertension; ASP - atherosclerotic plaque; ATSA - atherosclerosis of the aorta; SCD - sudden cardiac death; LVMH - left ventricular myocardial hypertrophy; DLP - dyslipidemia; BMI - body mass index; CR - creatininemia; MAU - microalbuminuria; FH CVD - family history of early cardiovascular disease; DM - diabetes mellitus, type 2, mild; GFR - glomerular filtration rate; RP - retinopathy; TIM - intima-media thickening; EAC - excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor / confounder interaction

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Table 1

Comparison of the prevalence of risk factors, target organ damage in individuals without CVD and with the outcome of sudden cardiac death in an observation group [4, 5]

Risk factors, cardiovascular target organ damage, *n* = 7959	VSS, *n* =15		Fisher's criterion (*p*)	(–) CVD, *n*=7798	
	n	%		*n*	%
Arterial hypertension	10	66.7	0.00	1920	24.6
Smoking	12	80		4821	61.7
Dyslipidemia	6	40		2470	31.6
Hyperglycemia	1	6.7		426	5.5
Family history of early CVD	2	13.3		882	11.3
Psychosocial stress	5	33.3		1604	20.5
Excessive alcohol consumption	3	20	0.00	68	0.9
BMI=25.0–29.9 / Overweight	9	60		3071	39.4
BMI=30.0–34.9 / Class I obesity	1	6.7		1170	15
BMI=35.0–39.9 / Obesity stage II	1	6.7		224	2.9
BMI≥40.0 / Obesity stage III	1	6.7	0.02	21	0.3
Retinopathy grades I–II	2	13.3		305	3.9
Left ventricular myocardial hypertrophy	3	20		557	7.1
Atherosclerosis of the aorta	2	13.3		434	5.6
TIM/ASP	0	0		15	0.2
PWR above 12 m/s	0	0		16	0.2
Creatininemia	1	6.7		111	1.4
Microalbuminuria	0	0		7	0,1
Reduced GFR	1	6.7	0.01	5	0,1
Ankle-brachial index below 0.9	0	0		0	0
Diabetes mellitus, type 2, mild	0	0		36	0.5

Notes: ASP - atherosclerotic plaque; SCD - sudden cardiac death; BMI - body mass index; GFR - glomerular filtration rate; PWV - pulse wave velocity; CVD - cardiovascular disease; TIM - intima-media thickening. Statistically significant results are shown. The age of locomotive crew workers without CVD: 38.48±10.33 years, Min–18; Me–38; Max–66; and with the outcome of SCD: 47.93±7.4 years, Min–25; Me–50; Max-54. Criterion Mann–Whitney U=28315.5; Z=3.45; p <0.001

Table 2

Prognostic value of SCD predictors in multivariate analysis [4–6]

Predictors	Sudden cardiac death (*n* = 15)			
	β	*t*	OR [±95% CI]	*r*
R^2 >0.08; *F* =66.05 *p* <0.000 (*n*=6130)*				
Age 18-66 years	0.03	2.41	2.4 [0.3; 18.2]	0.01
Age 34-66 years			7.9 [1.04; 60.15]	
Psychosocial stress	0.04	3.49	7.7 [2.6; 22.4]	0,00
Reduced GFR	0.04	4.22	19.3 [2.6; 140.8]	0,00
BMI≥40.0 (obesity stage III)	0.13	10.42	111.7 [18.9; 659.75]	0,00
EAC	0.25	20.36	155.7 [51.7; 468.9]	0,00
R^2 =0.23; *F* =27.53 *p* <0.000 (*n*=7959)				
Age 18-66 years	0.03	2.19	1.6 [0.2; 12.12]	0.03
Age 34-66 years			8.33 [1.10; 63.36]	
Psychosocial stress	0.02	1.43	1.93 [0.66; 5.65]	0.15
Reduced GFR	0.10	9.35	94.67 [14.68; 610.68]	0,00
BMI≥40.0 (obesity stage III)	0.05	4.36	23.63 [3.23; 172.54]	0,00
EAC	0.09	8.02	27.77 [8.01; 96.29]	0,00
Arterial hypertension	0.03	2.12	5.82 [1.99; 17.03]	0.03

Notes: CI - confidence interval; RR - relative risk; BMI - body mass index; EAC - excessive alcohol consumption; β — significance level; *F* — evaluation criterion; $R2^{-}$ determination coefficient; *t* — ratio of the regression coefficient to its standard error; *p* —significance criterion. * — The analysis was initially performed on the 2011 observation data. The RR estimate with n-1 degrees of freedom in the age range of 25–54 years of SCD cases included 1.0 in the 95% CI and was not statistically significant, but was statistically significant in the age range of 34–66 years. The odds ratio of predictors of sudden cardiac death: age 25–54 years — 1.03 [0.31; 18.26], age 34–66 years - 11.31 [1.48; 86.07], excessive alcohol consumption - 222.71 [51.39; 965.07], stress - 7.89 [2.68; 23.20], reduced glomerular filtration rate - 20.19 [2.54; 160.31], body mass index≥40.0 — 148.57 [14.55; 1516.62] [4, 6]

Table 3

Significance of predictors of sudden cardiac death, chronic kidney disease, retinopathy degrees I-II in various statistical models [4, 5]

Predictors of Outcomes	Mathematical models				
	Table 2x2	Multiple - regression	OR	Kaplan -Meier model	Cox model
Microalbuminuria, *n* =8					
EAC	1	1	1	1	1
Dyslipidemia	1	1	1	1	0
Retinopathy grades I–II	1	1	1	1	0
FH CVD	1	1	1	1	0
Arterial hypertension	1	0	1	0	0
Smoking	1	0	0	1	0
Creatininemia, *n* =116					
Reduced SCF	1	1	1	1	1
Retinopathy grades I–II	1	1	1	1	1
BMI=25.0 and above	0	1	1	1	1
BMI=30.0–34.9 / obesity I	1	1	1	1	1
BMI=35.0–39.9 / obesity II	1	0	1	0	0
BMI≥40.0 / obesity III	1	1	1	1	1
Dyslipidemia	1	1	1	1	0
Hyperglycemia	1	0	1	1	0
FH CVD	1	0	1	1	0
LVMH	1	0	1	1	0
Arterial hypertension	1	0	1	1	0
Age 27-66 years	1	0	1	0	0
Reduced glomerular filtration rate, *n* =6					
Creatininemia	1	1	1	1	1
Hyperglycemia	1	1	1	1	0
Atherosclerosis of the aorta	1	1	1	0	0
Arterial hypertension	1	0	1	0	0
Retinopathy grades I–II, *n* =337					
Arterial hypertension	1	1	1	1	1
Age 26-66 years	1	1	1	0	1
Age 39-66 years	1	1	1	1	1
LVMH	1	1	1	1	1
Microalbuminuria	1	1	1	1	0
FH CVD	1	1	1	1	1
Diabetes mellitus type 2	1	1	1	1	1
Creatininemia	1	1	1	1	1
BMI=30.0–34.9 / obesity I	1	0	1	1	0
BMI=35.0–39.9 / obesity II	1	1	1	1	1
BMI≥40.0 / obesity III	1	0	1	1	0
TIM/ASP	1	1	1	1	1
Dyslipidemia	1	1	1	1	0
Hyperglycemia	1	1	1	0	0
Atherosclerosis of the aorta	1	0	1	1	1
Smoking	1	0	0	1	0
Sudden cardiac death, *n* =15					
EAC	1	1	1	1	1
Reduced GFR	1	1	1	0	1
Age 34-66 years	1	1	1	0	1
BMI≥40.0 / Obesity III	1	1	1	0	0
Arterial hypertension	1	0/1	0/1	1	0
Psychosocial stress	0	1/0	1/0	0	0

independent risk factor;

interacting risk factor;

confounding [19]

Notes: (1) — p <0.05; (0) — p >0.05. ASP - atherosclerotic plaque; LVMH - left ventricular myocardial hypertrophy; BMI - body mass index; GFR - glomerular filtration rate; FH CVD - family history of early cardiovascular disease; TIM - intima-media thickening; EAC - excessive alcohol consumption

RESULTS

Predictors of SCD showed statistical heterogeneity, showing contradictory results in the used statistical models, and therefore were classified. Comparison in the 2 × 2 table established the variables having a statistically significant association with SCD: hypertension, body mass index (BMI) of at least 40.0, EAC, rGFR, age. Multivariate stepwise regression analysis showed that predictors of SCD at the initial assessment in the 2011 sample of n = 6130 were the following RFs: age, stress, BMI of at least

40.0, excessive alcohol consumption (EAC), rGFR. In the sample of n = 7959 of the entire observation period with the final outcomes of all LCWs, the RFs were: age, hypertension, BMI of at least 40.0, EAC, rGFR. In the Cox proportional hazards model, statistically significant results were: EAC, age 34–66 years, and rGFR. When constructing Kaplan-Meier diagrams, statistically significant models were built for the predictors of hypertension and atrial fibrillation. The estimate of the OR in the sample of n = 6130 observations in 2011 was statistically significant for all predictors of SCD, in the sample of n = 7959 of the entire observation period, the stress risk factor did not have a statistically significant estimate of the OR. The predictor of atrial fibrillation, which had a statistically significant result in all statistical models, was hypothetically estimated as the main predictor capable of independently being realized in the outcome of SCD without the participation of other risk factors, atrial fibrillation → SCD. The predictors: age 34–66 years, eGFR, which had a statistically significant result in all models except one, were considered interacting risk factors, realized in the end point with the participation of other risk factors by adding their effect into a joint effect of damage. RFs that had a statistically significant result in less than 4 models were considered confounders – factors influencing the outcome and the main influencing variable [18, 19] (Table 3, Fig. 2). In epidemiology, the influence of a factor is defined as "a pathological agent, a source of disease, capable of entering the body upon contact or proximity to it and causing a specific disorder (disease)". The effect of a factor can be negative (damaging) or positive (protective) [20]. If a variable that should be in a statistical model is not included in it, or one that should not be in it is included, this will affect its effectiveness. The inefficiency of a regression model is not only due to the incorrect specification of triggers in it. Changes in their list, even in the absence of any dependence within the set, can affect the functioning of all factors. This is how their interaction is manifested [21]. Variables interact with each other when the influence of a predictor on the outcome depends on the value of a complex variable formed from two or more independent similar factors. In this case, the differences in the dependent feature between the levels of a trigger are different for one or more levels of another trigger. The composed complex variable is not a confounder or an independent FR; the factors in it do not act independently of each other on the final outcome [11, 18, 19] (Fig. 2). We believe that the qualitative property of factors — interaction — is manifested by the discrepancy between their statistical results in different types of analysis and is determined by the role of the factor in the total effect of influence (Table 3). The interaction of factors is manifested by the modification effect in the combined influence of two or more variables. It can be positive, enhancing the influence of factors on the final result, and negative, weakening their influence [20]. The following types of factor interaction are known: additivity — summation; synergism — mutual reinforcement; antagonism — mutual weakening of influence [22]. Predictors of CKD and RP I–II have been previously studied and assessed similarly using this method [4, 5, 13–17].

DISCUSSION

Modern science requires searching for promising directions and improving methodological support. These tasks are solved by analysis and synthesis of knowledge [23, 24]. Analysis is a method of dividing an object into parts, sides, properties. Synthesis is a process of combining disparate things (concepts) into a whole by connecting, linking, placing and determining their location, a method of cognition from simple to complex [23]. In complex systems, synthesis is preceded by analysis. Synthesis is an engineering structural construction of complex systems from pre-prepared modules of different types in order to describe and create a non-existent abstract model. Together with analysis, the synthesis method allows one to obtain an idea of the connections between the components of the subject of study [25]. The construction of the VSS continuum model is performed using an abbreviation that allows one to perform design actions and apply symbolic thinking. In this work, the VSS module was connected to the CKD continuum by means of the identified connection, the synthesis of which was performed earlier from the previously prepared (studied) symptomatic blocks of CKD: MAU, RP, CR and sGFR (Fig. 5). VSS ← sGFR ↔ CR ↔ RP ↔ MAU (Fig. 3A) . The synthesis of MAU, RP, CR, sGFR and CKD is shown outside the scope of this publication

[4, 5, 13–17, 19, 26, 27]. When impaired renal function leads to cardiovascular complications (in this case, to VSS), some authors speak of renocardial syndrome (RCS) [28], which may be a consequence of primary acute kidney injury followed by acute impairment of cardiac function, or chronic primary kidney damage may lead to impairment of the functional state of the heart [29]. The kidneys, regulating humoral systems, participating in important microcirculatory and metabolic processes, affect the formation and progression of cardiovascular pathology. Even a slight decrease in kidney function significantly progresses the main cardiac pathology, increasing the frequency of complications and the risk of death, and, conversely, a decrease in the contractility of the heart negatively affects the functioning of the kidneys through an interdependent relationship and the formation of cardiorenal syndrome (CRS). This is a syndrome in which different initial factors of pathogenesis lead to the activation of largely common mechanisms of disease progression and mutual aggravation of the condition of the heart and kidney [29], SCD ↔ cGFR ↔ CR ↔ RP ↔ MAU (Fig. 3B *)* . Close relationships SCD, CKD through CRS, acting in both directions, give stability to the entire cardiorenal system. Due to the difficulty of establishing the underlying cause of CRS, some authors believe that it is extremely difficult to determine what occurs first—heart failure or renal dysfunction—and consider cardiorenal - relationships as a cardiorenal continuum [30, 31] (Fig. 3B *)* .

Since the earliest kidney damage is MAU [32], and at the same time the RF of the EAC (systematic alcohol consumption of more than 2 standard doses of alcohol per day for men with 1 standard dose of alcohol of 13.7 g - 18 ml of ethanol, which corresponds to 330 ml of beer (content of ≈5 vol.% ethanol) or 150 ml of wine (≈12 vol.% ethanol), or 45 ml of strong drinks (≈40 vol.% ethanol) [8]) in the LCW of the ZabzhD was recognized as an independent main predictor of MAU and a predictor affecting the heart, then SCD was probably formed in two variants of the sequence of events (Table 3). Option 1 - primary kidney damage and the formation of RCS (Fig. 4A), CPA → MAU ↔ RP ↔ CR ↔ sGFR → SCD. Alcohol-induced latent chronic glomerulonephritis is manifested by MAU, hypertension and microhematuria. Its exacerbations are associated with excesses of the CPA, worsening of clinical symptoms and a decrease in SCF [33]. The risk of CVD increases with an increase in MAU, accompanied by ED [16, 19, 32, 34, 35] with the transition to the next stage of development of events of the CKD continuum - MAU ↔ RP. The changes are interdependent, since the MAU level correlates with the thickness of the choroid and retina of the eye [13, 15, 16, 36]. These manifestations are considered signs of systemic damage to the microcirculatory bed (MCB) and a pathological process in the kidneys. The MCB of the kidneys and eye are anatomically similar and react equally with complications in both organs [37]. Progression of CKD is accompanied by an increase in the serum CR level, sGFR and pathology of the microvascular retina of the eye [38], MAU ↔ RP ↔ CR → sGFR. It is believed that an increased level of CR in the blood forms sGFR through renal hyperfiltration [14, 26, 27]. On the contrary, with sGFR, tubular secretion of CR and an increase in its concentration in the blood are compensatorily increased [39, 40], CR ↔ sGFR.

RF of CVD may precede MAU [16, 17], CR, RP I–II [4, 5, 13–15, 17, 19], predisposing patients with a congenital small number of nephrons to the development of CKD [41] (Fig. 4B*)*. This may be the case in individuals with low birth weight [42] or congenital microangiopathy, manifested by an increase in MAU, CR, and sGFR [43], which occurs in premature infants [44] and/or in individuals with a genetic defect in MCB [45]. Hemolytic uremic syndrome (HUS) is the main cause of acute kidney injury in children and one of the causes of kidney pathology in childhood [46] and may be the cause of SCD. In children with HUS, polymorphism of the genes of the blood coagulation system is determined in 100%: *MTHFR C*677*T*, *FVLeiden G*1691*A*, *PTGG*20210*A*, *FGBG*(455)*A*, I*TGB*3 (glycoprotein III *a*), *C*176*T* (*L*33*P*), *PAI*-1 4*G*(675)5*G* [47]. Thrombotic microangiopathy is a special type of damage to small intraorgan vessels, mainly renal. Genetic thrombophilia affects the severity of kidney damage, activates blood clotting inside the glomeruli [48] and progresses thrombotic microangiopathy [47]. Five atypical cases of HUS in newborns have been described, caused by absolute deficiency of *vWF* protease associated with a hereditary defect of this

enzyme [49, 50], and, probably, with the cause of SCD in infants.

In the whole organism, specialized functional systems are closely interconnected. If the result of the activity of one of the functional systems deviates, the activity of other related functional systems of the organism immediately undergoes reorganization. Violation of the hierarchical and multiparametric harmony of information relationships of the functional systems of the organism leads to dysfunctions and then to pathology [51]. Since the LCW ZabZHD did not have heart diseases, the second pathway of SCD formation may have been acute CRS, manifested by a sudden deterioration in cardiac activity and leading to acute kidney injury, which can occur in acute coronary syndrome [29] caused by CPA [6], CPA □ SCD □ sGFR □ CR □ RP □ MAU. A single, one-time consumption of a large dose of alcohol in any form of drink is a reliable risk factor for SCD [52]. However, it has been established that in patients with alcohol dependence, on the 3rd–5th day after alcohol detoxification, a high concentration of all proinflammatory cytokines is detected, of which the interferon γ and interleukin 17 fractions were the most prominent. The content of other cytokines in the blood serum exceeded the control concentrations by 2–6 times. After 2 weeks of standard anti-alcohol therapy, the cytokine profile in patients did not change. Their concentration was still high [53], which indicates long-term oxidative stress, inflammation and their persistence in patients with systematic EAC. In acute and chronic alcohol intoxication (CAI), the intake of ethanol into the body initiates the formation of active oxygen species, reduces the production of relaxing endothelium-dependent factors, increases the concentration of vasoconstrictive factors and the development of ED [54]. With systematic EAC, ED becomes permanent with all the ensuing consequences, since ED is involved in the pathogenesis and clinical course of all CVD and is associated with the risk of subsequent adverse cardiovascular events [55], including SCD [4–6]. All other RFs of SCD and CKD aggravate the condition and bring the time of SCD closer (Fig. 6). At the same time, a screening study [56] of the causes and pattern of alcoholic beverage consumption in professional male athletes showed significant alcoholization, the absence of absolute abstinence, and a preference for consuming strong alcoholic beverages in the amount of 401.7±271.2 ml of absolute ethanol per month. About 1/3 of athletes EAC 2–3 times a week and more than 5 standard portions per day. About 93% of athletes in the observation group experienced negative consequences of EAC. This screening and study of the LCW Transbaikal Railway identified risk groups for whom the probability of favorable consequences from preventive intervention will be especially high, and show the need for preventive measures among athletes and persons of operator professions aimed at diagnosing CAI [57, 58] and correcting problems associated with EAC and preventing SCD [59, 60]. The latter is ensured by implementing an algorithm for diagnosing the state of CAI, especially in the case of its systematic latent consumption in a dose exceeding the safe norm recommended by WHO [4–6, 8, 59–61].

CONCLUSION

Further research is needed into the continuum of sudden cardiac death to determine which occurs first, cardiac or renal failure, the increase in the risk of sudden cardiac death with the addition of each predictor to the continuum of sudden cardiac death, the effects of damage to triggers, their increasing power with prolonged exposure, their exposure [59, 61], the magnitude of organ tissue damage, the probability of sudden cardiac death and the time of its occurrence, as well as the processes of the continuous dysfunctional pathological circle of the cardiorenal continuum, which is probably formed through the *re-entry mechanism* (Fig. 4A*)*.

Current methods of diagnosing cardiac dysfunction are not perfect. Therefore, in the preventive strategy of sudden cardiac death, the priority should be the diagnosis of kidney disorders and the main predictor of sudden cardiac death - "excessive alcohol consumption". It is necessary to search for new, more advanced methods for diagnosing cardiac dysfunction that precedes sudden cardiac death.

FINDING

1. The interdependence of pathological processes of the cardiovascular system and kidneys in a certain continuous sequence of events of the cardiorenal continuum leads to cardiorenal syndrome or renocardial syndrome and sudden cardiac death. The risk ratio of sudden cardiac death in individuals with renal dysfunction in the form of reduced glomerular filtration in relation to the group without this factor is 94.67-fold higher, according to the criteria: $p < 0.05$ Fisher's exact test, 95% confidence interval of the risk ratio and $t > 2.0$ at $p < 0.05$ multivariate regression.

2. The chronic kidney disease continuum is a component of the sudden cardiac death continuum, which includes microvascular disease.

3. Development of sudden cardiac death is possible as a result of exposure to various risk factors for cardiovascular diseases. The most dangerous predictor of sudden cardiac death is the risk factor "excessive alcohol consumption", which causes damage to the heart and (or) kidneys and closes the dysfunctional pathological circle of the cardiorenal continuum. The risk ratio of sudden cardiac death in individuals exposed to this factor in relation to the control group is 27.77-fold higher, according to the criteria: $p < 0.05$ Fisher's exact test, 95% confidence interval of the risk ratio and $t > 2.0$ at $p < 0.05$ multivariate regression.

4. Within the population, those most at risk of sudden cardiac death are those with an initially low number of nephrons and/or a congenital defect of the microcirculatory bed and/or a genetic defect of the microcirculatory bed.

REFERENCES

1. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes: Part I: Pathophysiology and Clinical Trial Evidence (Risk Factors Through Stable Coronary Artery Disease). *Circulation*. 2006;114(25):2850–2870. PMID: 17179034 http://doi.org/10.1161/circulationaha.106.655688
2. Stepin VS. (ed.) *Novaya filosofskaya entsiklopediya* . In 4 vol. Vol. 3 Moscow: Mysl' Publ.; 2010. pp. 73–76. (In Russ.)
3. Ozhereleva T.A. Structural Equation Modeling. *Perspectives on Science & Education*. 2017;26(2):63–67. (In Russ.)
4. Lazutkina AYu, Gorbunov VV. *The Continuum of Sudden Heart Death.* Khabarovsk: DVGMU Publ.; 2017. (In Russ.)
5. Lazutkina AYu. *Cardiorebrovascular continuum (Continuum of chronic obliterating diseases of the arteries of the lower extremities & Resurrection to sudden heart death and chronic kidney disease).* Khabarovsk: DVGMU Publ.; 2019. (In Russ.)
6. Lazutkina A.Yu. *Prognosis of cardiovascular diseases and their consequences in workers of the locomotive brigades of the Zabaykalsky railway (Results of a 6-year prospective study): cand. med. sci. diss. synopsis*. Chita; 2017. (In Russ.)
7. *Order of the Ministry of Healthcare and Social Development of the Russian Federation No. 796 of 19.12.2005 "On approval of the pereshknya medicinskikh protivopokazaniy k rabotam, neposredstvennyy svyazannyy poezdov i shunting rabotoy"* (In Russ.). Available at: https://base.garant.ru/12144914/ (Accessed Nov 27, 2024)
8. Britov AN, Pozdnyakov YuM, Volkova EG, Drapkina OM, Eganyan RA, Kislyak OM, et al. National recommendations for cardiovascular prevention. *Cardiovascular Therapy and Prevention*. 2011;10(6, Suppl 2):2–64. (In Russ.)
9. Podzolkov VI, Perepech NB, Perepech NB, Oshchepkova EV, Ostroumova OD, Oganov RG, et al. Diagnosis and treatment of arterial hypertension: Russian recommendations (third review). *Cardiovascular Therapy and Prevention*. 2008;7(6, Suppl 2):1–32. (In Russ.)
10. Okorokov N.A. *Diagnosis of diseases of internal organs: practical guidance. Vol. 6. Diagnosis of diseases of the heart and blood vessels (diagnosis of ateroscleroses and ischemic heart disease)* . Moscow: Meditsinskaya Literature Publ.; 2002. (In Russ.)
11. Petrie A, Sabin C. A *Medical Statistics at a Glance.* 2nd [ed]. Wiley-Blackwell, 2005. (Russ. ed.: Petri MA, Sebin K. *Naglyadnaya meditsinskaya statistika* . 2nd [ed]., rev. and add. Moscow: GEOTAR Media Publ., 2010.)
12. Analysis of survival and regression for statistical data. In: *StatSoft: Statistica. Official Handbook. In 5 vol.* Vol. 3. Statistiki. StatSoft Publ., 1995. Ch. 10. pp. 3473–3534. (In Russ. .)
13. Lazutkina AY. Origin of stage I-II retinopathy. *Aspirantskiy Vestnik Povolzhiya* . 2023;23(4):38–43. (In Russ.) http://doi.org/10.55531/2072-2354.2023.23.4.38 -43
14. Lazutkina AY. Predictors of creatininemia in locomotive crew workers: Prospective observational study. *Therapy*. 2024;10(3):52–60. (In Russ.) http://doi.org/10.18565/therapy.2024.3.52-60
15. Lazutkina A.Yu. Origin and formation of early changes in the retina under the influence of atherosclerosis factors. *Aterosclerosis* . 2023;19(4):385–403. (In Russ.) https://doi.org/10.52727/2078-256X-2023-19-4-385-403
16. Lazutkina AYu. Predictors of microalbuminuria in workers of locomotive crews: prospective observational study. *Cardiosomatics*. 2023;14(1):27–36. (In Russ.) http://doi.org/10.17816/CS321275
17. Lazutkina AJu, Gorbunov VV. Predictors of Chronic Kidney Disease in Workers of Locomotive Crews. *Clinical Nephrology*. 2015;(2–3):21–26. (In Russ.)
18. Rumyantsev PO, Saenko VA, Rumyantseva UV, Chekin SYu. Statistical methods for the analyzes in clinical practice. Part 2. Survival analysis and multivariate statistics. *Problems of Endocrinology.* 2009;55(6):48–56. (In Russ.) https://doi.org/10.14341/probl200955648-56
19. Lazutkina AYu. Four Types of Destructive Influence of Confounding Effects of the Cardiorenal Continuum. *Medicina* . 2024;12(2):25–47. (In Russ.). http://doi.org/10.29234/2308-9113-2024-12-2-25-47
20. Kornysheva EA, Platonov DYu, Rodionov AA, Shabashov AE. *Epidemiology and statistics as instruments of evidence-based medicine*. 2nd [ed], rev. and add. Tver: TGMA Publ.; 2009. (In Russ.)

21. Dougherty C. *Introduction to econometrics.* New York: Oxford University Press; 1992.
22. Zabolotskikh VV, Vasilyev AV, Tereshchenko YuP. Synergetic Effects During Combined Impact of Physical and Chemical Factors. *Izvestia RAS SamSC* . 2016;18(5–2):290–294. (In Russ.)
23. Babailov VK. Analysis and Synthesis. *Business Information.* 2012;(4):16–19. (In Russ.)
24. Babaylov VK. *Theory of the method*. Kharkiv: KhNADU Publ.; 2011. (In Russ.)
25. Sintez. (In Russ.) Available at: http://dic.academic.ru/dic.nsf/ruwiki/74900 [Accessed Nov 27, 2024].
26. Lazutkina AYu. Predictors of reduced glomerular filtration rate. *Pathogenesis*. 2023;21(2):55–61. (In Russ.) http://doi.org/10.25557/2310-0435.2023.02.55-61
27. Lazutkina AYu. Pathogenetic mechanisms of reduced glomerular filtration rate. *Pathogenesis*. 2023;21(3):19–27. (In Russ.) http://doi.org/10.25557/2310-0435.2023.03.19-27
28. Schrier RW. Cardiorenal versus renocardiac syndrome: Is there a difference? *Nat Clin Pract Nephrol.* 2007;3(12):637. PMID: 18033224 http://doi.org/10.1038/ncpneph0673
29. Melnyk OO. Cardiorenal Syndrome: Diagnosis and Treatment. *Pochki*. 2017;6(10):2–14. (In Russ.) http://doi.org/10.22141/2307-1257.6.1.2017.93777
30. Smirnov AV, Dobronravov VA, Kayukov IG. Cardiorenal Continuum, Pathogenetic Grounds of Preventive Nephrology. *Nephrology (Saint-Petersburg)* . 2005;9(3):7–15. (In Russ.) https://doi.org/10.24884/1561-6274-2005-9-3-7-15
31. Shutov AM, Serov VA. Cardiorenal continuum or cardiorenal syndrome? *Clinical Nephrology.* 2010;(1):44–48. (In Russ.)
32. Kobalava ZhD, Dmitrova TB. Cardiorenal syndrome. *RMJ*. 2003;11(12):699–702. (In Russ.)
33. Mukhin NA. (ed.) *Nephrologiya* . Moscow: GEOTAR-Media Publ.; 2009. (In Russ.)
34. Ivanov DD. Microalbuminuria: a nephrologist's perspective. *Health of Ukraine*. 2008;21(1):18–19. (In Russ.)
35. Sigitova ON, Bikmuhammetova EI, Nadeeva RA. Microalbuminuria – diagnostic and prognostic significance in arterial hypertension. *Arterial Hypertension*. 2009;15(6):627–632. (In Russ.) https://doi.org/10.18705/1607-419X-2009-15-6-627-632
36. Kasumovic A, Matoc I, Rebic D, Avdagic N, Halimic T. Assessment of Retinal Microangiopathy in Chronic Kidney Disease Patients. *Med. Arch.* 2020;74(3):191–194. PMID: 32801434 http://doi.org/10.5455/medarh.2020.74.191-194
37. Balmforth C, van Bragt JJ, Ruijs T, Cameron JR, Kimmitt R, Moorhouse R, et al. Chorioretinal thinning in chronic kidney disease links to inflammation and endothelial dysfunction. *JCI Insight.* 2016:1(20):e89173. PMID: 27942587 http://doi.org/10.1172/jci.insight.89173
38. Fursova AZh, Vasilyeva MA, Derbeneva AS, Tarasov MS, Chubar NV, Nikulich IF, et al. Optical coherence tomography angiography in the diagnosis of retinal microvascular changes in chronic kidney disease (clinical observations). *Russian Annals of Ophthalmology*. 2021;137(3):97–104. (In Russ.) https://doi.org/10.17116/oftalma202113703197
39. Kutyrina IM. Treatment of arterial hypertension in chronic renal disease. *RMJ*. 1997;5(23):7. (In Russ.)
40. Weber JA, van Zanten AP. Interferences in current methods for measurements of creatinine. *Clin Chem*. 1991;37(5):695–700. PMID: 2032322
41. Korotaeva NV, Nastausheva TL, Ippolitova LI. Functional state of the kidneys in the neonatal period in children with very low and extremely low body weight. *Nephrology (Saint-Petersburg)* . 2022;26(4):89–96. (In Russ.) https://doi.org/10.36485/1561-6274-2022-26-4-89-96
42. Yanin VL, Ugleva TN, Petukhova SN, Biktimirov TR, Alexeenko LA, Khadieva ED. Functional and Morphological Characteristics of the Kidneys of Newborns With Extremely Low Birth Weight. *Forcipe* . 2020;3(3):5–12. (In Russ.)
43. Rodrigues DE, Bobrova LA, Kozlovskaya NL, Stolyarevich ES. Thrombotic microangiopathy in a patient with a genetic form of thrombophilia as a factor of the risk of progression of IgA-nephropathy. *Clinical nephrology*. 2017;(4):66–71. (In Russ.)
44. Trifanenkova IG, Tereshhenko AV. Iris fluorescein angiography in the diagnostics of active retinopathy of prematurity. *Fyodorov Journal of Ophthalmic Surgery*. 2020;(4):67–72. (In Russ.). http://doi.org/10.25276/0235-4160-2020-4-67-72
45. Rogozina LA, Davydkin IL, Danilova OE, Fatenkov OV, Gimatdinova GR, Khayretdinov RK. Atypical hemolytic uremic syndrome: A case study. *Ul'yanovskiy mediko-biologicheskiy zhurnal.* 2023;(1):6–13. (In Russ.) http://doi.org/10.34014/2227-1848-2023-1-6-13
46. Baiko SV, Sukalo AV. Risk factors for poor outcome of hemolytic uremic syndrome in children. *Nephrology and Dialysis.* 2016;18(4):404–415. (In Russ.)
47. Popa AV. *The role of thromboembolism in the development of thrombotic microangiopathies in hemolytic-uremic syndrome in children: PhD thesis.* Moscow; 2014. (In Russ.) Available at: https://viewer.rsl.ru/ru/rsl01005552004?page=1&rotate=0&theme=white [Accessed Nov 27, 2024]
48. Bobrova LA, Kozlovskaya NL, Shkarupo VV, Varshavsky VA, Stoliarevich ES. Influence of hereditary thrombophilia (HT) on clinical features and pathology found in chronic glomerulonephritis (CGN) patients. *Nephrology and Dialysis*. 2010. 12(1):025–033. (In Russ.)
49. Loirat C. Post-diarrhea hemolytic-uremic syndrome: clinical aspects. *Arch Pediatr*. 2001;8(Suppl 4):776–784. PMID: 11582927 http://doi.org/10.1016/s0929-693x(01)80196-2
50. Raife T, Montgomery R. New aspects in the pathogenesis and treatment of Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Rev Clin Exp Hematol.* 2001;5(3):536–561. PMID: 11703817 http://doi.org/10.1046/j.1468-0734.2001.00044.x
51. Makarova IN. Functional Interconnections and Interrelations of Various Systems in Organism as a Basis of Rehabilitation (Sequei). *Russian Journal of Physiotherapy, Balneology and Rehabilitation*. 2008;(2):36–46. (In Russ.)
52. Drapkina OM, Drozdova LYu, Kalinina AM, Ipatov PV, Egorov VA, Ivanova ES, et al. *Organization of proven preventive medical examination and dispensary inspection of certain groups of adult population.* 2nd ed. Moscow: FGBU «NMITs TPM» Ministry of Health of the Russian Federation Publ.; 2020. (In Russ.)
53. Vetlugina TP, Prokopieva VD, Epimakhova EV, Mandel AI, Boyko AS. Pro-inflammatory cytokines, oxidized proteins, and lipids in alcohol dependence. *Pathogenesis*. 2022;20(3):73–74. (In Russ.) https://doi.org/10.25557/2310-0435.2022.03.73-74
54. Chernov IA, Kirillov YuA, Areshidze DA, Kozlova MA, Makartseva LA, Shtemplevskaya EV. The effect of ethanol on the development of oxidative stress and endothelial dysfunction. *Medical Science and Education of Ural.* 2020;21(3):143–149. (In Russ.) http://doi.org/10.36361/1814-8999-2020-21-3-143-149
55. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101(16):1899–1906. PMID: 10779454 http://doi.org/10.1161/01.cir.101.16.1899
56. Medvedev SA, Zverev YP. Prevalence of Problem Drinking and Alcohol Related Problems Among Team Sports Players. *Journal of Clinical Practice*. 2011;(3):24–28. (In Russ.)

57. Petrov DV. *Diagnosis, treatment and prevention of disorders caused by alcohol consumption.* Yaroslavl: YaGMA Publ.; 2002. (In Russ.)
58. Myagkova MA, Pushkina VV, Petrochenko SN, Morozova VS. Determination Marker of Chronic Alcohol Abuse by Capilary Electrophoresis. *International scientific journal of comparative and fundamental studies*. 2015;(12):1640–1643.
59. Lazutkina AYu. Method for Determining the Exposure to Latent Excessive Alcohol Consumption in Groups of Operator Professions, the Impact of the Factor on Cardiovascular Morbidity and Mortality. *Medicina*. 2024;12(3):25–44. (In Russ.) http://doi.org/10.29234/2308-9113-2024-12-3-25-44
60. Lazutkina AYu. Quality Assessment of the Screening Test for Sudden Cardiac Death Predictors. *Current Problems of Health Care and Medical Statistics*. 2023;(3):149–165. (In Russ.) http://doi.org/10.24412/2312-2935-2023-3-149-165
61. Lazutkina AYu. Determining cardiovascular disease risk factor exposure among locomotive crew workers of the Trans-Baikal Railway. *Siberian Scientific Medical Journal*. 2024;44(5):209–221. (In Russ.) https://doi.org/10.18699/SSMJ20240525

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