ISSN-L 0254-2307

ROMANIAN JOURNAL OF GERONTOLOGY AND GERIATRICS

ESTABLISHED 1980

Volume 10, No. 1-2, 2021, New Series

ROMANIAN JOURNAL OF GERONTOLOGY AND GERIATRICS
First Issue: 1980
FOUNDER: ANA ASLAN, Professor, PhD, Member of the Romanian Academy

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METABOLIC CHANGES IN VERY OLD PEOPLE

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Abstract. The aim of the study is to highlight the dynamics of metabolic parameters, to calculate the prevalence of metabolic and atherogenic risk factors and the correlation of metabolic parameters with age in very old people. Material and methods: We investigated 112 patients, grouped according to age: a) between 80 and 84 years (control); b) between 85 and 89 years and c) over 90 years. Serum metabolic parameters were evaluated: glucose, creatinine, urea, uric acid, total cholesterol (CT), HDL-cholesterol, non-HDL-cholesterol, LDL-cholesterol, triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT). Were calculated: ratios CT/HDLc, LDLc/HDLc, non-HDLc/HDLc, TG/HDLc, TyG index; prevalence of metabolic and atherogenic risk factors and correlation of metabolic parameters with the age of the subjects. Results: The very old people aged 85-89 years showed a significant reduction in CT ($p<0.001$), LDLc ($p<0.001$), non-HDLc ($p<0.001$), triglycerides ($p<0.034$), CT/HDLc ($p<0.046$), LDLc/HDLC ($p<0.005$) and non-HDLc/HDLc $p<0.046$) compared to subjects aged 80-84 years. Subjects over 90 years showed a significant increase in creatinine ($p<0.02$) compared to subjects aged 80-84 years and 85-89 years. They had a significant decrease in CT ($p<0.009$), LDLc ($p<0.01$), non-HDLc ($p<0.019$), triglycerides ($p<0.011$), AST and ALT ($p<0.01$) compared to 80-84 year olds. Significant reductions were in non-HDLc ($p<0.038$), AST and ALT ($p<0.01$) compared to 85-89 year olds. The prevalence of atherogenic risk factors decreases with increasing age of the subjects. The elderly aged 85-89 have the lowest prevalence of CT/HDLc (10.52%), LDLc/HDLc (5.26%) and TG/HDLc (2.04%). Significantly positive correlations of serum creatinine and urea and significant negative correlations of CT, LDLc, non-HDLc, AST and ALT with the age of the subjects were evidenced. Conclusions: Metabolic parameters undergo significant changes in very old subjects. Reduction of transaminase activities and some lipid parameters, within the reference range considered normal, in subjects over 85 years may illustrate an apparently healthy aging due to a healthy lifestyle adoption and/or adherence to an appropriate medication strategy.
Key words: very old subjects, metabolic parameters dynamic, metabolic and atherogenic risk factors prevalence, correlation study

Rezumat. Scopul studiului este să evidenţieze dinamica parametrilor metabolici, să calculeze prevalenţa factorilor de risc metabolic şi aterogen, şi corelaţia parametrilor metabolici cu vârsta la persoane peste 80 ani. Material şi metode: S-au investigat 112 pacienţi, grupaţi în funcţie de vârstă: a) subiecţi cu vârstă între 80 şi 84 ani (control); b) subiecţi cu vârstă între 85 şi 89 ani şi c) subiecţi cu vârstă de 90 ani şi peste. S-au evaluat parametrii metabolici serici: glucoză, creatinina, uree, acid uric, colesterol total (CT), HDL-colesterol, non-HDL-colesterol, LDL-colesterol, trigliceride (TG), aspartat aminotransferaza (AST), alanin aminotransferaza (ALT). S-au calculat: rapoartele CT/HDLc, LDLc/HDLc, non-HDLc/HDLc, TG/HDLc, TyG index; prevalenţa factorilor de risc metabolic şi aterogen şi corelaţia parametrilor metabolici cu vârstă subiecţilor. Rezultatele au arătat că vârstnicii între 85-89 ani au prezentat o reducere semnificativă a CT ($p<0,001$), LDLc ($p<0,001$), non-HDLc ($p<0,001$), trigliceridelor ($p<0,034$), CT/HDLc ($p<0,046$), LDLc/HDLC ($p<0,005$) şi non-HDLc/HDLc ($p<0,046$) comparativ cu subiecţii cu vârstă între 80-84 ani. Persoanele cu vârstă de 90 ani şi peste au prezentat o creştere semnificativă a creatininei ($p<0,02$) comparativ cu subiecţii cu vârstă între 80-84 ani şi 85-89 ani. Aceştia au avut o scădere semnificativă a valorilor CT ($p<0,009$), LDLc ($p<0,01$), non-HDLc ($p<0,019$), trigliceridelor ($p<0,011$), AST şi ALT ($p<0,01$) comparativ cu persoanele cu vârsta de 80-84 ani. S-au evidenţiat reduceri semnificative ale non-HDLc ($p<0,038$), AST şi ALT ($p<0,01$) comparativ cu persoanele de 85-89 ani. Prevalenţa factorilor de risc aterogen se reduce cu creşterea vârstei subiecţilor. Bătrânii de 85-89 ani au cea mai mică prevalenţa a CT/HDLc (10,52%), LDLc/HDLc (5,26%) şi TG/HDLc (2,04%). S-au evidenţiat corelaţii semnificativ pozitive ale creatininei şi ureei serice şi semnificativ negative ale CT, LDLc, non-HDLc, AST şi ALT cu vârstă subiecţilor. Concluzii: Parametrii metabolici suferă modificări semnificative şi la vârste înaintate, la subiecţi vârstnici. Reducerea activităţilor transaminazelor, şi a unor parametri lipidici - în cadrul intervalului de referinţă considerat normal, la subiecţii de peste 85 ani poate ilustra o îmbătrânire aparent sănătoasă datorită adoptării unui stil de viaţă sănătos sau/şi a respectării unei strategii medicamentoase adecvate.
Cuvinte cheie: subiecţi cu vârsta peste 80 ani, dinamica parametrilor metabolici, prevalenţa factorilor de risc metabolic şi aterogen, studiu de corelaţie

INTRODUCTION

A number of longitudinal studies have evaluated changes in metabolic indicators during the aging process [1, 2, 3, 4]. Although ageing may occur even in the absence of diseases
(e.g., centenarians), ageing may be a major risk factor for most disorders with a significant public health impact [5]. These are known as age-related diseases and include chronic metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease (CVD), cancer, neurodegenerative diseases and kidney diseases. Some diseases associated with the aging process can also be found in young adults. Among the mechanisms involved in the aging process and in the pathological conditions associated or not with the aging process can be included the modifications of some metabolic pathways. To establish the involvement of metabolic parameters in the development of diseases associated with aging was investigated the metabolic indicators changes in the elderly with different pathological states [3, 6, 7, 8]. Changes in circulating glucose, lipid, and plasma lipoprotein levels were observed in subjects over 65 years of age, the elderly over 85 years of age, in apparently healthy nonagenarians, but also in the centenarians [9]. Mortality studies have also been performed in the old subjects and the elderly related to changes in lipid profile in order to assess their association with mortality rate [10-13]. Studies have been performed to establish the efficacy and / or need for the implementation of a lipid-lowering drug treatment in old and elderly subjects with cardiovascular disease, or atherosclerosis who have high levels of total cholesterol and / or LDL cholesterol [14, 15]. In this context, the aim of the study is to highlight the dynamics of metabolic parameters, to calculate the prevalence of atherogenic risk factors and the correlation of metabolic parameters in elderly subjects (over 85 years of age).

MATERIAL AND METHODS

Experimental groups: The study included 112 subjects over the age of 80. The subjects were informed about the purpose of the study and the confidentiality of personal data. They were included in the study only after giving their written consent.

Subjects were grouped according to age: A) subjects aged between 80 and 84 years old as control; B) subjects aged between 85 and 89 years old and C) subjects aged over 90 years old.

Determinations: Systolic and diastolic blood pressure, anthropometric and metabolic parameters were measured. Measurement of anthropometric parameters such as body weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR), waist-height ratio (WHtR), body fat index (BAI) was performed in subjects from the three age groups. Serum metabolic parameters were evaluated: glucose, creatinine, urea, uric acid, total cholesterol (CT), HDL-cholesterol (HDLc), non-HDL-cholesterol (non-HDLc), LDL-cholesterol (LDLc), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein. Were calculated: ratios CT/HDLc, LDLc/HDLc, non-HDLc/HDLc, TG/HDLc, TyG index; prevalence of atherogenic risk factors and correlation of metabolic parameters with the age of the subjects.

Statistical analysis: The results were expressed as mean ± standard deviation. The comparison between the two results was achieved by Student's "t" test, and the values for $p < 0.05$ were considered significant. For the calculation of "t" and the correlation coefficient r (Pearson) the program Microsoft Office Excel was used.

RESULTS

No anthropometric parameters changed significantly in subjects in the 85-89 and 90+ age groups. The measurements showed that there was a tendency to reduce

body weight, BMI, waist and hip circumference, waist to hip and waist to height ratios and BAI in 85-89 year-old subjects and those over 90 years compared to subjects in the age group 80-84 years (Tab. I). Systolic (138±26 mm Hg) and diastolic (78±9 mm Hg) blood pressure increased significantly in subjects aged 85-89 years compared with subjects aged 80-84 years. In subjects in the age group 90 years and over systolic blood pressure increased significantly compared to subjects aged 80-84 years and those aged 85-89 years. At the same age group, diastolic blood pressure increased significantly compared to subjects aged 80-84 years (Tab. I).

Tab. I Basic characteristics of patients over 80 years

Age (Years) / **Parameter**	**A** **80 – 84**	**B** **85 – 89**	**C** **90 +**
Age (years)	82.02 ± 1.36	86.66 ± 1.24	92.36 ± 2.26
Number Sex (W/M) (n,%)	36 (33W / 3M)	57 (37W / 20M)	19 (12W / 7M)
TA syst (mmHg)	128 ± 7	138 ± 26 **p = 0.0261 vs A**	156 ± 20 **p = 0.0013 vs A** **p = 0.0448 vs B**
TA diast.(mmHg)	73 ± 4	78 ± 9 **p= 0.0039 vs A**	83 ± 9 **p = 0.0054 vs A**
Weight (kg)	65.62 ± 13.03	66.85 ± 12.46	63.00 ± 12.20
Hight (cm)	156 ± 8	160 ± 10	158 ± 10
BMI (kg/m2)	26.72 ± 4.98	26.07 ± 4.45	25.17 ± 4.11
Waist (cm)	96.91 ± 14.39	94.15 ± 12.09	90.58 ± 8.88
Hip (cm)	105.95 ± 12.89	103.97 ± 11.84	100.76 ± 8.75
Waist-Hip ratio	0.90 ± 0.04	0.90 ± 0.05	0.89 ± 0.05
Waist-Hight ratio	0.61 ± 0.08	0.59 ± 0.07	0.57 ± 0.06
BAI (%) (body adiposity index)	35.08 ± 5.74	33.82 ± 6.87	32.98 ± 5.89

Some metabolic parameters changed with age (Tab. II). Thus, there was a significant increase in serum creatinine in patients aged 90 years and over compared to patients aged 80-84 years and those aged 85-89 years (p=0.02). Serum urea levels showed an increase close to the statistically significant limit in 90-year-old subjects compared to subjects in the other age groups. Also, results showed significant reductions in total cholesterol in patients 85-89 years old (p<0.001) and those over 90 years old (p=0.009) compared with those of 80-84 years. LDLc significantly decreased (p<0.001) in subjects 85-89 years old and over 90 years old compared with those of 80-84 years old.

Tab. II Metabolic profile in very old people

Age (years) / **Parameter**	**80 – 84 (A)**	**85 – 89 (B)**	**p**	**90 + (C)**	**p**
Age (years)	82.02 ± 1,36	86.66 ± 1,24		92.36 ± 2,26	
Glucose (mg/dl)	100 ± 18	109 ± 38	0.14693	98 ± 26	0.749377 vs A 0.449061 vs B
Creatinine (mg/dl)	0.96 ± 0,17	0.99 ± 0,24	0.432888	1.34 ± 0.79	**0.02 vs A, B**
Urea (mg/dl)	47.72 ± 14,34	48.78 ± 16,48	0.750234	60.64 ± 36.18	0.06007 vs A 0.05746 vs B
Uric acid (mg/dl)	5.77 ± 1,82	5.98 ± 1,92	0.608443	6.07 ± 1.74	0.893407 vs A 0.787321 vs B

CT (mg/dl)	217.19 ± 35,82	180.12 ± 42,98	**< 0,001**	191.35 ± 37.85	**0.009 vs A** 0.551189 vs B
HDLc (mg/dl)	56.91 ± 14,81	57.06 ± 20,29	0.966325	56.15 ± 16.35	0.669319 vs A 0.667885 vs B
LDLc (mg/dl)	141.41 ± 28,62	106.82 ± 27,22	**< 0.001**	110.00 ± 27.15	**0.001 vs A** 0.535948 vs B
Non-HDLc (mg/dl)	160.19 ± 36.50	126.44 ± 31.16	**<0.0001**	134.22 ± 39.19	**0.019 vs A** **0.0388 vs B**
TG (mg/dl)	112.93 ± 39,95	99.63 ± 34,62	**0.034275**	97.57 ± 27,68	**0.011177 vs A** 0.382553 vs B
TyG index	8.60 ± 0.39	8.51 ± 0.32	0.31013	8.41 ± 0.37	0.08885 vs A 0.40667 vs B
CT / HDLc	4.024 ± 1,157	3.520 ± 1,190	**0.0467**	3.810 ± 1,551	0.57102 vs A 0.420206 vs B
LDLc / HDLc	2.658 ± 0,955	2.110 ± 0,872	**0.0055**	2.305 ± 1.193	0.24435 vs A 0.455102 vs B
Non-HDLc / HDLc	3.023 ± 1.155	2.522 ± 1.195	**0.046**	2.817 ± 1.570	0.587 vs A 0.396 vs B
TG / HDLc	2.223 ± 1,060	2.041 ± 1,124	0.439663	1.940 ± 1.168	0.37658 vs A 0.74377 vs b
AST (U/l)	24.50 ± 12.52	23.65 ± 11.88	0.742597	17.50 ± 5.61	**< 0.1 vs A, B**
ALT (U/l)	20.97 ± 16.83	17.51 ± 8.31	0.189671	9.71 ± 2.92	**< 0.1 vs A, B**

Non-HDLc significantly decreased in patients 85-89 years old ($p < 0.0001$) and over 90 years old ($p=0.0197$). Triglycerides significantly decreased in patients 85-89 years old ($p=0.034$) and in those of 90 + years old ($p=0.011$). Also, were significantly reduced the ratios CT/HDLc ($p=0.0460$), LDLc/HDLc ($p=0.005$) and non-HDLc/HDLc ($p=0.0466$) in subjects aged 85- 89 years old compared those of 80-84 years old (Tab. II, Fig. 1). Aspartate amino transferase (AST) and alanine aminotransferase (ALT) values were significantly lower only in patients 90+ ($p<0.01$) compared to values in patients 80-84 and 85-89 years (Tab. II).

Some metabolic parameters, under certain conditions, can be risk factors for diseases such as type 2 diabetes, atherosclerosis, dyslipidemia, etc. Metabolic risk factors are considered glucose>110 mg/dl, CT >220 mg/dl, LDLc 130 mg/dl, TG > 150 mg/dl and HDLc at values <40 mg /dl in men and <50 mg/dl in women. We aimed to evaluate the prevalence of these metabolic risk factors in elderly subjects grouped in the three groups, depending on age: A-80-84 years, B-85-89 years and C-90 and over.

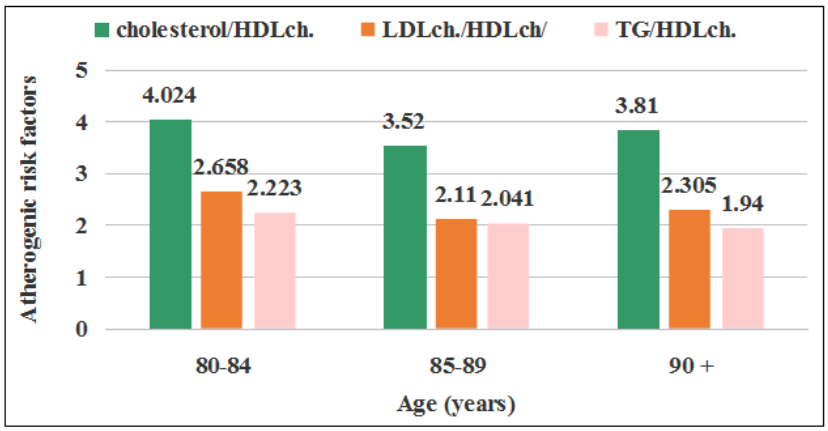

Fig. 1 Atherogenic risk factors in very old subjects related to their age

The evaluation showed that a significant number of patients of all ages are at metabolic risk for some diseases, such as type 2 diabetes, cardiovascular disease or atherosclerosis (Fig. 2). Serum glucose values above 110 mg/dl were 22.22% of patients aged 80-84 years, 21.05% of patients in the 85-89 age group and only 10.53% of patients aged 90 and over.

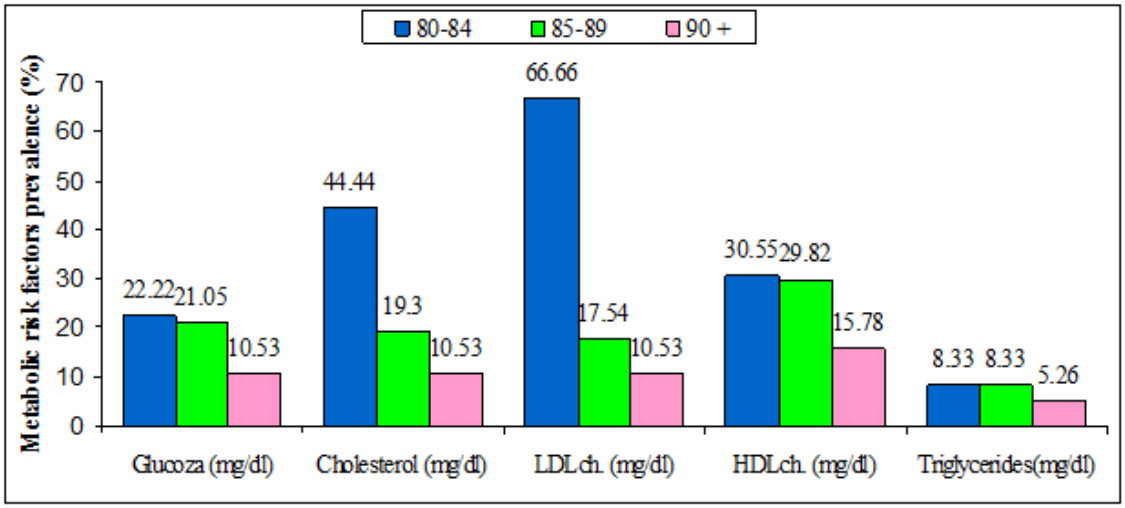

Fig. 2 Prevalence of metabolic risk factors in very old subjects (%)
Legend: 1- Glucose > 110 mg/dl; 2 – CT > 220 mg/dl; 3 – LDLc > 130 mg/dl; 4 – HDLc < 40 mg/dl(men)/50 mg/dl (women); 5 – TG > 150 mg/dl

Values greater than 220 mg/dl of CT were measured in 44.44% of patients in the 80-84 age group, in 19.30% of patients in the 85-89 age group, and in 10.53% in patients aged 90 and over.

Values greater than 130 mg/dl of LDLc were reported in 66.66% of patients in the 80-84 age group, 17.54% in patients in the 85-89 age group, and 10.53% in patients aged 90 years and over.

Values greater than 150 mg/dl of serum TG levels were observed in 8.33% of patients in the 80-84 age group, in 8.33% of patients in the 85-89 age group, and in 5.26% of patients over 90 years of age.

Values lower than 40 mg/dl in men and lower than 50 mg/dl in women were registered in 30.55% of patients in the age group 80-84 years, in 29.82% in patients in the group 85-89 years, and in 15.78% of patients over 90 years of age.

It is estimated that high cardiometabolic risk requires the presence of 2 or more CVD risk factors: Ex: increase in BP + glucose >110 mgdl + Tg >130 mg/dl (or HDLc <40 mg/dl for men and < 50 mg/dl for women).

It is known that the ratios of CT/HDLc, LDLc/HDLc, TG/HDLc most accurately express the high risk for the development of atherosclerosis, being considered atherogenic risk factors. Thus it was shown that the values for the ratios: CT/HDLc >5 for men and >4.5 for women; LDLc/HDLc >3.5 in men and >3 in women and TG/HDLc >3.5 in men and >2.5 in women has atherogenic risk. Our results showed that in all age groups there are patients with atherogenic risk (Fig. 3).

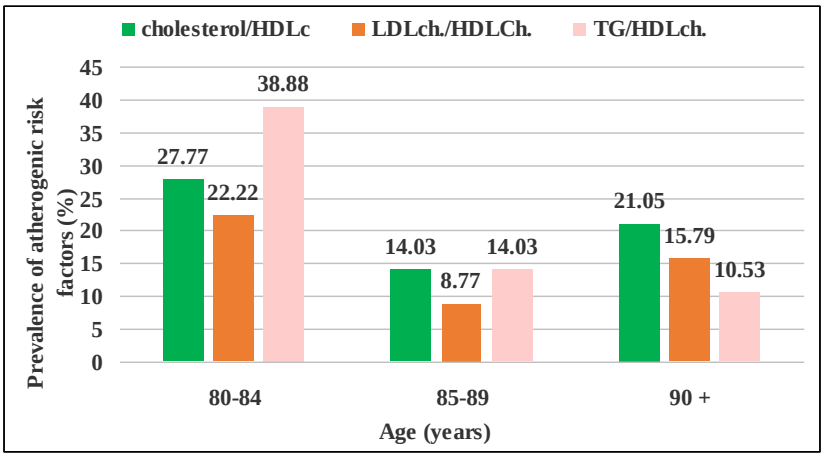

Fig. 3 Prevalence of the atherogenic risk factors in the very old patients (%)
Ratios significance of atherogenic risk is: CT/HDLc > 5M/4.5W;
LDLc / HDLc > 3.5M/3W and TG/HDLc > 3.5M/2.5W

Patients in the 80-84 age group (control) have the highest prevalence of atherogenic risk factors: 27.77% for CT/HDLc, 22.22% for LDLc/HDLc and 38.88% for TG/HDLc, compared to patients aged 85-89 years and those aged 90 years and older. The lowest prevalence of LDLc/HDLc was recorded in patients aged 85-89 years and the lowest prevalence of TG/HDLc was in patients older than 90 years (Fig. 3).

In order to better highlight that the aging process has an important role in inducing metabolic changes in the elderly, we conducted studies correlating the metabolic parameters with the age of the patients studied. The results of the correlations between the metabolic parameters and the age of the patients are presented in Tab. III. Significant positive correlations with subjects age were found for creatinine ($r=0.27906$; $p<0.01$) and urea ($r=0.28249$; $p<0.01$). Significant negative correlations with age were found for CT ($r= -0.2532$; $p< 0.02$), LDLc ($r= -0.3473$; $p<0.001$) and non-HDLc ($r= -0.2476$; $p<0.01$). Atherogenic risk factors did not correlate with patients' age.

Transaminases, aspartate aminotransferase ($r= -0.2004$; $p<0.05$) and alanine amino-transferase ($r = - 0.3284$; $p <0.01$) correlated significantly negatively with patient age.

Tab. III Pearson correlations of the metabolic parameters with age in very old people

Parameter	R^2	r	T exp.	p
Glucose (mg/dl)	0.00065	0.02567	0.278	> 0.05
Creatinine (mg/dl)	0.0778	**0.27906**	3.0199	< **0.01**
Urea (mg/dl)	0.0225	**0.28249**	2.9695	< **0.01**
Uric acid (mg/dl)	0.0026	0.05069	0.5275	> 0.05
CT (mg/dl)	0.0595	**-0.2532**	2.7133	< **0.02**
HDLc (mg/dl)	0.0024	-0.0487	0.5067	> 0.05
LDLc (mg/dl)	0.1206	**-0.3473**	3.8488	< **0.001**
Non-HDLc (mg/dl)	0.06131	**-0.2476**	2.6558	< **0.01**
TG (mg/dl)	0.0225	-0.1501	1.5778	> 0.05
TyG index	0.01973	-0.14047	1.488	> 0.05
CT / HDLchol	0.00064	-0.02539	0,3618	> 0.05
LDLc / HDL chol	0.01147	-0.1071	1.1195	> 0.05
Non-HDLc / HDL chol	0.00048	-0.0219	0.2278	> 0.05
TG / HDLc	0.00413	-0.0643	0.6702	> 0.05
AST (U/L)	0.0402	**-0.2004**	2.1259	< **0.05**
ALT (U/L)	0.1078	**-0.3284**	3.6131	< **0.01**

DISCUSSIONS

Previous longitudinal studies have evaluated changes in carbohydrate, lipid, and nucleoprotein metabolism in aging and the possibility that these transformations may be risk factors for some pathological conditions associated with the aging process. Thus, an increase in circulating glucose levels and the incidence of developing type 2 diabetes has been observed with age. There has also been an increase in serum uric acid content, which may indicate altered energy metabolism in aging. Regarding the lipid profile, the age-induced changes in the serum content of total cholesterol, lipoproteins such as LDLc and HDLc, and TG were followed. A different pattern of age-related changes in lipid metabolism parameters was observed in women and men [1, 2]. Women had higher concentrations of total cholesterol, LDLc and HDLc than men in all investigated age groups: 65-69 years, 70-74 years, 75-79 years, 80-84 years, >85 years [1, 2, 3]. TG content was similar in men and women [1,2], except for women aged 80 -84 years (131±66 mg/dl) and over 85 years (133±57mg/dl) [1], in which TG have significantly higher values compared to men in the same age groups (124±52 mg/dl and 115±72 mg/dl, respectively). Women had a lower CT/HDLc ratio except for those over 85 years of age. After the age of 65, there is a reduction in the plasma total cholesterol content, especially in men [1]. Thus, the CT level in men decreased significantly ($p \leq 0.0001$) from 205±35 mg/dl at the age of 65-69 years to 188±33 mg/dl at the age of over 85 years. In women, the CT level decreased significantly ($p \leq 0.01$) from 226 ±39 mg/dl at the age of 65-69 years to 219±43 mg/dl at the age of over 85 years. LDLc concentrations decreased significantly ($p \leq 0.0001$) in older men, especially in those over 85 years of age (114±29 mg/dl) compared to those aged 65 to 69 years (130±32 mg/dl). Women did not show LDLc reductions with age: 135±39 mg/dl at over 85 years compared with 139±37 mg/dl at 65 to 69 years. There were no significant changes in HDLc in women over 85 years of age (57±16 mg/dl) compared with those aged 65 to 69 years (59±16 mg/dl), while men over 85 years of age years had significantly higher HDLc values ($p \leq 0.0005$) (51±14 mg/dl) compared to those aged 65-69 (48±13 mg/dl). The CT/HDLc ratio decreased significantly ($p \leq 0.0001$) only in men (from 4.61±1.32 to 4.49±1.29). Analyzing the relationship between lipid and plasma lipoprotein levels and the incidence of cardiovascular disease in 75-year-old subjects, in a 10-year longitudinal study (75-85 years) some authors [2] showed a high level of LDLc (≥171 mg/dl) was associated with myocardial infarction in women, and consistently low levels of HDLc (≤30 mg/dl) were independently associated with the development of myocardial infarction. Studies in subjects over 90 years of age have shown that a high concentration of TG has been associated with a lower risk of cognitive decline, ADL decline, frailty aggravation, and mortality [14]. This paradox suggests the clinical importance of revising the "less better" concept for older subjects.

Our results are in agreement with those of other authors regarding the significant reduction of total cholesterol and LDLc in elderly subjects over 85 years of age (Tab. II). We also noted a significant reduction in non-HDLc, TG, and atherogenic risk factors: CT/HDLc, LDLc/HDLc, and non-HDLc/HDLc (Tab. II), in elderly subjects over 85 years of age, although the analyzed age range was quite narrow, and the control was represented by subjects aged between 80-84 years. Our study also showed a significantly positive correlation between serum creatinine and urea levels, and a significant negative correlation between total cholesterol, LDLc, non-HDLc, and the CT/HDLc ratio with the age of the subjects investigated (Tab. III).

Data from the literature have analyzed the relationship between total cholesterol and LDL cholesterol values and mortality in the elderly [7, 8, 12, 13, 16, 17, 18]. Most works showed that there was no association, or an inverse association, between LDLc and mortality in the elderly. In a review, Ravnskov et al (2016) investigated 19 studies that included 30 cohorts with a total of 68,094 elderly subjects (≥60 years), where the all-cause mortality rate was addressed in 28 cohorts and mortality associated with cardiovascular disease in 9 cohorts. The conclusion of the study was that elevated LDLc levels were inversely associated with the mortality rate in most subjects over 60 years of age. Because older people with high LDLc values lived as long or even longer than those with low LDLc, the paper discusses the role of the cholesterol hypothesis that predicts that LDLc is associated with increased mortality from multiple causes or cardiovascular disease. Recently Ravnskov [15, 20] presented new arguments for people with high LDLc to live longer than those with normal or low LDLc. It suggests that high LDLc is beneficial because it most likely modulates the immune response by adhering and inactivating microorganisms and their toxic products. It suggests that high LDLc is beneficial because it most likely modulates the immune response by adhering and inactivating microorganisms and their toxic products.

The international MONDO (Monitoring Dialysis Outcomes) study [19] used data from 37,250 patients to evaluate the association between lipids and infection-related or cardiovascular mortality. The results showed that higher LDLc, HDLc and TG were independently associated with lower all-cause death risk. LDLc and TG were not associated with cardiovascular death, and HDLc was associated with lower cardiovascular risk. Higher LDLc and HDLc were associated with a lower risk of death from infection or other non-cardiovascular causes.

Other longitudinal studies have shown that subjects aged 75 to 85 years and over 85 years, women and men with low total cholesterol and LDLc had a lower survival rate compared with subjects with high CT and LDLc values [10]. These results suggest that low CT and low LDLc may be independent predictors of increased mortality in the very elderly [18].

Studies concerning the relationship between CT, LDLc and HDLc levels and mortality from specific causes [21] evidenced that, in the oldest people aged 85 years, HDLc but not total or LDLc, is associated with mortality from coronary artery disease and stroke. Low HDLc level was associated with a 2- to 3-fold higher risk of fatal cardiovascular disease. LDLc and HDLc levels were inversely associated with all-cause mortality mainly because mortality from infections. Although the present strategies in cholesterol intervention are based on lowering LDLc level in middle and old age, this paper suggests that increasing HDLc levels is more advantageous than lowering total cholesterol among old people.

Moreover, recent studies show changes in metabolism in the elderly and centenarians [9]. Significant differences was obtained for blood glucose, ALT, CT reduced in centenarians respect to the old subjects (age range 65-85 years old), whereas blood urea nitrogen were significantly increased in centenarians.

Population aging is a global problem that is becoming more serious and raising new challenges for public health. That is why it is important to study models of healthy aging and extreme longevity: centenarians (≥100 years), semisupercentenarians (≥105 years), and supercentenarians (≥110 years) [22]. Biochemical measurements in two long-lived sisters, D: 114 years and F: 105 years, showed that F had higher values than the reference values for CT (248 mg/dl) and LDLc (178 mg/dl). Both sisters had lower albumin values (D: 34.7 g/l and F: 34.1 g/l) and HDLc (D: 38 mg/dl and F: 50 mg/dl) and higher values for urea (D:

49.7 mg/dl and F: 73.4 mg/dl) compared to the values in the reference range. These measurements were supplemented with anthropometric, body composition, inflammatory and oxidative status measurements. The authors suggest that supercentenarians and semi-supercentenarians have a relative increase in resistance to diseases associated with aging, and inflammatory status and oxidative stress play a role in predicting mortality in centenarians.

CONCLUSIONS

Metabolic parameters undergo significant changes in very old subjects. Reduction of transaminase activities, and some lipid parameters, within the reference range considered normal, in subjects over 85 years may illustrate an apparently healthy aging due to a healthy lifestyle adoption and/or adherence to an appropriate medication strategy. Our results are consistent with those of other authors.

Although high levels of CT, LDLc and TG are risk factors for cardiovascular disease in adults, they are associated with a low risk for all-cause and cardiovascular mortality in elderly.

Our and other researchers' findings draw attention to the relationship between serum lipid and lipoprotein concentration and age on the one hand, and the need for the use of lipid-lowering drugs (such as statins) in the elderly. The strategy used must take into account a balance between risk and benefit for the patient.

Conflicts of interest

The authors declare no conflicts of interest.

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COVID-19 IMPACT ON SENIOR PATIENTS WITH CARDIOVASCULAR DISEASE. ROLE OF COMPLEX GERIATRIC EVALUATION IN REHABILITATION

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Abstract. According to recent data, pre-existing cardiovascular pathology is among the factors associated with increased mortality in COVID-19. The potentiation of the precursors of fragility and the increase the risks of physical, cognitive and emotional decline have been precipitated especially in the most vulnerable segment – elderly people. The present paper refers to the top comorbidities that predispose the elderly to moderate-severe forms of COVID-19. In these situations, geriatric reassessment is required to assess the complex impact of the infection on the pluripathology of the elderly, especially in terms of cardiovascular, cognitive and last but not least, quality of life point of view. Cardiovascular re-evaluation will also allow a complex therapeutic re-evaluation of these patients, with the reconciliation of previous therapeutic regimens according to the post-COVID-19 situation. We could concluded that cardiovascular disease, obesity, fragility, cognitive or psycho-emotional disorders, in the context of SARS-COV2 infection, lead to the induction of an acute status of systemic inflammation, predisposing the elderly to severe disease. The post-COVID-19 recovery of these patients remains an open topic for research, as cases of "post-COVID syndrome" require a holistic, diversified and individualized therapeutic approach.
Key words: COVID-19, cardiovascular disease, comorbidities, elderly

Rezumat. Potrivit datelor recente, patologia cardiovasculară preexistentă se numără printre factorii asociați cu creșterea mortalității în COVID-19. Potențarea precursorilor fragilității și creșterea riscurilor de declin fizic, cognitiv și emoțional s-au precipitat în special în segmentul cel mai vulnerabil – persoanele în vârstă. Lucrarea de față se referă la principalele comorbidități care predispun vârstnicii la forme moderat-severe de COVID-19. În aceste situații se impune reevaluarea geriatrică pentru a evalua impactul complex al infecției asupra pluripatologiei vârstnicilor, mai ales din punct de vedere cardiovascular, cognitiv și nu în ultimul rând, al calității vieții. Reevaluarea cardiovasculară va permite și o reevaluare terapeutică complexă a acestor pacienți, cu reconcilierea regimurilor terapeutice anterioare în funcție de situația post-COVID-19. Am putea concluziona că bolile cardiovasculare, obezitatea, fragilitatea, tulburările cognitive sau psiho-emoționale, în contextul infecției cu SARS-COV2, conduc la inducerea unui status acut de inflamație sistemică, predispunând vârstnici până la boală severă. Recuperarea post-COVID-19 a acestor pacienți rămâne un subiect deschis de cercetare, deoarece cazurile de „sindrom post-COVID" necesită o abordare terapeutică holistică, diversificată și individualizată.
Cuvinte cheie: COVID-19, boli cardiovasculare, comorbidități, vârstnici

INTRODUCTION

In the context of biological aging, to senior patients, a multitude of conditions that make them more susceptible to the disease add up. There exists, however, variability in the means of response to pathological phenomena. In this sense, it seems that a number of factors, such as age segment, degree of fragility or individual resilience play an important role. Therefore, the evolution or prognosis of senior patients, regardless of associated comorbidities, can sometimes be difficult to predict, even under a standard, well-known therapeutic approach [1, 2].

Moreover, the phenomenon of a new disease - such as the COVID-19 pandemic - with a treatment in the experimental stage, makes it difficult to predict the evolution of the elderly patient and is a challenge for clinicians, requiring them to reconsider how to evaluate and approach [3, 4].

The COVID-19 pandemic had an important resonance globally, but by far

the most vulnerable segment was the elderly population. In this new context of the disease, the potentiation of the precursors of fragility and the increase of the risks of physical, cognitive and emotional decline have precipitated. With measures to prevent the spread of the disease and restrict access to health services, the following have worsened: depression, sleep disorders, the risk of falling, pain, stigma and self-stigmatization. Conversely, factors varied, such as: quality of life with its subsidiary elements (e.g. access to a proper diet, access to physiotherapy / physiotherapy programs, control of the acute pain component), physical condition, and vitamin D production [5].

According to statistics, the highest mortality rate due to COVID-19 was recorded in elderly patients. Apparently, the highest percentages were reported at the beginning of the pandemic, in outbreak areas such as Lombardy or Madrid. Also, early data in 2019 from China signaled an increased predisposition to severe forms of disease and mortality, including in the young elderly which associated significant comorbidities. Preliminary descriptive reports of the evolution of patients with COVID-19 in the US, showed that the fatality was 10-27% in the elderly over 85 years, followed by 3-11% in those between 65-84 years [6-8].

The same data did not report deaths among young people under 19 years of age. Also, the most severe results were later related, also among the elderly, to prolonged hospitalizations in ICU wards.

The present paper refers to the top comorbidities (mainly cardiovascular damage) that predispose the elderly to moderate-severe forms of COVID-19 and which, in turn, are strongly affected by viral infection and/or its treatment. In these situations, geriatric reassessment is required to assess the complex impact of the infection on the pluripathology of the elderly, especially in terms of cardiovascular, cognitive and last but not least, quality of life point of view.

Subsequent research, relying on longer experiences, will investigate the feasibility of these perspectives, as modern medicine is, according to more sensitive predictions, at the confluence of fundamental changes in the epidemiological future.

Cardiovascular damage - risk factor that predisposes the elderly to moderate and severe forms of COVID-19 pathology

According to recent data, pre-existing cardiovascular pathology is among the factors associated with increased mortality (10.5%) in COVID-19, followed by diabetes (7.3%), chronic respiratory failure (6.3%), hypertension (6%), neoplasm (5.6%) and the group without associated comorbidities (0.9%) [9].

The same data show that cardiac biomarkers, such as HS troponin, can be detected at the onset of symptoms and have prognostic value. The continuous increases in troponin, together with the high level of cytokines predict the need for hospitalization in the ICU department and tracheal intubation, also predisposing to vascular complications. Increased NTproBNP may predict the risk of myocarditis or heart failure [9-11].

The older the age segment, the more numerous and forceful the cardiovascular consequences of COVID-19 are.

The pathogenic mechanisms by which viral infection affects the cardiovascular system are direct cardiac injury / stress, attachment of viral antigen to T cells, endothelium and inflammation.

SARS-Cov-2 has an early impact on the heart and metabolic abnormalities that characterize elderly patients.

In the subsequent stages of the infection, the storm of harmful cytokines exacerbates the pro-inflammatory state, leading to cardiovascular events and organ failure [1-14].

A US study from March 2020, included in a review that looked at the characteristics

of patients with cardiovascular comorbidities and COVID-19 pathology, showed that the highest rate of cardiovascular events (60.4%) was recorded in the age segment over 80 years, with a much higher incidence in women (68.3%) [15-17].

Other data suggest the direct impact of SARS-Cov 2 infection on the myocardium, by using the angiotensin 2 conversion enzyme receptor to enter the cell. The infection can cause myocardial injury, acute coronary syndrome or cardiac arrhythmias and can be associated with haemostatic disorders and elevated troponin levels.

Procoagulant status results in venous thromboembolism, myocardial infarction or, in the case of an additional hemostatic disorder, disseminated intravascular coagulation [15,18-20]. Coagulation disorders appear to be triggered by an inflammatory response that leads to endothelial and hemostatic activation, with an increase in von Willebrand factor and tissue factor.

Researchers warn clinicians about certain drugs used in the treatment of COVID-19 that have cardiovascular side effects [15]. Thus, drugs used to counteract the invasion / replication of the virus, such as antimalarials (chloroquine / hydroxyl-chloroquine), protease inhibitors (lopinavir / ritonavir) and macrolides (azithromycin) may prolong the corrected QT interval (QTc) and increase the risk of polymorphic ventricular tachycardia. In addition, chloroquine and hydroxychloroquine, which have been shown to be effective in antiviral therapy, also appear to predispose to sinoatrial or atrioventricular block and ventricular arrhythmias.

The cytokine storm triggered by the viral infection induces hyperactivation of the cardiac sympathetic system, increasing electrical instability of the heart [21] and predisposes to arrhythmic events, including malignant ventricular arrhythmias. IL-6 promotes the prolongation of QTc both directly, by modulating the ion channels of cardiomyocytes, and indirectly, by increasing the bioavailability of concomitant drugs that prolong QT. Also, plasma TnT levels in patients with COVID-19 were significantly correlated with both plasma levels of high-sensitivity C-reactive proteins and of NT-proBNP [13, 22, 23].

Evaluation of cardiovascular complications of COVID-19 pathology and cardiovascular rehabilitation

The most common cardiovascular complications recorded during / after COVID-19 infection are: various arrhythmias, heart failure with decreased ejection fraction, and severe myocarditis with systolic dysfunction. For these reasons, after curing the viral infection, elderly patients need a careful and complex cardiovascular reassessment to detect possible cardiac sequelae (laboratory tests, ECG, 24-hour ECG, echocardiogram, cardiopulmonary exercise tests and / or cardiac MRI). These investigations will also evaluate the evolution of pre-existing and neglected cardiovascular diseases during COVID-19 infection.

Cardiovascular re-evaluation will also allow a complex therapeutic re-evaluation of these patients, with the reconciliation of previous therapeutic regimens according to the post-COVID-19 situation. A variable period of post-infection rest, depending on the symptoms and complications, will reduce the risk of post-infection heart failure, secondary to myocarditis [13].

In the presence of a newly diagnosed cardiac pathology or worsening of the pre-existing one, specific cardio-respiratory rehabilitation programs will be developed in collaboration with specialists in the field, in order to improve cardiac and respiratory functions, but also to improve the physical abilities and quality of life of the patient.

Assessment of cognitive impairment and psychological complications of COVID-19 pathology and psychological rehabilitation

The current literature cites a directly proportional relationship between the severity of COVID-19 forms and the severity of cognitive impairment in the elderly. Stress acts on the rough hypothalamic-pituitary axis and generates an increase in the concentration of glucocorticoid hormones and subsequently, an increase in the resistance to them, which seems to stimulate the storm of pro-inflammatory cytokines, just like the SARS viral material. The results show a severity of COVID-19 forms in those with cognitive impairment, but also a worsening of cognitive impairment in the elderly with COVID-19 [8, 24, 25].

The main neuro-cognitive complications of COVID-19 infection are: prolonged confusional states with mental problems, periods of delirium, prolonged states of anxiety and depression, psychosis and dementia. These situations can be prevented or improved by an effective communication of the medical staff with the patient in the acute period. Ensuring a social and family contact with the help of modern technologies helps the elderly patient to overcome the moments of great psychological stress in this phase of the disease.

In the post-COVID-19 period, elderly patients require careful neuro-cognitive reassessment to identify those with psychological adverse reactions as a result of their COVID-19 experiences. Active monitoring (continuous review) should be performed for those with psychological symptoms below the threshold. Psychotherapy and consideration of behavioral cognitive therapy focused on trauma, as well as cognitive processing therapy are useful for those with moderate to severe symptoms of acute stress disorder [13, 26]. Particular importance will be given to the social reintegration of the patient in his familial and home environment, in order to ensure a quality of life as close as possible to that before the COVID-19 infection.

CONCLUSIONS

Comorbidities such as cardiovascular disease, obesity, fragility, cognitive or psycho-emotional disorders associated with increased serum inflammatory cytokines, in the context of SARS-COV2 infection, lead to the induction of an acute status of systemic inflammation, predisposing the elderly to severe disease.

Also, conditions favored by pandemic restrictions such as isolation, poor diet, chronic stress, lack of physical activity, obesity and sleep disorders, in the context of activated proinflammatory cytokines, lead to worsening of common diseases such as cardiovascular disease, immune-senescence, fragility, insulin resistance, sarcopenia and to the promotion of a chronic inflammation status.

In our experience, chronic cardiovascular treatment has been neglected, patients not keeping in touch with the attending physician or family doctor. These cases subsequently required hospitalization in the Geriatrics Clinic, for therapeutic scheme readjustment.

The post-COVID-19 recovery of these patients remains an open topic for research, as cases of "post-COVID syndrome" require a holistic, diversified and individualized therapeutic approach.

Conflicts of interest

The authors declare no conflicts of interest.

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PREDICTION ABILITY OF ATHEROGENIC INDEX AND HEARTSCORE IN DIABETES MELLITUS PATIENTS

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Abstract. Type 2 diabetes mellitus (DM) is associated with changes in lipid metabolism which induce atherogenic risk and also risk of developing cardiovascular diseases. Atherogenic index (AI) can provide information about serum atherogenic status and HeartScore is a useful tool in cardiovascular risk monitoring. The objective of the study was to determine if AI and HeartScore are good cardiovascular risk predictors in older DM patients. Present work included 199 patients: 91 DM and 108 healthy control patients, over 65 years old. Study revealed at DM patients vs. control: increase triglycerides ($p<0.001$), decrease HDL-cholesterol ($p<0.0001$), increase AI ($p<0.01$) and increase HeartScore ($p<0.0001$). Linear regression equation revealed that HeartScore is positive significantly correlated with AI ($r=0.47$; $p<0.0001$). AI test has 90.1% sensitivity, 31.48% specificity, relative risk estimate=2.51; HeartScore test has 93.4% sensitivity, 42.59% specificity, relative risk estimate=5.02. Multivariate logistic regression analysis showed that patients with high AI had 4.18-fold risk for DM [OR 4.18, 95% CI: 1.88-9.30; $p=0.0004$]. Also, patients with high HeartScore were 10.51 times likely to have DM [OR 10.51, 95% CI: 4.22-26.15; $p<0.0001$]. There is a strong direct correlation between AI, HeartScore and DM: as AI/HeartScore increases, the more likely it is to develop DM. Our results suggest that AI and HeartScore could be used in predicting cardiovascular complications at DM patients.
Key words: type 2 diabetes mellitus, atherogenic index, HeartScore, older patients

Rezumat. Diabetul zaharat tip 2 (DM) este asociat cu modificări ale metabolismului lipidic care induc riscul aterogen şi, de asemenea, riscul de a dezvolta boli cardiovasculare. Indexul aterogenic (AI) poate furniza informaţii despre starea aterogenă serică, iar HeartScore este util în monitorizarea riscului cardiovascular. Obiectivul studiului a fost de a determina dacă AI şi HeartScore sunt buni predictori de risc cardiovascular la pacienţii vârstnici cu DM. Cercetarea de faţă a inclus 199 pacienţi: 91 DM şi 108 pacienţi sănătoşi control, cu vârste peste 65 de ani. Studiul a evidenţiat la pacienţii cu DM faţă de control: creştere a trigliceridelor ($p<0.001$), scădere a HDL-colesterolului ($p<0.0001$), creştere a AI ($p<0.01$) şi o creştere a HeartScore ($p<0.0001$). Ecuaţia de regresie liniară a arătat că HeartScore este pozitiv semnificativ corelată cu AI ($r=0.47$; $p<0.0001$). Testul AI are sensibilitate de 90.1%, specificitate 31.48%, estimare a riscului relativ=2.51; Testul HeartScore are sensibilitate de 93.4%, specificitate 42.59%, estimare a riscului relativ=5.02. Analiza de regresie multivariată a arătat că pacienţii cu AI ridicat au avut un risc de 4.18 ori mai mare pentru DM [OR 4.18, 95% CI: 1.88-9.30; $p=0.0004$]. De asemenea, pacienţii cu HeartScore ridicat au de 10.51 ori mai mare probabilitatea de a avea DM [OR 10.51, 95% CI: 4.22-26.15; $p<0.0001$]. Există o puternică corelaţie directă între AI, HeartScore şi DM: cu cât AI/HeartScore creşte, cu atât este mai probabil ca pacientul să dezvolte DM. Rezultatele noastre sugerează că AI şi HeartScore ar putea fi folosite în predicţia complicaţiilor cardiovasculare la pacienţii cu DM.
Cuvinte cheie: diabet zaharat tip 2, indice aterogenic, HeartScore, pacienţi vârstnici

INTRODUCTION

For decades, the link between lipoprotein levels and type 2 diabetes mellitus (DM) has been studied [1-4].

In DM and its cardiovascular complications, dyslipidemia has a major role and is one of the most important risk factor [2, 4]. Risk stratification for diabetes should include, besides traditional risk factors, other risk calculators. And a better quality and personalized treatment needs a better stratification [1, 4].

The major cause of morbidity and mortality in DM patients are cardiovascular diseases. Changes in lipid metabolism, including dyslipidemia, raise the risk of cardiovascular diseases. Dyslipidemia is characterized by increased cholesterol, triglycerides, LDL-cholesterol and decreased HDL-cholesterol and also

changes in LDL composition that triggers endothelial dysfunction [1, 4].

It was demonstrated that atherogenic index (AI) is a good indicator for dyslipidemia, diabetes, metabolic syndrome. AI reflects atherogenic potential of full lipoprotein fractions spectrum and has been described as a biomarker of plasma atherogenicity [5-7]; good predictor, very valuable and useful for assessing atherogenic risk. An abnormal report indicates an atherogenic lipid profile and a risk of developing myocardial infarction [8]. Sharaye KO [9] confirmed the statistical reliability of AI as a tool in the assessment of cardiovascular risk factors among non-obese adults.

DM is an important risk factor for several cardiovascular diseases and is associated with 2-4 fold increased cardiovascular morbidity and 1.5 to 3.6 fold increased mortality [10, 11].

The need to estimate total cardiovascular risk in apparently healthy individuals has since 1994 been strongly advocated by the joint recommendations from The European Society of Cardiology, European Society of Hypertension, European Atherosclerosis Society and other societies [12-14]. HeartScore is aimed at optimizing cardiovascular risk reduction and is the interactive version of SCORE - Systematic COronary Risk Evaluation - a cardiovascular disease risk assessment system initiated by the European Society of Cardiology, using data from 12 European cohort studies (N=205,178) covering a wide geographic spread of countries at different levels of cardiovascular risks [14]. This risk estimation is based on the following risk factors: gender, age, smoking, systolic blood pressure and total cholesterol [15]. The program chart shows absolute cardiovascular risk, and the contribution of modifiable risk factors to total risk in a chart of pie. The expected effect of intervention is calculated using large randomized clinical trials in hypertension and hypercholesterolemia. However, the program is designed so that it can be adapted to local conditions (national charts and translation), by National Societies of Cardiology [12-15].

Therefore, study aim to evaluate the utility of AI and HeartScore in DM older patients for prediction of future cardiovascular diseases.

MATERIALS AND METHODS

Subjects

Observational cross-sectional study was conducted among 199 patients (41 men and 158 women) over 65 years old, hospitalized in National Institute of Gerontology and Geriatrics „Ana Aslan". We compared 91 DM patients to 108 control patients. The subjects' selection for the study was made respecting the exclusion and inclusion criteria that were initially set.

Exclusion Criteria: Patients with co-morbid conditions which may affect the values of the laboratory parameters of the study: like hormone-related disorders, stroke, acute and chronic inflammatory state, neoplasia, and liver dysfunction. Written informed consent was obtained from all the study participants prior to their enrollment.

Body mass index was calculated as weight (kg) divided by square of height (m^2).

From lipid serum panel we computed atherogenic index (AI) as log (Triglycerides/HDL-cholesterol) and values are associated with:

- Low risk -0.3 ÷ 0.1
- Medium risk 0.1 ÷ 0.24
- High risk above 0.24

Total cardiovascular risk was estimated with HeartScore, an interactive version of SCORE initiated by the European Society of Cardiology [14].

The HeartScore risk was divided into three subclasses according to the various algorithms [14]:

- Low risk (HeartScore<2%),
- Intermediate risk (HeartScore2% but<5%) and
- High risk (HeartScore>5%)

Blood samples were taken from all participants after 12-14 hours fasting, by venopuncture into vacutainers without anticoagulant. Lipid serum profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) was assayed using commercial laboratory kits on automated analyzer Konelab 301 SC.

Statistical analysis

Data were collected and statistically analyzed through SPSS version 18.0. Graphs and tables are generated with Microsoft Word and Excel program. For quantitative values, results were expressed as means ± S.D. The general characteristics of patients were compared using Student's "t" test for continuous variables. Pearson test was used to compare categorical variables. Correlation between AI and HeartScore was made by linear regression equation. The odds ratios (OR) and their 95% confidence intervals (CI) were estimated by multivariable logistic regression analyses. In all calculations, $p<0.05$ was considered as statistically significant level.

RESULTS

Lipid metabolism disruptions lead to changes in atherogenic status consequently to high risk AI [2, 4, 16, 17].

Tab. I Characteristics of the study patients

	Diabetes mellitus patients (n=91)	**Control (n=108)**
Age (years)	68.50±6.68*	65.25±7.17
Body mass index (kg/m^2)	29.91±4.81***	28.08±4.37
Glycemia (mg/dl)	137.27±45.47^{tt}	97.57±17.31
Cholesterol (mg/dl)	193.52±56.20**	210.51±42.16
Triglycerides (mg/dl)	152.65±72.51*	120.64±69.34
HDL-Cholesterol (mg/dl)	45.39±14.67^{tt}	58.50±21.02
LDL-Cholesterol (mg/dl)	117.22±49.35^{t}	131.00±41.14
Atherogenic index	0.47±0.32^{tt}	0.27±0.31
HeartScore	4.23±2.92^{tt}	2.41±1.90

Results are presented as means±S.D.; $p^{*}<0.001$ vs. C, $p^{**}<0.01$ vs. C, $p^{***}<0.005$ vs. C, $p^{t}<0.05$ vs. C, $p^{tt}<0.0001$ vs. C

As seen in Tab. I, our study revealed increased values of triglycerides ($p<0.001$) at DM patients vs. control group. In contrast, HDL-cholesterol levels were found to be significantly decrease in DM patients when compared to control ($p<0.0001$). On the other hand, atherogenic index and HeartScore values are significantly elevated in DM patients vs. control group ($p<0.0001$).

According to Pearson coefficient, both atherogenic index and HeartScore are negatively correlated with HDL-cholesterol and positively correlated with triglycerides (Tab. II).

Tab. II Correlation of Atherogenic Index and HeartScore with clinical parameters

	Atherogenic Index		**HeartScore**	
	r	p	r	p
Age (years)	-0.02892	0.7856	0.017867	0.867
Body mass index (kg/m^2)	0.050346	0.6358	-0.04463	0.6746
Glycemia (mg/dl)	0.172432	0.1022	0.062666	0.5555
Cholesterol (mg/dl)	0.107325	0.3113	0.141565	0.1809
HDL-Cholesterol (mg/dl)	-0.74826	**<0.0001**	-0.43839	**0.000014**
LDL-Cholesterol (mg/dl)	0.097692	0.3573	0.158093	0.1347
Triglycerides (mg/dl)	0.869801	**<0.0001**	0.433709	**0.000018**
HeartScore	0.470989	**<0.0001**		

r= Pearson correlation coefficient; significant at $p<0.05$

Linear regression equation revealed and a negative significant correlation ($p<0.0001$) between AI and HDL-cholesterol at DM patients (Fig. 1).

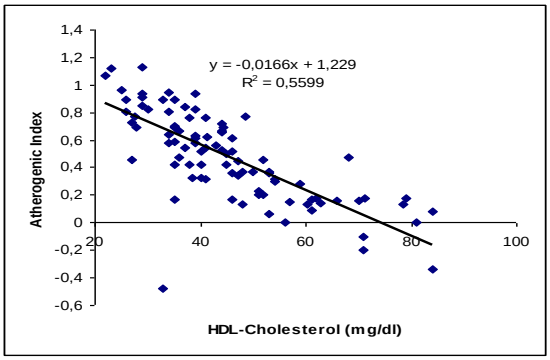

Fig. 1 Correlation between AI and HDL-cholesterol at DM patients
Curve fitting was by linear regression;
r = correlation coefficient

As shown in Fig. 2, correlation between HeartScore and HDL-cholesterol at DM patients is also a negative significant one ($p<0.0001$).

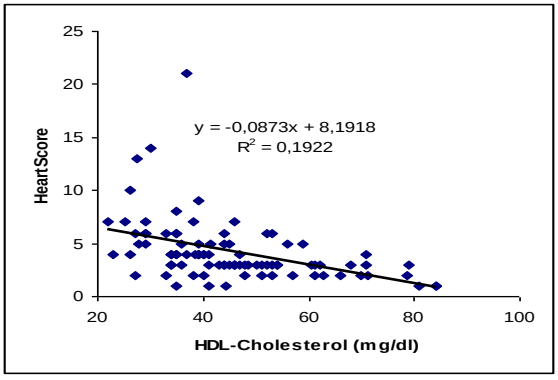

Fig. 2 Correlation between HeartScore and HDL-cholesterol at DM patients
Curve fitting was by linear regression;
r = correlation coefficient

Positive significant association between HeartScore and AI ($p<0.0001$) at DM patients, were also observed (Fig. 3).

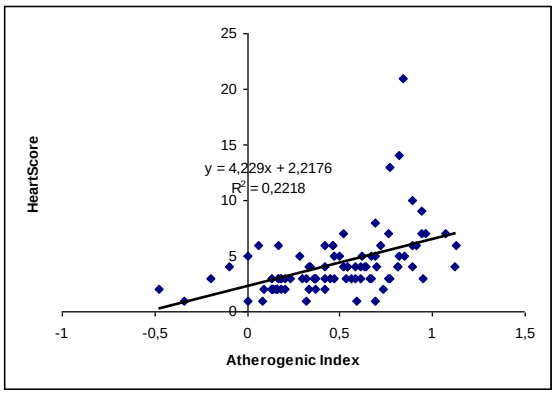

Fig. 3 Correlation between HeartScore and AI at DM patients
Curve fitting was by linear regression;
r = correlation coefficient

AI test has 90.1% sensitivity, 31.48% specificity, relative risk estimate=2.51; HeartScore test has 93.4% sensitivity, 42.59% specificity, relative risk estimate=5.02.

Multivariate logistic regression analysis showed that, compared to low risk, patients with high AI had 4.18-fold risk for DM [OR 4.18, 95% CI: 1.88-9.30; p=0.0004].

Also, patients with high HeartScore were 10.51 times likely to have DM [OR 10.51, 95% CI: 4.22-26.15; p<0.0001].

DISCUSSIONS

Changes in lipid metabolism and dyslipidemia are well known to play in important role in DM development [1, 4, 16]. Studies have shown that in DM many factors may affect lipid metabolism, because of interrelationship between carbohydrates and lipid metabolism. Researchers have shown that lipid abnormalities are prevalent in DM because insulin resistance or deficiency affects key enzymes and pathways in lipid metabolism [18-20].

Kopelman PG [21] reported alteration in lipid profile associated with obesity, elevated LDL-cholesterol and high concentrations of triglycerides which raise the coronary heart disease risk.

By now, numerous studies concluded that AI could be a good marker of plasma atherogenicity, positively correlated with

cardiovascular risk [11, 22-25]. In a study by Nimmamapalli DH et al. [26] and also Ranjit PM et al. [27] it was shown that lipid ratios contribute significantly to the estimation of cardiovascular risk in DM patients.

In the present study we observed significant elevation of AI in DM patients when compared to controls. Similar findings were reported by Hussein TA and Al-Rubaei ZM [18] in their study to assess that elevated AI in DM patients could be used as a marker for predict cardiovascular diseases. These results are also in concordance with a study by Okpa HO et al. [28] who confirmed that patients with DM have high AI and in consequence high cardiovascular risk. Moreover, Zhu XW et al. [29], in a meta-analysis, demonstrated that lipid parameters have the ability to reflect the risk of DM but AI may be more closely associated with the risk of DM.

Multivariate logistic regression analysis of our study showed that high AI had 4.18-fold risk for DM and high HeartScore were 10.51 times likely to have DM. Therefore, there is a strong correlation between AI, HeartScore and DM: the higher AI/HeartScore, the more likely it is to develop DM.

Some limitations should be considered. The paper work is a cross-sectional analysis and cannot set a causal relationship. We study only older patients, not all age group are included. Differences in gender, diet, lifestyle and demographic characteristics could affect AI values. Medications used, especially lipid-lowering drugs, could also interfere. Longitudinal studies are needed to confirm whether AI and HeartScore maintain his prognostic capacity in long term.

CONCLUSIONS

According to our results, at DM patients, despite low levels of LDL-cholesterol, plasma atherogenicity is high and the risk of complications is elevated. Therefore, levels of lipids alone may not always be an accurate indicator of risk at DM patients.

So, AI might be a better and closely marker in risk assessment in DM patients and its association with HeartScore could be helpful in predicting cardiovascular complications.

Conflicts of interest

The authors declare no conflicts of interest.

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PHYSICAL SIGNS AND SYMPTOMS OF BURNOUT IN HEALTHCARE WORKERS DURING COVID-19 PANDEMIC

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Abstract. There has always been a greater predisposition for health personnel to develop burnout syndrome. The new pandemic context, by adding the conditions of restriction, prevention measures in the spread of COVID-19 and excessive media coverage seems to precipitate the mental and physical symptoms of stress. Those in the provision of medical care remain a severely affected category in this regard. Purpose: To monitor the frequency of manifestation of physical symptoms of stress in the medical staff, during the COVID-19 pandemic. Material and methods: The prospective study, from which we present the preliminary data, was performed on a group of 147 subjects, medical staff and auxiliary staff from COVID and non-COVID hospitals from Iași, who gave their free consent to answer questions about the occurrence of reactive symptoms caused by the COVID-19 pandemic. The questionnaire used was adapted according to the original published in 1993 in "In the Tiger's Mouth: An Empowerment Guide for Social Action", intended to investigate burnout syndrome. Particular attention was paid to the physical manifestations of stress. Results: Most frequently answered the nurses (42.2%), representing 45.9% of the staff working in hospitals and the resident doctors (29.3%), representing 27.9% of the staff working in hospitals. Within the studied cases, a share of 31.3% with mild, 46.9% moderate and 21.8% severe physical impairment was noted. Mild impairment of physical functions was more frequently mentioned by subjects from the traumatology specialization (44.1%), and severe impairment of physical functions by subjects from the oncology specialization (27.3%) (p=0.354). Physicians reported more moderate physical impairment (60.9%), while 71.4% of support staff and 50% of nurses reported mild physical impairment (p = 0.139). Conclusions: The results of this study confirm the predictive value of the physical symptoms of stress on the psychic manifestations. The current pandemic context favors a different reactivity to stress, especially to medical staff exposed to multiple consumptive factors.
Key words: burnout syndrome, physical stress symptoms, medical staff

Rezumat. A existat întotdeauna o predispoziție mai mare pentru personalul medical de a dezvolta sindromul de burnout. Noul context pandemic, prin adăugarea condițiilor de restricție, măsuri de prevenire în răspândirea COVID-19 și mediatizarea excesivă pare să precipite simptomele psihice și fizice ale stresului. Personalul medical rămâne o categorie grav afectată în acest sens. Scop: Monitorizarea frecventei de manifestare a simptomelor fizice de stres in cadrul personalului medical, in perioada pandemiei de COVID-19. Material și metode: Studiul prospectiv, din care prezentăm datele preliminare, a fost realizat pe un grup de 147 de subiecți, cadre medicale și personal auxiliar din spitalele COVID și non-COVID din Iași, care și-au dat acordul pentru a răspunde întrebărilor despre apariția simptomelor reactive cauzate de pandemia COVID-19. Chestionarul folosit a fost adaptat conform originalului publicat în 1993 în „In the Tiger's Mouth: An Empowerment Guide for Social Action”, menit să investigheze sindromul burnout. O atenție deosebită a fost acordată manifestărilor fizice ale stresului. Rezultate: Cel mai frecvent au răspuns asistenții medicali (42,2%), reprezentând 45,9% din personalul care lucrează în spitale și medicii rezidenți (29,3%), reprezentând 27,9% din personalul care lucrează în spitale. În cadrul cazurilor studiate, s-a observat o pondere de 31,3% cu deficiențe fizice ușoare, 46,9% moderate și 21,8% severă. Deteriorarea ușoară a funcțiilor fizice a fost mai frecvent menționată de subiecții de la specializarea traumatologie (44,1%), iar afectarea severă a funcțiilor fizice de subiecții de la specializarea oncologie (27,3%) (p=0,354). Medicii au raportat deficiențe fizice mai moderate (60,9%), în timp ce 71,4% din personalul de sprijin și 50% dintre asistente au raportat deficiențe fizice ușoare (p=0,139). Concluzii: Rezultatele acestui studiu confirmă valoarea predictivă a simptomelor fizice de stres asupra manifestărilor psihice. Contextul actual de pandemie favorizează o reactivitate diferită la stres, în special la personalul medical expus la multipli factori de consum.
Cuvinte cheie: sindrom de burnout, simptome de stres fizic, personal medical

INTRODUCTION

The spread of the new outbreak of coronavirus disease (COVID-19) happened very quickly, affecting the entire population of China. The first cases of pneumonia were identified in Wuhan City, Hubei Province, China (Huang et al., 2020). As of March 5, 2019, 80,565 people have been infected in China, with Hubei Province accounting for 67,466 cases. Meanwhile, 14,759 cases have been reported outside China (WHO, 2020a). The World Health Organization (WHO) declared COVID-19 a public health emergency of international interest on 30 January 2020 (WHO, 2020b) [1-5].

As of January 25, 2020, more than forty thousand medical personnel from other provinces have been deployed to Hubei Province in an attempt to prevent an increase in the number of fatal consequences.

Previous research has shown that the burnout syndrome is the result of a permanent imbalance between chronic stress and adequate coping resources. Recent studies have shown a two-way relationship between adverse psychological effects and physical symptoms among those working in the health field during the Covid-19 pandemic [6-8]. Under conditions of somatization of mental stress or traumatic events, they appear to develop physical symptoms which they interpret in the context of a possible infection. Thus, a vicious circle of distortions is outlined and maintained, with the over-excitement of the fear of being infected and of becoming vectors of disease transmission [9-13].

All medical staff (attending physicians, resident physicians, nurses, nursing aids) suffers the impact of a new circuit, being subjected to a limited range of interaction with patients and the brevity of the anamnesis and clinical examination, sometimes with the risk of truncating some fundamental elements. In addition, the stress of the program and the modified shifts, the prolonged wearing of equipment and protective masks, with unhealthy hermeticity, lack of food, hydration and rest are included [6, 14, 15].

There are no known effective methods of combating the burnout syndrome, the manifestation or the sincerity of the respondents regarding their symptoms, for the time being remaining weak benchmarks for establishing an exact prevalence of exhaustion among the medical staff. Therefore, a first step, essential in discovering future therapeutic strategies, is the screening method. [16-18]. The screening tool also has a potential to prevent the worsening of symptoms. In Romania, it is imperative to have a feasible tool that can be used for adequate screening for the diagnosis of burnout syndrome. However, current data attribute this deficiency to the difficult-to-achieve differential diagnosis of burnout syndrome [19, 20].

MATERIAL AND METHODS

We present a prospective study, which took place in January-March 2021 on a group of 147 medical staff and support staff from COVID hospitals, COVID support and non-COVID in Iasi, who gave their free consent to answer questions regarding the occurrence of reactive symptoms caused by the COVID-19 pandemic.

The questionnaire used was adapted with the author's consent from the items in a form published in 1993 in “In the Tiger's Mouth”: An Empowerment Guide for Social Action intended to investigate the burnout syndrome. The distribution of the questionnaires was done after obtaining the opinion of the Ethics Commission. Completion of the questionnaires was started after obtaining the informed consent of all participants. In the processing of reactions, the principle of scores was used, applied individually, but which varied by framing the answers in a qualitative value, designated by reference

to percentiles. We will present the results of the physical manifestations within the burnout syndrome on the studied cases.
Data were collected by a team of physicians and analyzed using SPSS 18.0 software. The ANOVA test, the F test (ANOVA), the multivariate analysis, the ROC curve, the χ^2 2 test and the t-Student test, the Kruskall-Wallis and Pearson correlation were applied in the quantitative interpretation of the data. Statistical significance was defined in the 95% confidence interval ($p < 0.05$).

RESULTS

Depending on the occupation of the respondents, most frequently answered nurses (42.2%), representing 45.9% of the staff working in the hospitals and the resident doctors (29.3%), 27.9% of the working staff (Fig.1, Tab. I).

Tab. I Structure of the lot according to occupation

Occupation	Hospital (n=122)	Ambulatory (n=25)	Total (n=147)
Specialist / senior physician	13 (10.7%)	10 (40.0%)	23 (15.6%)
Resident physician	34 (27.9%)	9 (36.0%)	43 (29.3%)
Nurse	56 (45.9%)	6 (24.0%)	62 (42.2%)
Auxiliary staff	7 (5.7%)	-	7 (4.8%)
Nurse aid	12 (9.8%)	-	12 (8.2%)

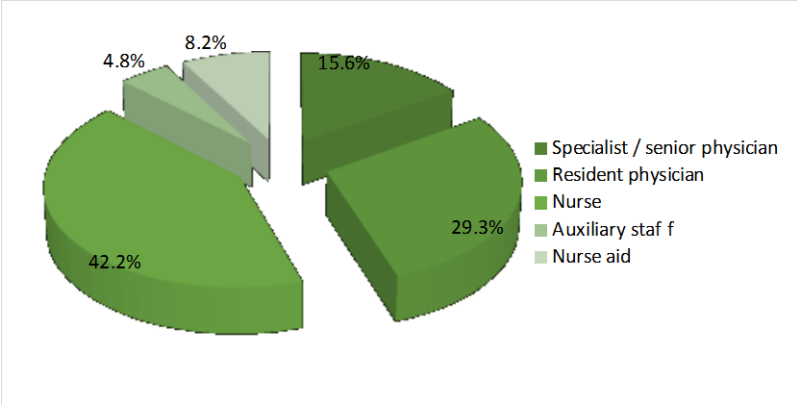

Fig. 1 Distribution of subjects according to occupation

The answers to the question *Do you have physical symptoms of stress?* highlighted the following aspects (Fig. 2):
- Never, 53.7% of subjects reported gastrointestinal reflux or 57.1% memory disorders;
- Sometimes, 40.8% had stomach pains, 42.2% persistent headaches, 45.6% of the subjects; difficulty concentrating and 38.1% sleep disorders;
- Often, 22.4% of the subjects answered that they had sleep disorders, 20.4% unjustified physical fatigue, 19.7% stomach pain and 19% a significant hair loss;
- Very often they mentioned 13.6% of the subject's unjustified physical fatigue and 11.6% persistent headaches, the rest of the symptoms being below 6.8%.

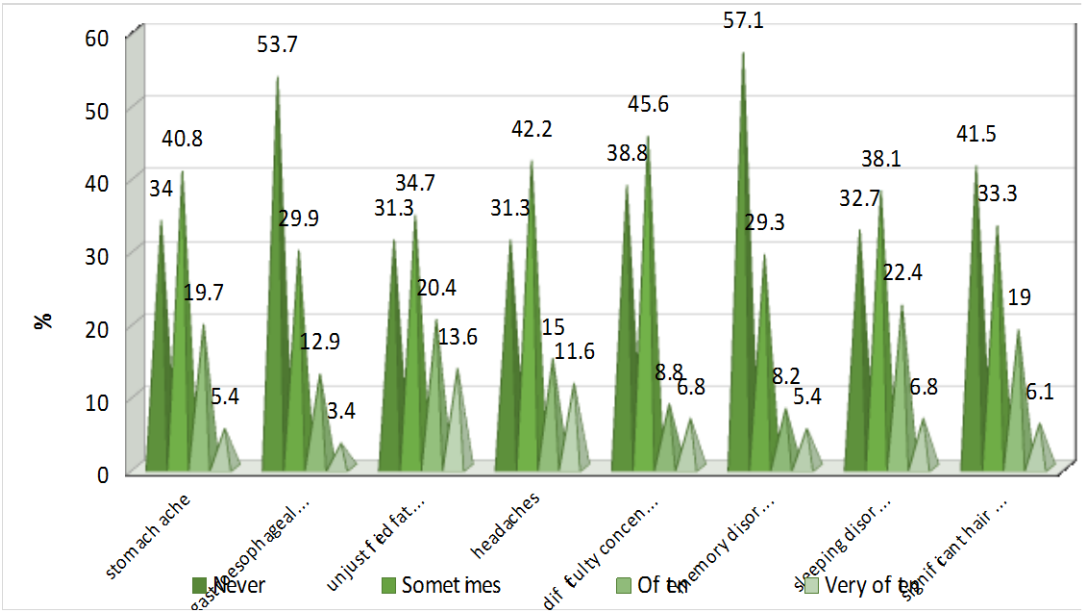

Fig. 2 Share of answers to the question "Do you have physical symptoms of stress"

The answer to the question *Have you experienced any symptoms from wearing protective equipment lately?* highlighted the following aspects (Fig. 3):

- After wearing protective equipment, 53.1% of the subjects stated that they had never had acne, and 49% had pharyngeal pain or 48.3% had never had contact dermatitis;
- Sometimes, 40.1% had pharyngeal pain, 33.3% dehydration and 32% of subjects, contact dermatitis;
- Often, 22.9% of the subjects answered that they had acne, 22.4% dehydration and 10.2% contact dermatitis;
- Very often mentioned 15% of dehydration subjects and 9.5% contact dermatitis.

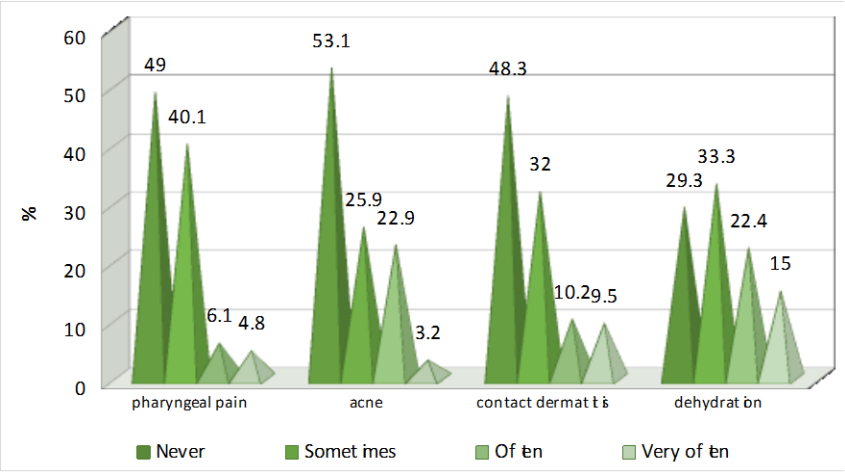

Fig. 3 Share of answers to the question "Do you have consecutive symptoms from wearing protective equipment"

The answer to the question *Have you recently had?* highlighted the following aspects (Fig. 4):

- 70.1% of the subjects did not notice any weight loss in the last period;
- Weight gain was never noticed by 57.8% of the subjects, but 26.5% of them sometimes noticed the increase and 15.7% often and very often;
- 63.9% have not noticed colds lately, 85.7% flu and 58.5% allergies.

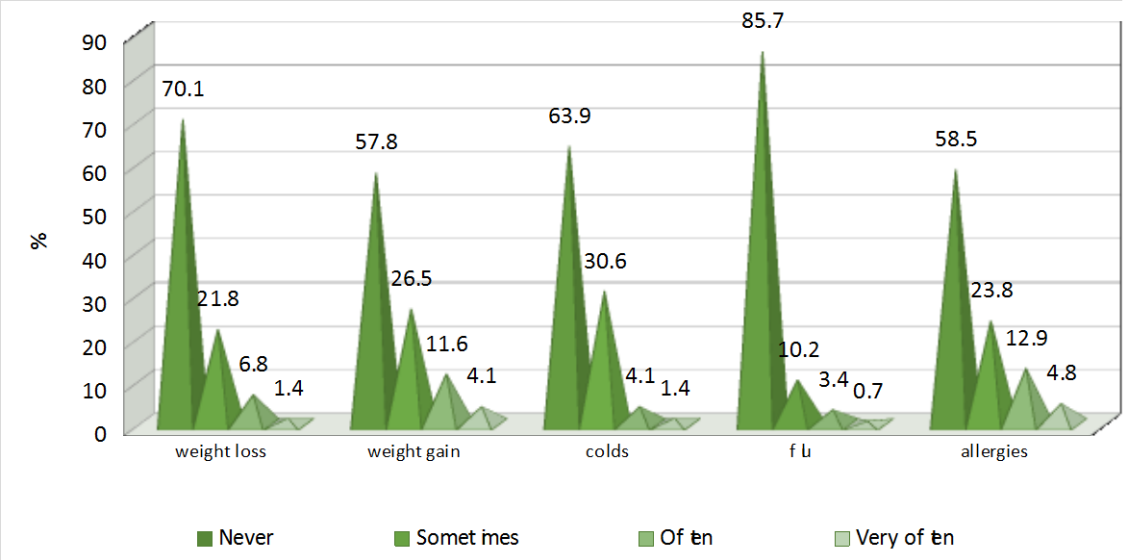

Fig. 4 Share of answers to the question "Have you noticed lately"

From the studied cases, 44.2% of the subjects noticed a slight predisposition to the appearance of some diseases, 46.9% moderate and 8.8% severe (Fig. 5).

In the studied cases, a share of 31.3% with mild, 46.9% moderate and 21.8% severe physical impairment was noted (Fig. 6).

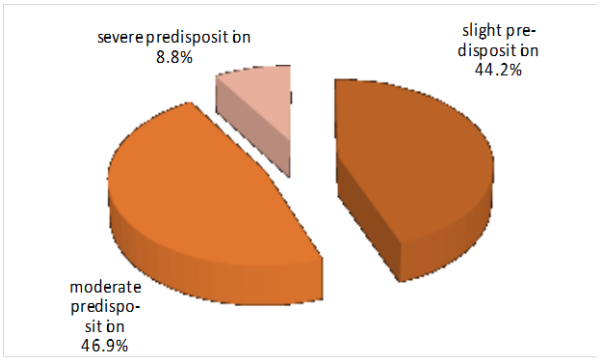

Fig. 5 Distribution of cases based on the score for predispositions in the last period

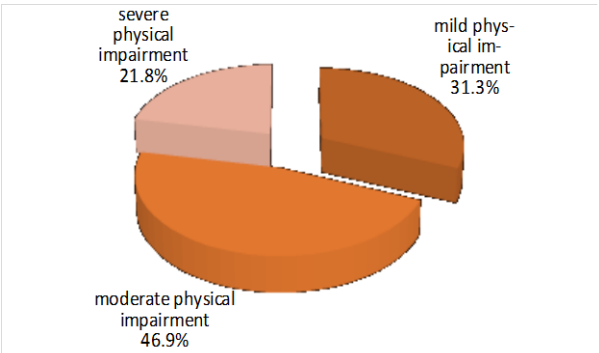

Fig. 6 Distribution of cases based on the score for physical symptoms

Depending on the specialization from which the respondents come, the following aspects were noted (p=0.354) (Fig. 7):

- Mild impairment of physical function was more frequently mentioned by subjects from the traumatology specialization (44.1%);
- The answers regarding the physical functions indicated a moderate impairment regardless of specialization with variations between 45.2% (internal medicine) and 48.1% (geriatrics);
- Severe impairment of physical functions was more frequently mentioned by subjects in the oncology specialization (27.3%).

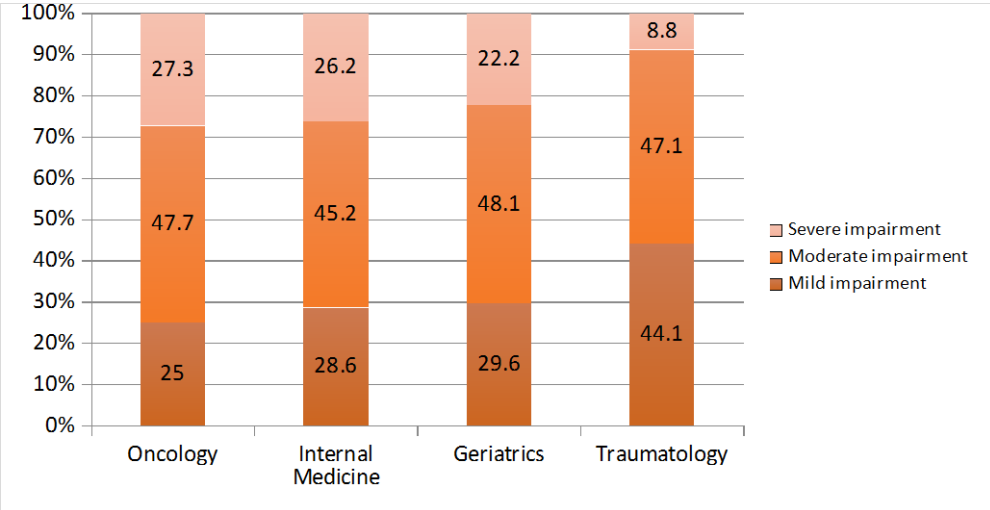

Fig. **7** Distribution of cases by specializations in relation to the score for physical symptoms

Physicians reported moderate physical impairment more frequently (60.9%), while 71.4% of support staff and 50% of nurses reported mild physical impairment more often, but the percentage distributions were not statistically significant (p=0.139) (Fig. 8).

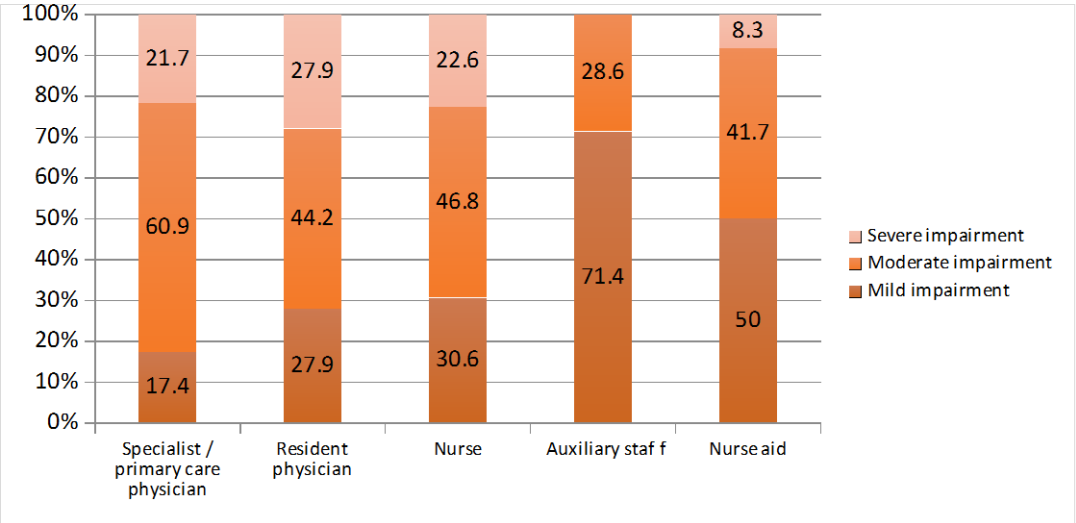

Fig. 8 Distribution of cases by occupations in relation to the score for physical symptoms

DISCUSSIONS

Within the studied cases, there was a moderate impairment regarding the physical symptoms of stress, without significant differences between specializations and occupation. Regardless of the pandemic context, staff in certain specializations, such as medical oncology, a priori associates a vulnerability factor by the different nature of relating to and interacting with patients. However, recent literature reports a high prevalence of physical symptoms related to burnout in medical staff in the first line of combating the disease, in surgical specializations and especially in nurses. Indeed, psychic burnout symptoms are more commonly cited in these categories than physical ones [16-18, 21, 22].

According to our data, the consecutive symptoms from wearing protective equipment have a lower frequency of occurrence, regardless of specialization or occupational role. At the same time, in our study it was shown that about half of the respondents had pharyngeal pain. A recent study showed that the most experienced symptoms among medical staff in the last month of the COVID outbreak were those related to prolonged wearing of masks:

pharyngeal pain and headache, all in moderate degree [23].

Most current studies illustrate the prolonged wear of equipment as a predictor of burnout in medical staff in the pandemic context, without speculating a clear link to physical somatization [24-26].

Also, our results show that specialization or occupational role did not influence, during the pandemic, the development of specific symptoms such as weight loss or gain, the predisposition to develop colds, flu or allergies, which occur with a moderately low frequency. Recent research specifically focuses on respiratory and digestive somatization, respectively pharyngeal pain and epigastralgia, in those in the first line compared to those in the other lines, although there were no significant differences between coping styles, an aspect also illustrated in our study [11].

The overall score of physical manifestations shows a moderate impairment in about 1/2 of subjects, without significant differences between specializations and occupation, and about 1/4 of doctors and nurses had severe physical manifestations. The current literature cites a higher predisposition to burnout among nurses, illustrating statistically significant results regarding mental symptoms of stress, the physical ones being greatly minimized, without a statistically significant impact highlighted in our study [27-29].

Conflicts of interest

The authors declare no conflicts of interest.

CONCLUSIONS

Our data show that the predictors of severe physical manifestations of burnout are the consecutive symptoms of wearing protective equipment and the predisposition to the development of diseases. The overall score of physical manifestations had prognostic value in the determination of severe psychic manifestations.

The assessment of psychological and physical symptoms in the case of burnout must be related to all dimensions of a social life, including contemporary values, economic aspects, the geographical region concerned and cultural particularities, independent of the pandemic crisis, as the initial psychological substrate can determine the means of response to the crisis state.

In addition, there are substantial overlaps between the clinical samples of burnout and non-burnout patients. The use of screening tools without a rigorous history also creates the risk of both false positive and negative results.

Current issues of particular relevance to the medical world, globally, include the links between the burnout syndrome and mental illness, with differential diagnosis being necessary and difficult to perform in certain clinical circumstances.

The main goal of treatment for the burnout syndrome remains the allowance of people to return to their professional activities at an effective and meritorious level.

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COMPARATIVE ASSESSMENT OF COVID-19 MORTALITY BETWEEN COUNTRIES DURING PANDEMIC

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Abstract. COVID-19 mortality can best express the severity of the disease. Comparisons between countries are often difficult due to several factors: population factors, pre-pandemic co-morbidities and the level of funding for the medical sector. The paper compares the evolution of COVID-19 mortalities in 14 European countries, in 2020. Demographic, socio-economic data and figures for cases and rates of illness, hospitalizations and deaths were collected from online databases. Death rates are picked for one day, at one week intervals, between 01.03-31.12.2020. Comparing the evolution of mortality expressed by absolute figures with mortality rates/100,000 inhabitants, we find larger differences in the case of Belgium (which moves to the first place from 7th position) and Romania (moving from the last place, to the 8th place). Instead, Germany and Russia have the opposite movement, from top positions in gross mortality (positions 6 and 5 for Germany, respectively Russia), moving down to positions 11 and 12. This change is the effect of reporting deaths to population size. If we consider the population densities, we can explain the higher volume of infections and deaths in: Belgium, UK, Switzerland and Italy. At the same time, the very high share of the elderly (which implies more co-morbidities -obesity, diabetes, hypertension) favours higher COVID-19 death rates in the listed states. On the other hand, although Germany has a high population density and many elderly people, its mortality rate is lower. The reason is the application of a massive testing policy, at the beginning of the pandemic, following the contacts of any infected person. Correlation analysis bring some clarifications regarding the mortality evolution: the tests rate correlates intensely with mortality (r=0.508/p=0.000) emphasizing the importance of a correct definition of COVID-19 deaths; the connection with the stringency index shows that the restrictions multiply with the increase of the infection and death rate; life expectancy is directly related to the death rate (r=0.250/p=0.000), but negatively (r= -0.202/p=0.000) with the infection rate; the fact explanation: the elderly die more, but the younger people become more infected; the connection with GDP/capita is also negative, suggesting that more people die when the country is poorer.
Key words: COVID-19 death, population factors, groups at risk

Rezumat. Mortalitatea COVID-19 poate exprima cel mai bine severitatea bolii. Comparațiile între tari sunt adesea dificile datorită mai multor factori: populaționali, comorbidități preexistente pandemiei și nivel de finanțare a sectorului medical. Lucrarea compara evolutia mortalităților COVID-19 in 14 țări europene, in anul 2020. Din baze de date online au fost culese date demografice, socio-economice și cifre privind cazurile și ratele de boală, spitalizări și decese. Ratele de deces sunt culese pentru câte o zi, la interval de o săptămână, în perioada 01.03 -31.12.2020. Comparând evoluția mortalităților exprimate prin cifre absolute cu ratele de mortalitate/100.000 locuitori, constatăm diferențe mai mari în cazul Belgiei (care ajunge pe primul loc de la poziția 7) și al României (de pe ultimul loc, pe locul 8). În schimb, Germania și Rusia au o mișcare opusă, de la poziții mai de top ale mortalității brute (pozițiile 6 și 5 pentru Germania, respectiv Rusia), coborând la pozițiile 11 și 12. Această schimbare este efectul raportării deceselor la mărimea populației. Dacă se consideră și densitățile populațiilor, este explicat volumul de infectări și decese mai mare în: Olanda, Belgia, UK, Elveția și Italia. Totodată și ponderea foarte mare a vârstnicilor (care presupune comorbidități mai numeroase-DZ, HTA, obezitate) favorizează rate mari de decese COVID-19 în statele enumerate. Germania în schimb, deși are și o densitate populațională mare și vârstnici mulți, are o rată de mortalitate mai mică. Motivul îl reprezintă aplicarea unei politici de testare masivă de la începutul pandemiei, urmată de urmărirea contacților fiecărei persoane infectate. Analiza corelațională aduce cateva lamuriri privind evolutia cifrelor mortalitatii: -corelatia intensa intre rata de testare si cea de mortalitate (r=0.508/p=0.000) subliniiaza importanța definirii corecte a deceselor COVID-19; legătura cu indicele de stringență, arată că restricțiile se înmulțesc odată cu creșterea ratei infectărilor și deceselor; speranța de viață este legată direct de rata deceselor (r=0.250/p=0.000), dar negativ cu rata de infectare (r= -0.202/p=0.000); aceasta înseamnă ca mor mai mult vârstnicii, dar se infectează mai mult persoanele mai tinere; tot negativă este și legătura cu PIB/cap de locuitor care sugerează o mortalitate mai mare în țările mai sărace.
Cuvinte cheie: deces COVID-19, factori populaționali, grupuri la risc

INTRODUCTION

Worldwide, for almost two years, SARS-CoV-2 [Severe Acute Respiratory Syndrome Corona-virus-2] has been having a major impact on human health. Prior to the identification of this coronavirus, six other pathogenic coronaviruses for humans were described, all of zoonotic origin:

- four coronaviruses causing common respiratory infections such as colds (two alpha-coronaviruses, with a tank of African bats, and two beta-coronaviruses, with a murine reservoir);
- two new beta-coronaviruses that caused severe acute respiratory syndromes:
  - SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus, belonging to the subgenus Sarbecovirus) was identified in 2002 in southern China, in the Guangdong region; derived from bats, it was transmitted to humans through an intermediate host represented by civet; by 2004, when it disappeared from circulation, it had already spread rapidly globally and caused more than 8,000 human cases and 774 deaths (9.5% mortality).
  - MERS CoV (Middle East Respiratory Syndrome Coronavirus), belonging to the subgenus Marbecovirus, appeared in 2012 in Saudi Arabia, coming from bats and transmitted to humans by dromedaries; MERS CoV is still circulating in the Middle East and has caused 2519 cases and 866 deaths so far (35% mortality).

SARS-CoV-2 is a Beta-coronavirus, belonging to the subgenus Sarbecovirus, antigenically distinct from SARS-CoV, with which it has genetic similarity in proportion of about 76% of the nucleotides. It was identified in January 2020 by bronchoalveolar lavage from patients diagnosed with severe pneumonia in Wuhan, China [1].

All viruses change over time, resulting in variants that allow them to adapt better to the environment, compared to the original virus. There are dedicated COVID-19 databases, such as offered by GISAID (Global Initiative on Sharing Avian Influenza Data). Their study allows scientists to know the mutations in the genome of the new coronavirus. Most changes have little or no impact on the properties of the virus. However, some changes may affect the transmissibility, severity of the associated disease, the performance of vaccines or therapeutic drugs. By January 2021, about 10,000 mutations had been discovered. Although mutations rarely produce a more dangerous viral strain, it is impossible to predict when and how a mutation will cause a strain that is easier to transmit or with immune escape potential [2].

MAIN STRAINS OF COVID-19

Reuters analysed more than 185,000 genomes in the GISAID database to monitor the progress of the virus and pandemic change. The analysis showed the existence of 7 main strains of SARS-CoV-2: the L strain is the original strain, detected in the Chinese city of Wuhan in December 2019 (which has almost disappeared now); the S strain appeared at the beginning of 2020; the V and G strains appeared later; The G strain underwent subsequent mutations with the appearance of subgroups GR, GH and GV.

In the world, in January 2021, the G strain was dominant, and the GV subgroup was dominant in Europe. This is important because G strains include a mutation that facilitates the binding of Spike protein to receptors on cells in the body. This variant 23403A> G (D614G) is associated with increased infectivity, but low clinical severity, in several studies [3].

In the GR subgroup, the variant VUI 202012/01 appeared, known also as

B.1.1.7 and alpha variant. It was declared Variant of Concern (VOC) in December 2020 in the UK. It seems to be characterized by a much higher transmission rate compared to other strains.

At the beginning of the pandemic, the virus spread relatively quickly around the world, being introduced repeatedly in different regions, and causing new outbreaks. A mix of several different strains of the virus was identified in the samples evaluated by GISAID. As countries began to close their borders, fewer new strains were introduced into those regions. Thus, in Asia, the original L strain persisted longer, as many countries, including China, quickly closed their borders and thus restricted the movement of people. In contrast, North America and Europe did not restrict movement as much, at least initially, which allowed G strains to spread and mutations with subgroup production to occur at a much faster rate. In countries where more resistant G strains were present, they began to be dominant. In the USA, which is the country with the highest number of infections and deaths, the most infections in the first, second and the third waves coincided with the growth of the three G subgroups (GR, GH and GV).

The Cleveland Clinic (Ohio) was among the first hospital systems in the U.S.A. to provide community screening for SARS-CoV-2, achieving insight into the early dynamics of the virus [3].

The clinical study conducted at the beginning of the pandemic aimed to find the association of identified SARS-CoV-2 variants, virus strains, and strain groups with disease severity and patient outcomes. Viral genome analysis of clinical specimens obtained from 302 patients infected with SARS-CoV-2 during the initial wave of infection (March 11 to April 22, 2020) was performed. Among the results we mention:

- 2531 variants were identified (of which 484 were unique);
- it turned out that the greatest genomic diversity of SARS-CoV-2 occurred in the first weeks, when five of the six strains described by GISAID (S, V, G, GH, GR) circulated in addition to the isolated ones similar to the Wuhan (L) reference strain; then a rapid reduction in strain diversity followed;
- All variants appearing for GH strain viruses were associated with a lower hospitalization rate;
- Those containing the 23403A> G mutation (D614G Spike) were associated with an ▪ increased survival when the patient was hospitalized; infections with strains without variant 23403A> G (D614G Spike) showed a higher mortality in multivariable analysis;
- Hospitalization and ICU care were similar, regardless of the strain;
- Infection with V strain variants demonstrated higher levels of creatinine and higher overall rates of mortality.

The conclusion was: knowing the viral variants that affect the outcome of the disease is important for the stratification of the clinical risk.

VARIANTS OF INTEREST AND VARIANTS OF CONCERN

WHO, in collaboration with partners, has been monitoring the evolution of SARS-CoV-2 since January 2020 [4]. At the end of 2020, the emergence of variants that pose an increased risk to global public health led to the characterization of some as "variants of interest" (VOI) and others as "variants of concern" (VOC), in order to give priority to their monitoring. Briefly, their definitions are:

Variant of interest (VOI) = a variant with genetic modifications that are predicted / or known to affect the characteristics of the virus, such as transmissibility, disease severity, immune escape, diagnosis or therapy escape; it may cause significant community transmission or more COVID-19 clusters in several countries with increasing relative prevalence.

Variation of concern (VOC) = a variant that meets the definition of a VOI and, is associated with one or more of the following changes of major importance for public health:
- Increased transmissibility or detrimental change in COVID-19 epidemiology; or
- Increased virulence or change in clinical disease presentation; or
- Decreasing the effectiveness of social and public health measures or available diagnoses, vaccines, therapy.

In countries where widespread transmission of VOC has occurred, evidence has shown that public health and social measures (PHSM), including infection prevention and control (IPC), have been effective in reducing COVID-19 cases, hospitalizations and deaths [4].

However, the number of countries reporting variants of concerns (VOCs) continues to rise. In the UK, a group of nine researchers conducted a laborious study in early 2021 using three mathematical models [5]. They imagined two scenarios for the third wave of the COVID-19 pandemic: one driven by increased transmissibility and another driven by immune escape. The models were calibrated according to the situation in the UK, in May 2021. The dynamics of infection and vaccination rates were accurately captured and used to explore the potential impact of a VOC new vaccine. Epidemiological trajectories for VOCs depend to a large extent on the transmissibility, immune escape capacity and when a VOC-targeted vaccine can be introduced.

The study showed that a VOC with a substantial transmission advantage over resident variants or the ability to evade the vaccine and previous immunity is expected to generate a wave of infections and hospitalizations comparable to those seen in the winter wave 2020-2021. Moreover, a less transmissible variant, but with a partial escape of immunity, could cause a wave of infection that would not be discovered until after the control measures were relaxed. Therefore, close monitoring of the evolution of SARS-CoV-2 over a wide geographical area is needed in order to raise awareness of the local situation and to quantify the risk that some viral variants may be of interest [5].

ASSESSING THE MORTALITY OF COVID-19

An important feature of an infectious disease is its severity, the final measure being the caused mortality. In addition to the severity of COVID-19 disease, a mortality indicator can assess the quality of care and identify groups at risk. Some therapeutic and also political decisions for allocating resources are made by comparing the experience of different countries, reflected in the mortality indicator.

First of all, assessing the mortality depends on what is considered COVID-19 death. National definitions generally fall into two groups: based on clinical diagnosis (confirmed and probable) and those based on tests [6].

1) The international standard for defining COVID-19 death based on clinical diagnosis was published by the WHO on 16 April 2020 and the guidelines updated on 7 June. A COVID-19 death is "a death resulting from another clinically apparent associated disease, in a probable or confirmed case of COVID-19, unless there is a clear alternative to the cause of death that cannot be linked to COVID-19 disease (e.g. trauma). There should be no complete recovery period after COVID-19 between illness and death. A death caused by COVID-19 cannot be attributed to another disease (e.g. cancer) and should be considered independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19".

Deaths based on death certificates are widely recognized as more reliable, but their reporting takes longer time. In addition, accuracy may vary depending on the implementation of international

guidelines and registration practices in different countries.

2) The other definition is based on a positive test and, consequently, on testing policies and the availability of accurate tests. But testing policies vary widely between countries and have evolved over the course of the pandemic. Once the spread within communities began, in some countries with limited testing capacity, eligibility for testing was restricted (e.g. applied only to people with severe symptoms). This has led to the limitation of reporting to hospital deaths only (e.g. Italy, Netherlands, Spain, and United Kingdom). At the same time, deaths in long-term care facilities and in residential settings have often been under-reported.

Countries that did many tests at the beginning of the pandemic, following the contacts of any infected person, seem to have had the greatest success in slowing the spread of the disease so far. This includes Germany and South Korea, which have had far fewer deaths than the most affected countries. The tests number per capita can be a good statistic predictor of low mortality rates.

Deaths occur in many situations, and all should be counted in a similar way to allow comparisons. Some countries, according to the clinical diagnosis, count the cases of COVID-19 clinically confirmed or probable that have died (Belgium, Canada, France) and do not depend on the availability of laboratory tests; others are based on a positive laboratory test (Austria, Italy, Netherlands, Spain, United Kingdom). However, the distinction is not always clear; there are countries that include probable deaths by COVID-19 in definition, but in practice, require laboratory confirmation (Cyprus, Greece, Romania, and Serbia).

For the correct monitoring of deaths, it is necessary to know:

a) Where the deaths occurred: In England, only hospital deaths were included in official figures until April 29; subsequently, COVID-19 deaths from nursing homes were added; -In Belgium, 46% of deaths were hospital (all confirmed) and 54% came from nursing homes (with 84% of these unconfirmed) [7];

b) When the deaths occurred: >In the US, in the first weeks of the pandemic, reported deaths were probably underestimated due to incomplete follow-up of all cases reported by COVID-19; >COVID mortality is also partially determined by the stage of the outbreak reached by a country, individually, at a given time; if the first case in a country was at the beginning of the global outbreak, then there was more time for the number of deaths to increase [8].

In the comparative assessment of mortality, there are other factors to consider, beyond the deaths numbers themselves [8]:

• Political factors - It is more difficult to trust data from countries with strictly controlled political systems, such as China and Iran. Their mortality rates from COVID-19 are suspiciously low. (Death rates per million for China are extraordinarily low, even after the death toll in Wuhan has been revised by 50%);

• Also, how different cultures adapt to social distancing, because accepting the restrictions is an important aspect;

• The different level of financing for health services which influences the evolution and severity of the disease;

• The level of pre-existing co-morbidities in the population – diabetes mellitus, obesity, heart disease, which often causes an unfavourable evolution of the infection, sometimes leading to death;

• Population factors:

a) Population size – When the death numbers are reported to the population size the mortality rate is obtained: the number of deaths per million (or 100,000 inhabitants). [7]

In non-pandemic periods it is a useful reported indicator in comparison between countries. But now it can be challenged for some reasons: the differences in testing for

COVID-19 in different countries; comparing of countries in a similar pandemic stage and because not all countries are homogeneously affected [9]. Especially in the larger countries, like China and the USA, epidemics can be (temporarily) focused on a localized level. For example, in China, the province of Hubei was severely affected, while the rest of the country was not. Therefore, correction for the total size of the Chinese population would not provide a representative figure. Of particular note, in panel A of Fig. 2 the numbers of deaths in China disappeared almost completely; this was due to false inflation of the denominator.

b) Population density: The population density overall in Hong Kong is 7096/km^2, in the UK is 275/km2 and in Ireland is 71/km^2. Hence, it may be more comparable to look at similarly population dense areas, such as comparable cities [7].

c) Rural and urban areas - There are striking differences in the spread of COVID-19 between rural and urban areas. Professor Donnelly, epidemiologist, said: "The more dense the population, the more you would expect virus transmission to happen [10].

d) The structure by age groups - Older people are much more likely to die of Covid-19. Therefore, a comparison of death rates between European and African countries would not work, as African countries have much younger populations. –It's the factor some experts say it explains why in Africa relatively small number of confirmed deaths are reported [10].

e) Comorbidities present before the pandemic - Older age is related to several comorbidities (obesity, diabetes, heart disease), which can promote SARS-CoV-2 infection and can lead to death.

f) Gender - Data from the literature show that SARS-CoV-2 infection is evenly distributed by gender. But evidence from a meta-analysis of 3,111,714 cases reported worldwide showed that male patients were nearly three times more likely to require hospitalization in an intensive care unit (ICU) (OR = 2.84; 95% CI = 2.06, 3.92) and higher risk of death compared to women (OR = 1.39; 95% CI = 1.31, 1.47). With few exceptions, this trend of gender differentiation is a global phenomenon [11]

g) Ethnicity - Early deaths among ethnic minority doctors in the UK sparked interest in the possibility of ethnic differences in the expression of angiotensin converting enzyme 2 and risk of both acute kidney injury and cardiac complications; this happens because of a higher prevalence of cardiovascular risk factors in ethnic minority populations. Fogarty et al. found a higher rate of coagulopathy in Caucasian patients in a series compared to Asian and African-American patients and concluded that pulmonary vasculopathy may contribute to the unexplained differences that are beginning to emerge highlighting racial susceptibility to COVID-19 mortality [7].

MORTALITY INDICATORS USED IN THE CURRENT PERIOD OF COVID-19 PANDEMIC

A. All death cases, in absolute figures

B. The mortality rate represented by the number of deaths per million (or 100,000 inhabitants) is a frequently reported rate.

C. Case fatality ratio (CFR) estimates the proportion of deaths among identified confirmed cases. In the case of deaths by COVID-19, some mentions are necessary:

- Ratio: number of deaths per cases of disease is influenced by testing for COVID-19; countries with limited testing criteria are likely to have comparatively high fatality rates due to the lower volume of tests (e.g. those testing only severe COVID-19 hospitalized cases).
- Reliable CFRs for assessing the mortality of an outbreak and the implemented public health measures are generally obtained at the end of the outbreak, after all cases have been resolved (affected people have died or recovered).

▪ CFR variations can also be explained by the different quality of care or interventions introduced at different stages of the disease. Finally, the profile of patients (e.g.: age, sex, ethnicity and underlying co-morbidities) may vary from country to country [12].

D. Monitoring of excess deaths better highlights the magnitude of the impact of COVID-19

The "excess of deaths" is a temporary increase in the mortality rate, compared to historical trends. The large number of excess deaths currently observed in many countries is much higher than the official number of deaths attributed to COVID-19.

The Financial Times shows that in the various outbreaks of March and April 2020, the global death toll was about 122,000 - much higher than the 77,000 official COVID-19 deaths reported for the same places and time periods. There are debates about the reasons for this discrepancy, ranging from under-reporting of COVID-19 cases, to the situation of patients who avoid hospital and die due to preventable conditions [10]. The Economist's analysis shows that countries where COVID-19 mortality reporting is related to positive test result show a comparatively lower proportion of total excess deaths which are coded as COVID-19 deaths. Thus, as of 27 May 2020, only 50% of the excess deaths in Italy, 60% in the Netherlands and 77% in the United Kingdom have been attributed to COVID-19. In contrast, in Belgium, where the defining deaths by COVID-19 reflects the WHO definition, the number of deaths by COVID-19 appears to be higher (106%) than the total number of excess deaths, while in France it reaches 95% [6].

However, the estimation for excess deaths could be used more for monitoring the actual scale of the COVID-19 pandemic impact with minimal delay. Both WHO and European Centre for Disease Prevention and Control (ECDC) advise European countries to monitor total mortality, as well as excess deaths (compared to the expected level based on that time of year) by age, at least weekly [6].

E. At the beginning of the pandemic (on May 26, 2020), the study of two Dutch researchers concluded: “Only the number of deaths expressed as a percentage of the number of deaths on day 25 after the first reported COVID-19-related death allowed a direct comparison between countries” [9].

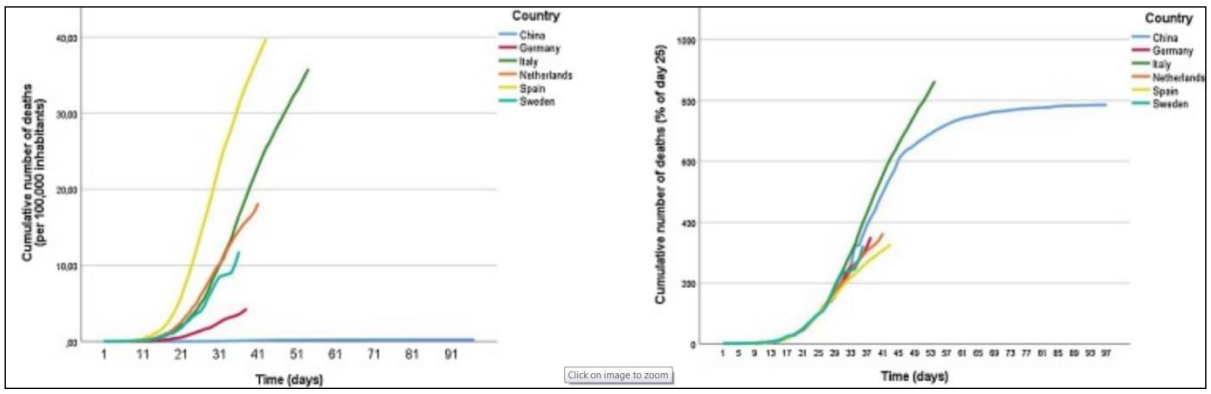
They compared the numbers of reported deaths between 1 January and 17 April 2020. The comparability of data between countries was increased in two distinct ways First, the start of the epidemic was synchronized between countries by using the date of the first reported COVID-19-related death as the index date. Second, all cumulative numbers of deaths were normalized to a reference number, represented by the cumulative numbers of deaths on day 25 (i.e. day 25 after the index date for each country). On day 25 after the first death, the epidemic had established itself and the number of deaths had increased to a level where random fluctuations were reduced to an acceptable level).

Temporal trends in cumulative numbers of deaths were compared with those for China, where the pandemic started, and where the temporal trends have therefore developed the furthest. After the comparison with China, countries were divided into three categories. First, in South Korea, strict preventive measures were put into place even before the virus substantially spread in the population. Second, the USA, preventive measures were not put into place until large numbers of deaths had already occurred. Third, these are the European countries, with a policy similar to that of China. There, governments waited for the epidemic to establish itself, but not for substantial numbers of COVID-19-related deaths to occur, before taking preventive measures. Germany, Italy, the Netherlands, Spain, and Sweden (alphabetic order) were used

as examples, but graph shapes for other European countries were rather similar, comparison.

Using this observation to further compare different countries, a clear difference was observed in the development of the COVID-19 epidemic between countries with different containment policies. In most European countries, the early stages of the epidemic seemed to have a temporal development very similar to that in China. The curves flattened about 3 weeks after the implementation of strict containment strategies. Except for the Italian curve, which continued to follow, and possibly even exceed, the Chinese one. A possible explanation could be that containment measures were taken too late in Italy. Italy was the first European county to be affected and the pandemic was therefore recognized relatively late [9].

Dates from different countries were synchronized with the date of the first death (Fig. 1A and 1B) as day 1. Height of the curves represents the cumulative number of deaths (Fig.1A) per 100,000 inhabitants or the cumulative number of deaths (Fig. 1B) expressed as a percentage of the number of deaths on day 25 in that country. These results clearly show that comparing numbers of deaths per 100,000 inhabitants falsely suggests huge differences between countries.



Figures 1A, 1B Different measures to compare the COVID-19 epidemic between countries.

In the past, health and socio-economic indicators were obtained in months or even years, after data collection and processing. Now online tables can be consulted, such as those published by the World Health Organization (WHO), Johns Hopkins University and Worldmeter, comprising the daily incidence of COVID-19 new cases, deaths and other indicators [13].

Fig. 2 shows the numbers of weekly COVID-19 cases and deaths, from the beginning of the pandemic to the present. The absolute figures of the two indicators outline the four waves of the pandemic [4].

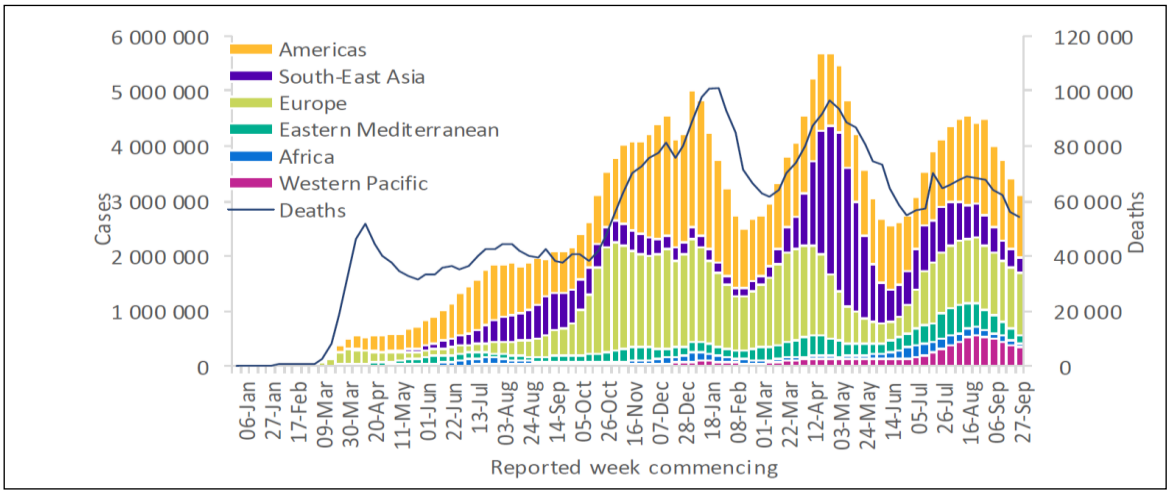


Fig. 2 COVID-19 cases reported weekly by WHO and global deaths, as of 3 October 2021

In this paper, the comparative study of the mortality will use statistical data collected from several sources on the Internet, mainly from Our World in Data dataset [13]. Those related to SARS-CoV-2 infection and some demographic data are from 2020 (incidents and rates of infection, death and hospitalization, average age, population size and density, stringency index, GDP per capita). Other indicators are older: life expectancy (from 2019), the weights of the population aged 65 and over and those aged 70 and over, as well as the prevalence of diabetes and mortality from cardiovascular diseases (CVD) are from 2017. We selected data regarding the infection and its results, for one day, at intervals of one week, between March 1 and December 31, 2020. The data refer to Romania and 13 other European countries: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Russia, Spain, Sweden, Switzerland and United Kingdom. Comparisons were made between data on SARS-CoV-2 infection and other indicators, using graphical method and correlational analyses.

In media reports about the evolution of cases of infections and deaths, absolute figures are often used (the situation of the Fig. 2). But absolute mortality figures do not allow comparisons between countries, because of the population size.

In the following, based on data from Romania and other 13 European countries, we will show the importance of some population factors (size, density, structure by age groups, comorbidities) and also of wealth and containment level, in the comparative assessment of mortality.

Fig. 3A and 3B illustrate the evolution of mortality rates, comparing it with that of absolute death counts, between March 1, 2020 - December 31, 2020 having daily data selected every 2 weeks, for 14 European countries. We find that Belgium, from position 7 based on the gross mortality (Fig. 3A) moves, when reported to the population, to the first place (Fig. 3B). Likewise, Romania, from the 14th position, moves up to the 8th place in the death rate graphic. Instead, Russia, from the 5th position, moves down to the 12th place, showing a lower mortality rate.

Population density - In Fig. 4, the sizes and densities of the populations of the fourteen European countries are presented. We find that Belgium has a dense population - 375 inhabitants per square kilometre, while Finland and Russia have the lowest densities, with values of 18 and 8.8 inhabitants per square kilometre, respectively; these are some reasons why death rates of the two countries are lower.

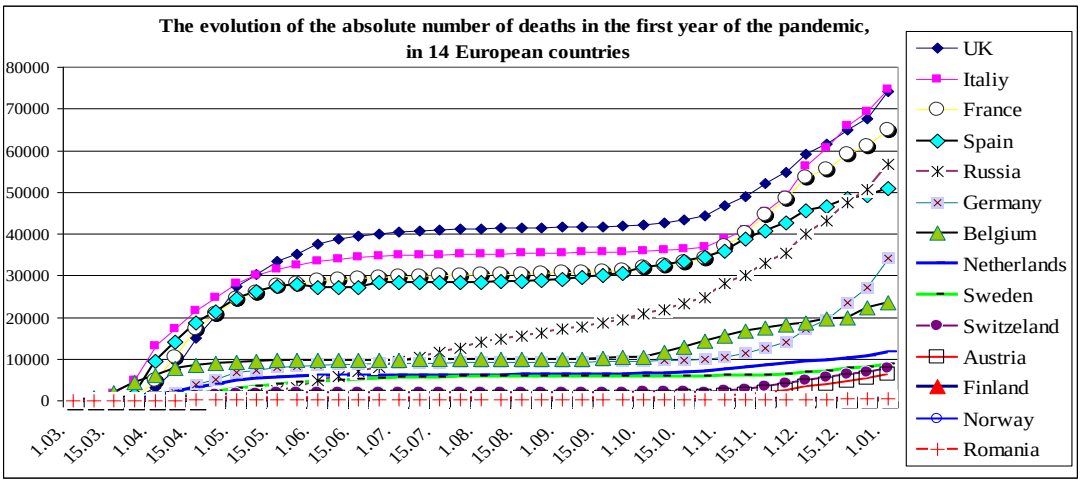


Fig. 3A The evolution of the absolute number of deaths in the first year of the pandemic, in 14 European countries

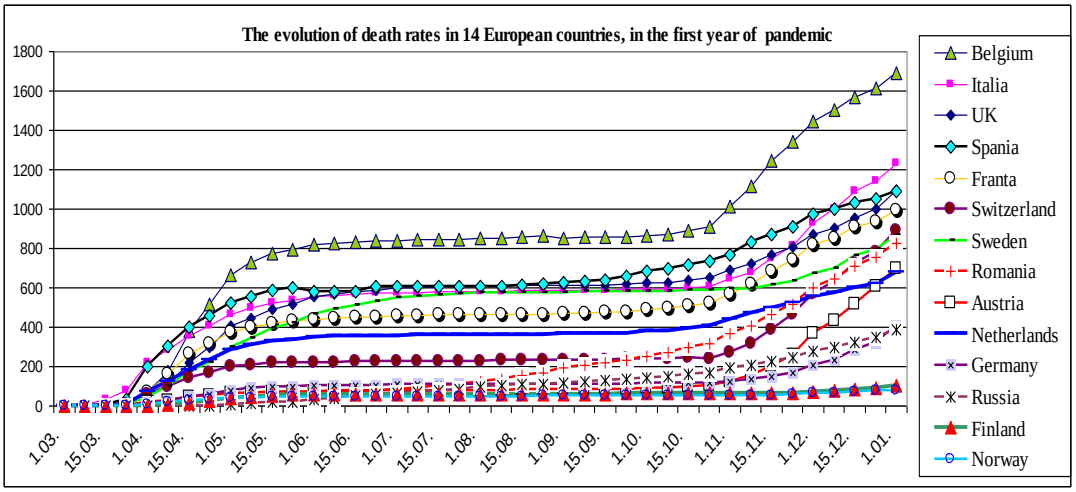
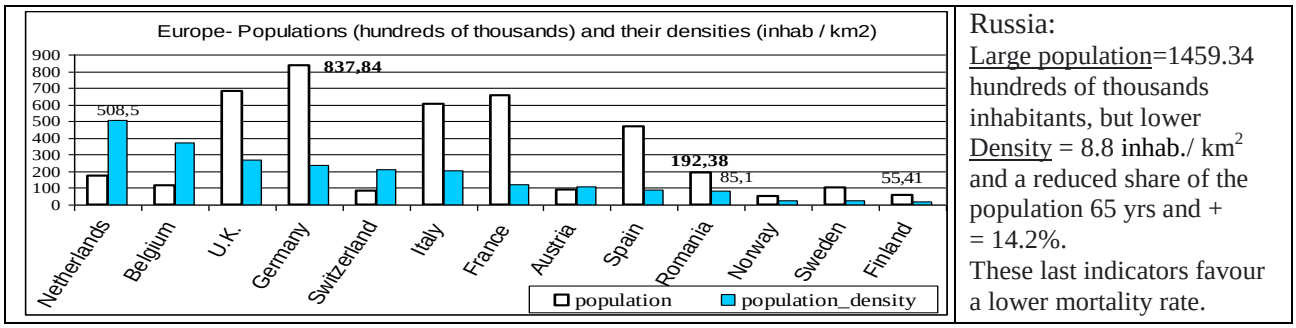


Fig. 3B The evolution of death rates in 14 European countries, in the first year of pandemic



Russia:
Large population=1459.34 hundreds of thousands inhabitants, but lower Density = 8.8 inhab./ km^2 and a reduced share of the population 65 yrs and + = 14.2%.
These last indicators favour a lower mortality rate.

Fig. 4 Europe- Populations (hundreds of thousands) and their densities (inhab/km2)

The structure by age groups

Tab. I The weights of populations aged 65yrs+ (%)

Netherlands	23.0	Norway	18.9
Belgium	21.5	Austria	18.8
UK	21.2	Spain	18.6
Germany	20.0	Romania	18.5
Switzerland	19.7	Sweden	18.4
Italy	19.7	Finland	17.9
France	19.2	Russia	14.2

Presenting the percentage values of people aged 65 and over in the listed countries, we highlight a reason for the high mortality rate in Belgium, UK, Germany, Italy. On the other hand, Finland and especially Russia, with younger populations, have low mortality rates.
Along with the demographic aging, these states also have large populations (UK, Germany, Italy, France, Spain), or high densities of their populations (Belgium, the Netherlands, UK).

In Romania, on January 5, 2021, the weights of COVID-19 infections by decades of age were as follows: adults between 40 and 49 years (21%) and between 50-59 years (19%), then young people aged 30-39 (17%) and the elderly - aged 60-69 (14%) and aged 70 and over (13%).
Some significant correlations between medico-social indicators and COVID-19 infection and mortality rates are shown in Tab. II and III [14].

Tab. II Correlations between the COVID-19 infection rates and the indicators studied in the paper

COVID-19 cases/ million corel with	r=	p=	**COVID-19cases/ million**	r=	p=
Tests number / thousand	0.674	0.000	Stringency Index	0.291	0.000
Hospitalized / million	0.560	0.000	Life expectancy	-0.202	0.000
ICU care numbers/ million	0.521	0.000	Population density	0.151	0.000
GDP / capita	-0.302	0.000			

Tab. III Correlations between the COVID-19 death rates and the indicators studied

COVID deaths/ million corel -->	r=	p=	**COVID deaths/ million** corel:	r=	p=
Tests number /thousand	0.508	0.000	Life expectancy	0.255	0.000
Hospitalized / million	0.428	0.000	Stringency Index	0.250	0.000
Population density	0.341	0.000	ICU care numbers/ million	0.245	0.000
Diabetes prevalence	0.329	0.000	GDP / capita	-0.140	0.001
Cardiovascular death rate	0.288	0.000			

More frequent testing means more COVID-19 cases identified (r=0.674/p=0.000 –Tab. II) and more frequent identification of COVID-19 deaths (r=0.508/p=0.000 –Tab. III) - (this correlation also emphasizes the importance of the correct diagnosis of COVID-19 deaths).
Of those infected, those with more severe COVID-19 forms end up in the hospital; the infection rate correlates significantly with the hospitalization rate (r=0.560/p=0.000 –Tab. II). The mortality rate of those hospitalized is higher than that of those not hospitalized (r=0.428/p=0.000 –Tab. III). A part of those hospitalized reach the ICU (r=0.521/p=0.000), of which, some die (r=0.245/p=0.000).
Pre-existing comorbidities also correlate significantly with the mortality rate (Tab. III): for the prevalence of diabetes cases (r=0.329/p=0.000), but also for CV deaths in the population (r=0.288/p=0.000). (Available data refer to previous mortality from CVD in those countries, indicating the existence of a population affected by these diseases; therefore, the intensity of the correlation with CVD is slightly lower, compared to that for diabetes mellitus).

Life expectancy correlates inversely with the number of infections in a population (r=0.202/p=0.000), which means that the youngest are infected more than the oldest. (We previously presented the share of those who were infected in Romania, on January 5, 2021 the most affected were the decades: 40-49 years (21%) and 50-59 years (19%)). On the contrary, the correlation of life expectancy is directly proportional to mortality, which means that the elderly die more (r=0.255/p=0.000).

The connection with GDP/capita is negative, suggesting that more people die when the country is poorer.

With the increase in COVID cases beyond certain limits, governments decide various restrictions [15]. Researchers from Oxford University created the stringency index, a score based on several indicators related to restrictions (e.g., closure of schools and jobs, travel restriction) where a higher score means stricter measures taken by that country [16]. The correlation of the stringency index is directly proportional to the infection (r=0.291/p=0.000) and to the death rate (r=0.250/p=0.000).

CONCLUSIONS

The work is mainly a review focused on the SARS-CoV-2 pandemic and on the possibility of comparing multiple countries by the COVID-19 mortality. This indicator can assess the severity of the disease, the quality of medical care, the therapeutic decisions and also the public health policies on allocating resources and also the efficiency of containment strategies.

Conflicts of interest

The authors declare no conflicts of interest.

Therefore, comparing COVID-19 mortality is necessary, but the differences between countries make it more difficult.

First, it must be remembered that media reports about COVID-19 infections and deaths often use absolute figures; but these indicators depend on many population factors. Simply, the study shows differences that appear comparing the evolution of gross mortalities with mortality rates, in 14 European countries. Subsequent, our correlational analysis brings some clarifications regarding the evolution of rate mortality.

But in an overview, five major areas of investigation can differentiate the countries in the pandemic:

• The proportion of the infected population before the lockdown; this depends on the place and the numbers of the infections, time virus spread, as well as on the timing of the lockdown measures.

• The spread of the virus in the population after the lockdown - some of the factors that affect this are the lockdown policies and the adherence, the availability of personal protective equipment for COVID-19, the way the tests were used and the protection provided to care homes.

• The degree of risk the population had (i.e. the prevalence of comorbidities).

• Access to and quality of health care received by patients with COVID-19.

• Health care for non-COVID-19 patients [17].

And the last criterion is especially important, although often neglected during the pandemic.

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MULTIDIMENSIONAL ASPECT OF FRAILTY SYNDROME OF ELDERLY IN REPUBLIC OF MOLDOVA

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Abstract. Frailty is the geriatric syndrome characterized by decreased physiological reserve and the functions of many body systems associated with age, which leads to an increased vulnerability of the elderly body to endogenous and exogenous factors with a negative impact on health - loss of autonomy, dependence and sometimes death. The study aimed to reveal the multidimensional aspect (medical-psycho-social) of the syndrome, with the detection of several physical, cognitive and social. A group of 1158 elderly patients aged between 65 and 96 years was evaluated, with an average of 71.64 ± 0.1 years, hospitalized in the geriatric wards of the PHI Clinical Hospital of the Ministry of Health, Labor and Social Protection during period 2015-2017. According to the results of the comprehensive geriatric evaluation and the Fried fragility criteria, general group was divided into two study groups: group 1 - elderly patients with fragility syndrome, who constituted n = 315 patients (27.20%) with a mean age of 74.37 ± 0.37 years and group 2 - non-fragile elderly patients, n = 843 (72.79%) with a mean age of 70.62 ± 0.18 years. The data obtained from the study showed a multidimensional aspect of the syndrome, for frail elderly patients determined a decrease of physical function, autonomy, more frequent cognitive and emotional disorders and a low socio-economic status, associated with a higher weight of geriatric syndromes, which had a negative impact on the quality of life of frail elderly patients.
Key words: frailty syndrome, elderly, multidimensional

Rezumat. Fragilitatea este sindromul geriatric caracterizat prin scăderea rezervei fiziologice și a funcțiilor multor sisteme ale organismului asociate vârstei, ceea ce duce la o creștere a vulnerabilității organismului persoanei vârstnice către factorii endogeni și exogeni cu impact negativ pentru sănătate - pierderea autonomiei, instalarea dependenței și, uneori deces. Studiul efectuat și-a propus relevarea aspectului multidimensional (medico-psiho-social) a sindromului, cu depistarea celor de ordin fizic, cognitiv și social. A fost evaluat un lot de 1158 de pacienți vârstnici cu vârsta cuprinsă între 65 de ani și 96 de ani, media fiind de 71,64±0,1 de ani, internați în secțiile de geriatrie al IMSP Spitalul Clinic al Ministerului Sănătății Muncii și Protecției Sociale în perioada anilor 2015-2017. Conform rezultatelor evaluării geriatrice standardizate și aplicării criteriilor de fragilitate Fried, din lotul general au fost formate două loturi de studiu: lot 1 - pacienți vârstnici cu sindrom de fragilitate, care au constituit n=315 pacienți (27,20%) cu vârsta medie de 74,37±0,37 de ani și lot 2 - pacienți vârstnici non-fragili, n=843 (72,79%) cu vârsta medie de 70,62±0,18 de ani. Datele obținute în urma studiului au evidențiat un aspect multidimensional al sindromului, la pacienții vârstnici fragili o scădere a funcționalității fizice, a autonomiei, dereglări cognitive și emoționale mai frecvent și un statut socio-economic mai scăzut, asociat cu o pondere mai înaltă a sindroamelor geriatrice, fapt care a avut un impact negativ asupra calității vieții pacienților vârstnici fragili.
Cuvinte chie: sindrom de fragilitate, vârstnic, multidimensional

INTRODUCTION

Population aging is one of the essential attributes of the contemporary era, being a demographic phenomenon common to all countries both advanced and developing [1]. In the context of the new changes, there is a need for new scientific research in the field of geriatrics, which would allow planning the scope and nature of health care for the elderly. There are still many questions worldwide about the causes of development, effective approach,

early detection, primary and secondary prevention of various geriatric syndromes: falls, incontinence, confusion, dementia, depressive syndrome; one of the most relevant but, at the same time, little understood is the frailty syndrome ("fragility") (FS). This concept includes various factors - such as psychological, physical and social health, mobility and quality of life satisfaction, financial stability, physical activity, spirituality and many others, this position being relevant for the elderly population [2].

FS is defined as a multifactorial medical syndrome characterized by a decrease in strength, endurance and physiological functioning, which leads to loss of reserve functions of the human body when exposed to pathological factors and contributes to the installation of dependence and loss of autonomy [3].

Numerous studies have highlighted the latest data on the prevalence of frailty and various factors that most often influence the appearance and development of FS. The prevalence of frailty varies among studies depending on definitions, countries and screening methods. According to the literature, the prevalence of FS among people aged 65 and older living at home is on average about 10.7%, and the incidence is 41.6% [4]. The prevalence of frailty increases with age, reaching 26.1% among 85-year-olds. FS is significantly more common diagnosed in women than in men. In nursing homes, the prevalence of frailty reaches 52.3% [5, 6]. Given the increasing incidence of FS among the population from different countries and the unfavorable prognosis of frail patients, there is a need for a number of clinical trials aimed for implementing measures for primary and secondary prevention, as well as effective methods of treatment for FS.

The evolution of FS is accompanied by a decrease in physical and functional activity, the reserve of adaptation and recovery of the body, increasing the risk of adverse consequences - hospitalizations, development of functional deficits, death, physical limitations, falls and fractures [7]. Risk factors for the development of FS include: age, low level of physical activity, inadequate nutrition, depression, polymedication, social factors (low income, loneliness, low educational level) [8]. Fried LP et al. [9], based on the clinical observation that the elderly have a low body mass, diminished grip, balance, low physical performance and low physical activity, conceptualize frailty as a vicious circle of decreased energy and reserves, whose elements represent the criteria of diagnosis to identify the syndrome and the basic elements of the pathophysiology of frailty (Fig. 1).

Elderly patients may have a number of nonspecific signs and symptoms that indicate a possible presence of FS or a pre-fragile condition that may progress to partial or total dependence in the elderly. The symptoms of frailty can be variable and may involve the decline of several areas (physical, cognitive, social or psychological). Thus, the frail elderly patient must benefit from complex, multidimensional interdisciplinary geriatric assessment, including an assessment of physical and psycho-emotional state, functional abilities and identification of social problems, in order to develop a treatment plan and observation aimed at restoring or maintaining functional activity of the elderly patient [3, 5, 10].

Frailty is the geriatric syndrome, characterized by decreased physiological reserve and the functions of many body systems associated with age, which leads to an increased vulnerability of the elderly body to endogenous and exogenous factors with negative impact on health - loss of autonomy and death. FS is closely associated with other geriatric syndromes and polymorbidity, can be potentially reversible and influences the patient's approach tactics [3, 4, 10].

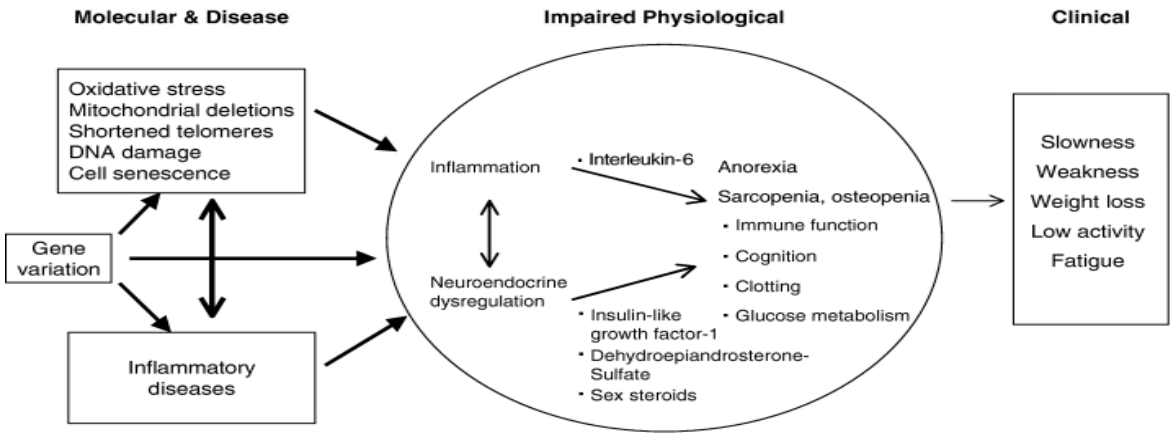


Fig. 1 Pathophysiology of frailty [10]

Based on the above, the purpose of the study was to make a multidimensional assessment of elderly patients in order to establish the FS and determine the impact of frailty on the health areas of elderly patients.

MATERIALS AND METHODS

The descriptive epidemiological study was part of the institutional project "Quality of life of the elderly population with polypathologies in the Republic of Moldova", which included 1158 patients aged 65 years and older, hospitalized in the geriatric wards of IMSP Hospital Clinic of the Ministry of Occupational Health and Social Protection during the years 2015-2017.

Patients were enrolled in research after signing the informed consent to participate in the study. The examination of the patients was performed consecutively as they were admitted to the geriatric ward. All patients were examined according to the complex geriatric assessment that includes clinical status (history, clinical examination), physical status (assessment of autonomy - Katz Score [11], Lawton Score [12]), assessment of gait and balance by performing the Tinetti test [13]), cognitive status (MMSE test [14]), nutritional status (BMI), psychological status (Hamilton test [15]), social and economic status (monthly income) and self-assessment of quality of life by completing the Nottingham questionnaire [16].

FS was established based on the Fried criteria [9]. According to this, the fragile patient is considered when at least 3 of the 5 criteria are present: weakness, self-reported exhaustion, reduced physical activity, unintentional weight loss (4-5 kilograms in last year), and reduced walking speed. Patients with 1 or 2 criteria are considered prefragile or vulnerable, and patients who do not meet any of the Fried criteria are considered robust patients (non-vulnerable, non-fragile).

RESULTS AND DISCUSSIONS

The general study group consisted of 1158 elderly patients aged between 65 and 96 years, the mean being 71.64±0.1 years. The results of the study revealed the predominance of females 58.54% of cases versus males 41.45% of cases. Elderly patients were from both, city and villages, by place of residence – predominantly 652 (56.30%) were rural area.

According to the results of the application of Fried criteria, two study groups were formed: group I, elderly patients with FS, who constituted n=315 patients (27.20%) with a mean age of 74.37±0.37 years, and group II, non-fragile elderly patients, n=843 (72.79%) with a mean age of 70.62±0.18 years.

According to the data from the general study group in patients, cardiovascular

pathology predominated, thus, systolic-diastolic hypertension was determined in 90.50% of elderly patients, of which 4.57% was isolated systolic hypertension. Rhythm disorders were established in 12.86% of patients, and conductivity disorders in 14.83% of patients. Angina pectoris functional class II was determined in 41.19% of cases, and functional class III in 10.10% of cases. Chronic heart failure (CHF) was experienced by 90.49% of patients, of which NYHA grade II HF predominated in 72.53% of patients (Fig. 2).

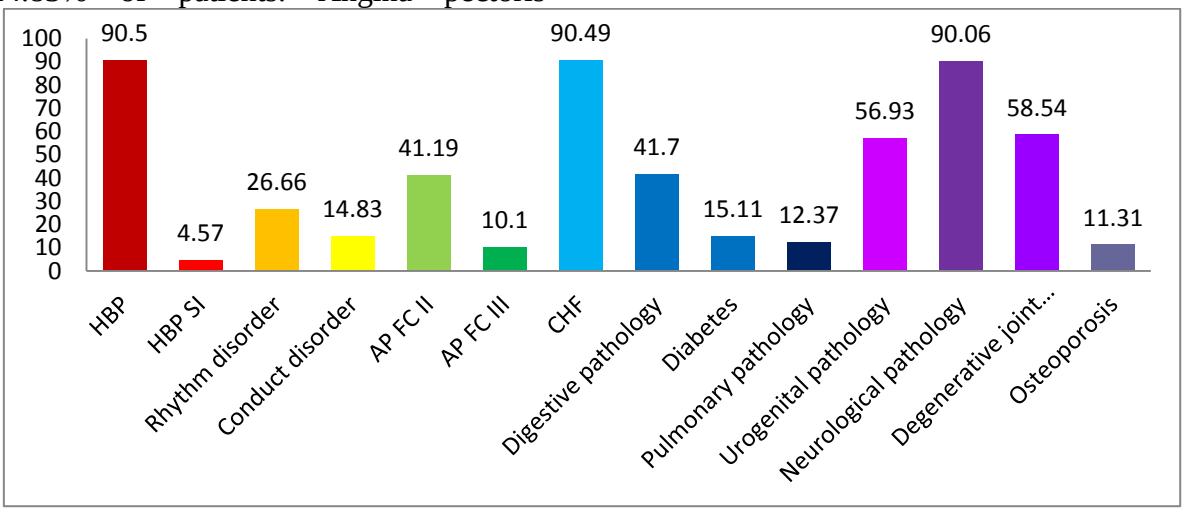


Fig. 2 Graphic representation of the morbidity of elderly patients in the general study group

The results of the assessment of sensory status revealed - hearing loss was established in 35.23% of cases versus 36.89% of cases in non-fragile patients (p=0.60). Decreased visual acuity was diagnosed in 80% of frail elderly patients compared to 75.91% of cases in non-fragile patients (p=0.14).

The nutritional status of elderly patients was established by according to the body mass index (BMI). The results of the evaluation determined an average value of BMI in patients with FS of 28.85±0.38 versus non-fragile patients, the average being 29.91±0.23, with a statistically significant difference between groups (p=0.017). Edentation was established in 66.60% of fragile patients versus 45.31% of non-fragile patients (p<0.017), being the frequent cause of nutrition disorders in the elderly, according to the literature.

The assessment of the functional status of elderly patients included the analysis of gait and balance, assessed by Tinetti score [13] and determination of the level of autonomy, assessed by Katz and Lawton scores [11, 12], the results of the assessment are represented in Fig. 3a. According to Tinetti score, there were 20.43±0.29 points for fragile elderly, lower than in non-fragile elderly patients - 24.21±0.15 points, out of a total of 28 points, which means that patients with FS they had more serious gait and balance disorders compared to patients without FS, but also a higher risk for falls, which is presented by the elderly with a Tinetti score lower than 20 points of the Tinetti score. The results of the assessment of patient autonomy revealed a lower score in frail versus non-fragile elderly patients. Thus, the average Katz score (self-care) in patients in group I was 10.23±0.13 points versus patients in group II - 11.39±0.05 points, out of a total of 12 points (p<0.001) which demonstrates a more obvious limitation of self-care activities in the frail elderly compared to the non-fragile elderly. Daily domestic and extracurricular activities assessed by the Lawton score were also more limited to frail versus non-frail elderly with average values of: group I - 12.77±0.20 points vs. group II - 14.79±0.08 points, without statistically significant difference between the study groups (p<0.08).

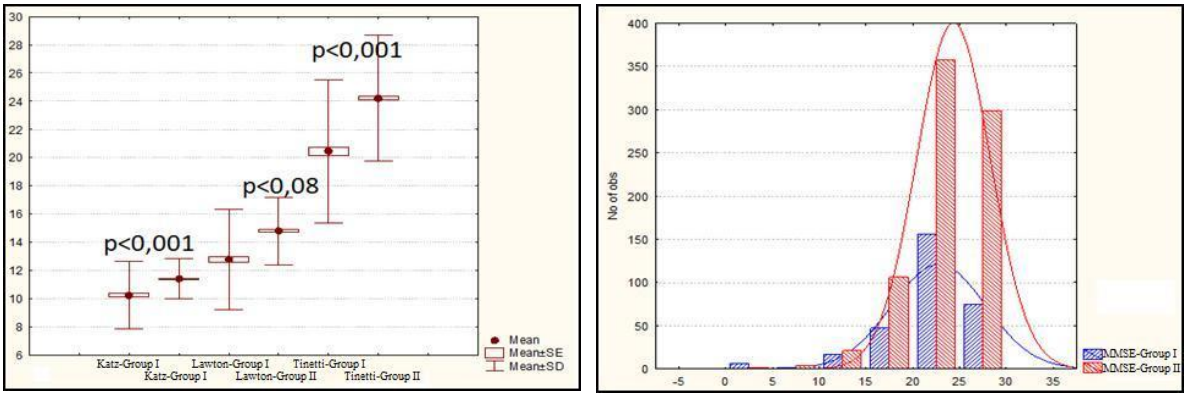


Fig. 3(a, b) Graphical representation of mean values of autonomy, physical activity (a) and cognitive in elderly patients in study groups 1 and 2

The results of the assessment of cognitive status (Fig. 3b) established that from the total number of elderly patients enrolled in the general study group, cognitive disorders presented 22.89% of cases, with an average MMSE score of 23.76±0.13, from it, frail elderly patients had a lower mean MMSE score compared to non-frail elderly patients, the mean score for group I - 22.62±0.28 vs. group II - 24.19±0.13, with statistically significant difference between groups ($p<0.001$).

The multidimensional assessment of FS also included research of the emotional status of elderly patients. In addition to the functional decline, the elderly also show a serious cognitive and emotional decline, thus a large number of depressed elderly were detected, especially against the background of chronic pathology and economic problems. In this case, depression is a condition that significantly reduces the quality of life and functional status of elderly patients and can be one of the types of FS, called cognitive frailty and increases the risk of mortality [17]. Analyzing the data of the research of the emotional state of the patients from the study groups, the depression syndrome was determined in frail elderly patients in 39.66% of cases versus non-fragile patients, at whom depression was established in 12.98% of patients, registering difference statistically significant between study groups ($p<0.001$).

Given the impact of social and economic problems, the social status of the elderly was also revealed, established by analyzing the results of areas such as loneliness, violence, monthly income, and the presence of social assistance. The group I of the elderly with FS, 40.95% stated that they live alone, while the solitary non-fragile elderly patients were 29.06% of cases ($p<0.001$). At the same time, it was determined that 14.28% of fragile elderly people are socially isolated vs. non-fragile - 5.57% of cases, with a statistically significant difference between the study groups ($p<0.001$). Family isolation was recorded in 4.44% of cases from study group I versus 5.10% of cases from study group II, without statistically significant difference ($p=0.64$). At the same time, the monthly incomes of the elderly from the study were evaluated, thus, the average monthly income being 1456.05±26.82 lei, without statistically significant difference between study groups. Social support received 19.36% of frail elderly patients vs. 16.27% of non-fragile elderly patients (Fig. 4) with no statistically significant difference ($p=0.21$). The results of the research on violence against the elderly did not reveal a statistically significant difference, a share of 0.6% of cases of physical violence reported frail elderly and respectively - 1.30% of cases reported non-fragile elderly ($p=0.33$). Moral violence was reported by 3.80% of fragile patients versus 2.37% of non-fragile patients ($p=0.18$).

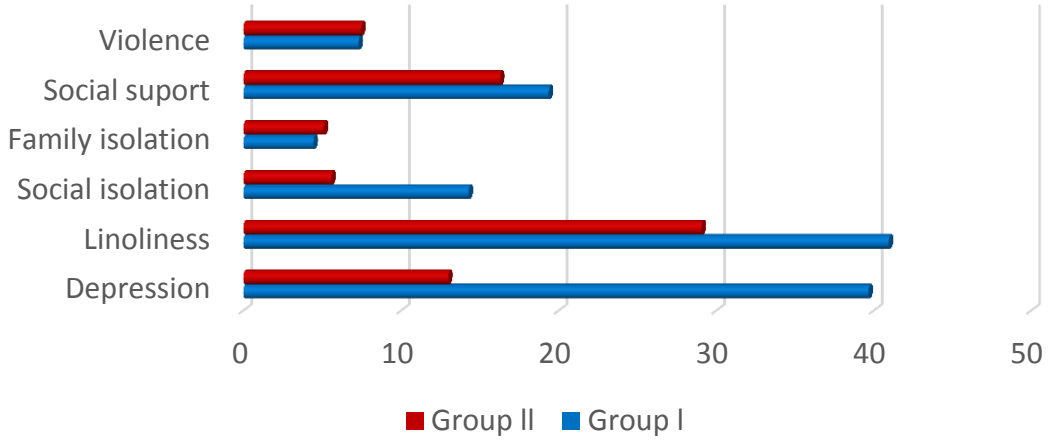
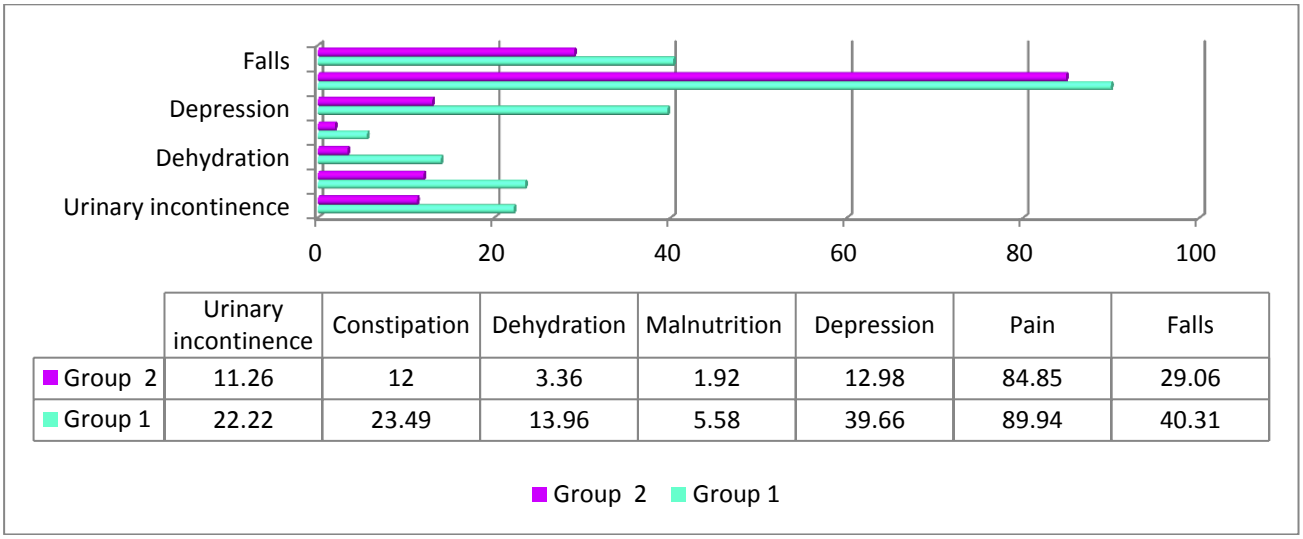


Fig. 4 Graphic representation of the social status of the elderly included in the study, group 1 and group 2

FS is closely related to other geriatric syndromes, it is recommended early detection of clinical conditions and potentially reversible geriatric syndromes that can induce loss of autonomy and decreased quality of life of elderly and senile patients [1]. Based on the results obtained, we revealed the weight of geriatric syndromes in elderly patients in the study groups, the results are represented in Fig. 5. Pain syndrome has the highest weight in both study groups, group I - 89.94% of cases versus group II - 84.85% of cases, without statistically significant difference (p=0.09). It was followed by the fall syndrome, which prevailed in frail elderly patients - 40.31% versus non-fragile patients - 29.06% of cases, registering a statistically significant difference between groups (p<0.001).



	Urinary incontinence	Constipation	Dehydration	Malnutrition	Depression	Pain	Falls
Group 2	11.26	12	3.36	1.92	12.98	84.85	29.06
Group 1	22.22	23.49	13.96	5.58	39.66	89.94	40.31

Fig. 5 Graphic representation of the social status of the elderly included in the study, group 1 and group 2

According to the Nottingham questionnaire, the quality of life of elderly patients in this study was assessed, which involved the areas: energy, pain, emotional reaction, quality of sleep, social isolation and physical ability (Fig. 6).

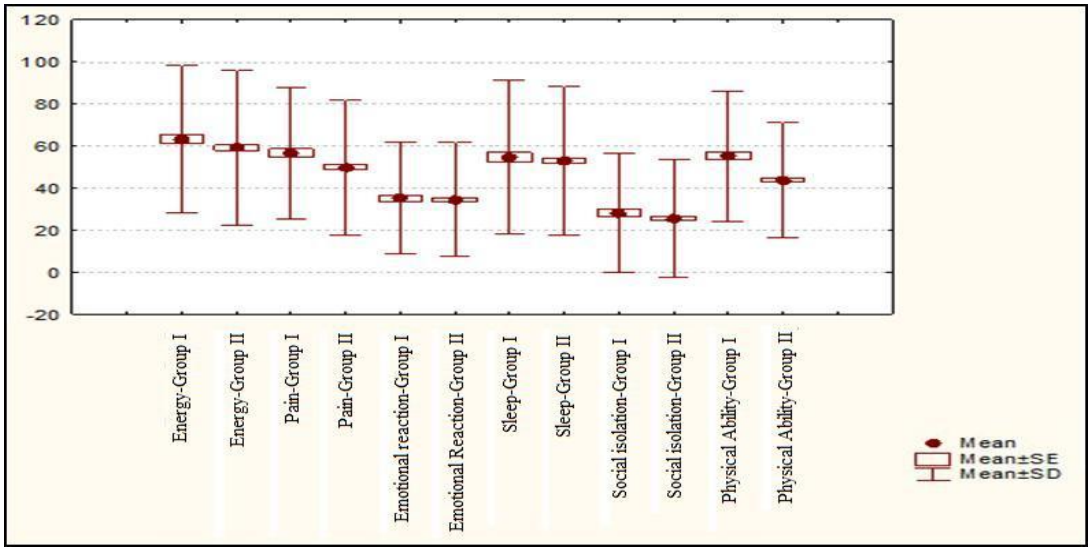


Fig. 6 Graphical representation of the average values of the Nottingham score

The feeling of fatigue and its impact on daily activities was more affected in frail elderly patients in group I than in non-fragile elderly patients in group II, with an average of 63.24±2.14 vs. 59.32±1.34 (p=0.13) the pain value demonstrated a statistical difference between the data of the patients in the study groups (group I - 56.83±1.91 vs. group II - 49.88±1.17, p<0.01).

The analysis of the emotional state of the elderly revealed a decrease of daily activities due to the emotional state in patients from both groups without statistically significant difference (group I - 35.13±1.62 vs. group II - 34.65±0.99, p=0.80).

Sleep quality was decreased in all patients, from both groups, with no statistically significant difference (group I - 54.75±2.24 vs. group II - 53.23±1.29, p=0.55), social relationships were disrupted in both groups of study (group I - 28.10±1.73 vs. group II - 25.51±1.02, p=0.19).

The physical ability of patients from study group I was more diminished, with a mean of 55.29±1.89, registering a statistically significant difference (p<0.001), compared to patients in group II - 43.82±1.01.

The results of the research on the quality of life of elderly patients in the study groups revealed that the most affected areas of quality of life in frail elderly patients were pain and physical ability with statistically significant difference between study groups I and II as well as energy, emotional reaction, sleep quality and social isolation were more affected in frail elderly patients, although without a statistically significant difference between groups. Analyzing the obtained data, it is demonstrative that the FS is closely associated with the presence of geriatric syndromes, polymorbidity and the quality of life affected, which influences the tactics of approaching this category of population.

CONCLUSIONS

• FS has gained increasing interest among health and social care professionals, scientists, public health experts and care planners, highlighting the diversity of the population's self-care capacity.

• The evolution of FS is accompanied by a decrease in physical and functional activity, the reserve of adaptation and recovery of the body, increasing the risk of adverse consequences - hospitalization, development of functional deficits, death, physical limitations, falls and fractures.

• Following the multidimensional approach was estimated the weight of FS in elderly

patients admitted to the geriatric ward, accounting for 27.20%, the study revealed the multidimensional (medical-psychosocial) aspect of FS, highlighting frail elderly with functional decline, disorders more frequent cognitive and emotional disorders, and a more unsatisfactory socio-economic status, associated with a higher share of geriatric syndromes with a serious impact on the quality of life of frail elderly patients.

• The results of the study raise important morbidity issues, which leads to the multidimensional assessment of FS in order to develop measures for early detection of conditions that can induce vulnerability with a negative impact on the quality of life of the elderly in the Republic of Moldova.

Conflicts of interest

The authors declare no conflicts of interest.

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OLDER PEOPLE AND PANDEMIC - COGNITIVE AND MOOD CHANGES

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Abstract. The COVID-19 Pandemic has had a significant and global impact on the daily lives of most individuals in the last almost two years. The imposed quarantine period, measures to prevent the spread of the virus have isolated people, fueled anxious and depressive tendencies, affected the economy and restricted access to health services, with profoundly effects on quality of life. Although these measures were essential to combat the pandemic, the effects on physical, psychological and social health are obvious. In response to these changes, defense and/ or resilience mechanisms have been activated that have shaped a different mode of adaptation and coping depending on the age variable. The general objective of this study was to analyze and evaluate the extent to which older people have been affected by the quarantine period imposed and to identify the possible mood and cognitive changes in response. In the study was considered a group of 199 patients, admitted to the National Institute of Gerontology and Geriatrics "Ana Aslan" Bucharest between August 2020 and October 2021. The data were collected using the Gerontopsychological Interview, the Pandemic Effect Assessment Questionnaire, the Short Disposition Scale, the Mini-Mental State Examination - 2 (Standard Version) and Gerontopsychological Assessment Sheet. The data analysis shows a high incidence of the existence of pandemic effects at the level of the studied group - 94% of respondents claiming the presence of a negative impact of the pandemic. The imposed quarantine and the effects of the pandemic were associated with the high presence of depressive and anxiety symptoms and the appearance of sleep disorders. The older people living alone were the most affected by the pandemic and the enforced measures. People who organized their daily lives and became mentally and physiologically active managed this period more effectively.
Key words: isolation, disposition, adaptation, older people

Rezumat. Pandemia COVID-19 a avut un impact semnificativ și global asupra vieții de zi cu zi a majorității indivizilor în ultimii aproape doi ani. Perioada de carantină impusă, măsurile de prevenire a răspândirii virusului au izolat oamenii, au alimentat tendințele anxioase și depresive, au afectat economia și au restricționat accesul la serviciile de sănătate afectând profund calitatea vieții. Deși aceste măsuri au fost esențiale pentru a combate pandemia, efectele asupra sănătății fizice, psihologice și sociale sunt evidente. Drept răspuns la aceste schimbări au fost activate mecanisme de apărare și/ sau reziliență care au conturat un mod de adaptare și conținere diferit în funcție de variabila vârstă. Obiectivul general al acestei lucrări a fost acela de a analiza și evalua măsura în care persoanele vârstnice au fost afectate de perioada carantinei impuse și de a identifica modificările dispoziționale și cognitive posibile ca răspuns. În cadrul studiului a fost luat în considerare un lot de 199 de pacienți, internați la Institutul Național de Gerontologie și Geriatrie "Ana Aslan" București în perioada august 2020 - octombrie 2021. Datele au fost recoltate cu ajutorul Interviului Gerontopsihologic, a Chestionarului de Evaluare a Efectelor Pandemiei, a Scurtei Scale de Dispoziție, a Mini-Mental State Examination - 2 (Varianta Standard) și Fișei de Evaluare Gerontopsihologice. Analiza datelor arată o incidență ridicată a existenței efectelor pandemiei la nivelul lotului studiat - 94% dintre respondenți afirmând prezența unui impact negativ al pandemiei. Carantina impusă și efectele pandemiei s-au asociat cu prezența ridicată a unei simptomatologii depresive și anxioase și cu apariția tulburărilor de somn. Persoanele vârstnice care trăiesc singure au fost cele mai afectate de pandemie și de măsurile luate. Persoanele care și-au organizat viața de zi cu zi și s-au activat mental și fiziologic au gestionat mai eficient această perioadă.
Cuvinte cheie: izolare, dispoziție, adaptare, vârstnici

INTRODUCTION

The year 2020 has brought about a real epidemiological revolution worldwide. The COVID-19 pandemic has made many changes in all areas, affecting everyone. The changes brought about by SARS-CoV-2 have forced the population of the earth to adapt to new situations and usual patterns. Limiting outings, meetings, restricting social activities, have led to global isolation. The pandemic has managed to open everyone's personal resources to adapt to new situations and to adapt to unforeseen situations.

Comorbidities, along with SARS-CoV-2 infection, have killed 5,224,519 people

worldwide [1]. In first phase, the main risk group was represented by the older people. According to Elsevier Public Health Emergency Collection, the pandemic was perceived as a real "attack" on the older people [2]. As a measure to combat the pandemic, the elderly had been instructed to stay home, order online shopping for groceries and medications, and avoid social contact with family and friends. On the other hand, it is well documented that the isolation of the elderly is a serious public health problem due to the increased risk of cardiovascular, autoimmune, neurocognitive and mental health problems [3]. Moreover, social disconnection acts for the elderly as a risk factor for depression and anxiety [4]. If before they were encouraged to get involved in community service, after the pandemic broke out, they were forced to give up these activities and protect themselves. The pandemic turned society into a conservative one.

Household chores returned to the older people, who were encouraged to work outside the house after retirement, they became the vulnerable and helpless group of society again [5]. If previous recommendations regarding to older people were to move as much as possible, to participate in senior groups, to find a daily activity that would take them out of their homes and get as involved as possible in social activities, after the outbreak of the pandemic, the recommendations were quite the opposite.

Early studies have already reported an increase in anxiety, and depression in the general population, especially those facing extended lockdowns [6].

Even outside of crisis times, the elderly population has relatively high rates of depressive symptoms, which is troubling in the face of evidence that those suffering from pre-existing mental health conditions have been most affected by the negative psychological consequences of lockdowns [7]. Studies have shown that depression in the elderly is linked to the subsequent cognitive decline, and risk of Alzheimer's disease [8].

Resilience is described as the capacity to cope with difficult situations, which usually fluctuates across the lifespan and is often interrelated with some psychological conditions.

In terms of resilience a lot of studies suggest that older adults cope better because of life experience and lower psychological vulnerability [9]. Many older people have redefined their experiences in terms of time left to live, and they focus on what is most meaningful now. They let go of what they can't do anything about. Instead of looking back, older adults are motivated to enjoy the time they have left. Early studies during the COVID-19 pandemic seem to confirm this, showing that older adults struggle better with stresses and daily life challenges associated. A qualitative study which aims to identify ways of coping with worries and stress during the pandemic from the perspectives of older adults in the United States provides novel qualitative evidence on their coping strategies [10]. Frequently - reported strategies included exercising and going outdoors, modifying routines, following public health guidelines, adjusting attitudes, and staying socially connected. Most of the strategies encouraged self-improvement, positive adjustment, and wellness.

Another important resource-factor which has been explored during the pandemic restrictions was the incorporation of internet and mobile technology. Before this pandemic was a steady growth in the number of tech-savvy older people. It was documented that between 2013 and 2017 smart phone ownership in USA increased by 24% in adults over 65 [11]. The pandemic has been an opportunity for older adults to get more comfortable using technology and for community and health-care providers to offer remote programming. A cross-sectional study conducted on 400 older people >65 years who lives in British Columbia, Canada

identified that slightly more than half of the respondents (n=224, 56%) reported that, since the beginning of the pandemic, they used technology differently to connect with others during the pandemic. Additionally, 55.9% (n=223) of respondents reported that they adopted new technology since the beginning of the pandemic. This demonstrated that older adults used technology to mitigate social isolation during the pandemic [12]. Web-based socialization is the most promising method for mitigating potential mental health effects that are related to virus containment strategies. Providing telephone training; creating task lists, facilitating socialization activities; these strategies can be implemented during and beyond the pandemic to bolster the mental health needs of older adults.

These findings are in line with core gerontological theories on successful aging demonstrating that older people are able to adapt, select, and optimize in seemingly adverse conditions [13]. Older adults who reported excellent or good quality of life had built and maintained a balance among body, mind, and spirit and were in harmony with their environment. More than that they explore and cultivate the possibilities of their environment. They did not deny and diminish the pandemic effects but felt satisfaction by overcoming them.

OBJECTIVES

The general objective of this study was to analyze and evaluate the extent to which older people have been affected by the quarantine period imposed and to identify the adaptation mechanisms activated in response. The specific objective was to measure the psychoemotional and cognitive status of the elderly during the pandemic.

MATERIALS AND METHODS

The team of psychologists from the Research Laboratory of Social Gerontology of National Institute of Gerontology and Geriatrics (NIGG) ”Ana Aslan” initiated in 2019 a longitudinal study ”GeRoPsi – Biopsychological factors and the dynamics of the gerontopsychological profile” with duration of five years. The data presented in this article are part of the second stage of this research and contains information collected from a sample of 199 subjects from the NIGG ”Ana Aslan”, patients hospitalized between August 2020 and September 2021.

Terms of inclusion: Inpatients admitted to the clinics of NIGG ”Ana Aslan” Bucharest, age between 50-95 years.

Exclusion conditions: Rejection from their sight to answer.

Prior to GeRoPsi study initialization, all subjects signed the Informed Consent form. The patients who did not sign the Informed Consent were excluded.

The evaluation and screening methods used for this purpose included:

- Gerontopsychological Interview;
- Pandemic Injury Questionnaire/ added to the Gerontopsychological Interview;
- Mini-Mental State Examination - 2 (MMSE-2) Standard Version, 30 items [14];
- Short Disposition Scale, 9 items for Anxiety and 9 items for Depression [15];
- Gerontopsychological Evaluation Sheet [16], a tool developed in GeRoPsi project. It is a complex tool and global that includes subjective accounts of the patient’s symptoms at emotional, cognitive, behavioral, psychophysiological, personological and social level, as well as specific and standardized tests and scales.

RESULTS

The patients were admitted to the NIGG “Ana Aslan”, between August 2020 and September 2021. Respondents included 199 older adults aged an average of 73 years, gender distribution shows an increase presence of female gender 86.93% (n=173) within the studied group (Fig. 1).

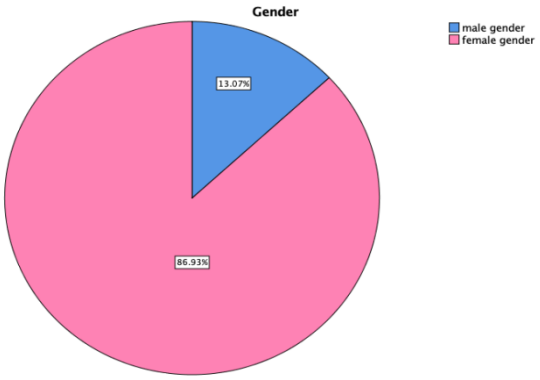

Fig. 1 Gender distribution of respondents

Most respondents 93.97% (n=187) at the question regarding if the pandemic affected them responded positively (Fig. 2) with simillary gender distribution.

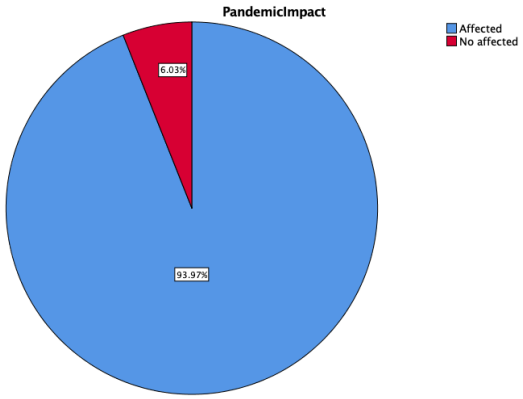

Fig. 2 Distribution of pandemic affected respondents

The variable Affected Covid depending on gender distribution indicates a greater impact felt by the female gender. 87.16 % (n=163) of respondents who were considered to be affected by the pandemic were female (Tab. I).

Tab. I Gender distribution of pandemic affected respondents

Gender * CovidAffected Crosstabulation

Count

		CovidAffected		
		0	1	Total
Gender	male gender	2	24	26
	female gender	10	163	173
Total		12	187	199

Distribution by age groups shows that the most affected was 50-64 age group 25% followed by the 65-74 age group 24.09% and the least affected was 75-84 age group 21.77% (Fig. 3).

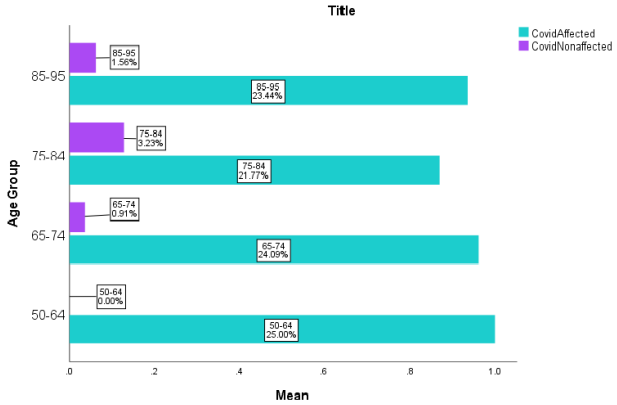

Fig. 3 Age groups distribution of pandemic affected respondents

Regarding the habitual conditions of the sample of 187 subjects who were considered to be affected by the pandemic, the greatest impact is bourne by people living alone 43.85% (n=85) (Fig. 4).

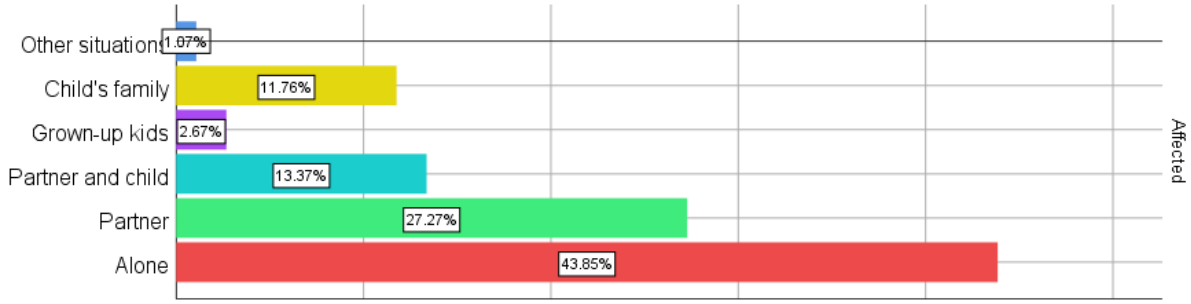

Fig. 4 Habitual conditions distribution of pandemic affected respondents

People living with their families reported a low pandemic impact, but due to specific habitual conditions, they were associated with acute stress (Fig. 4). In relation to the type of associated stress, the existence of the pandemic generated a high acute and equal stress 40% in case of variable living with the partner and living with the child and his family (Fig. 5).

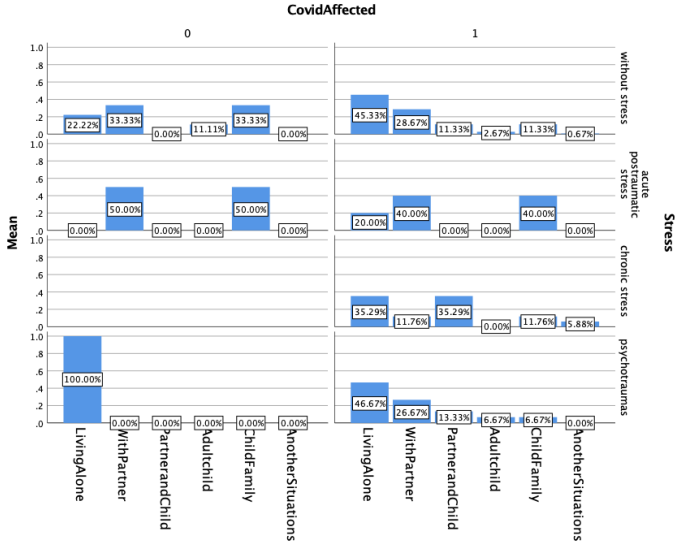

Fig. 5 Stress and pandemic impact

The subjective accusations that the evaluated person expresses and identifies were recorded in the Gerontopsychological Evaluation Sheet, elaborated in the first stage of GeRoPsi project. The correlation with the perceived distress from the pandemic impact is significant, $p<0.05$ (Tab. II). The statistical correlation obtained between the Covid impact variable and the types of subjective accusations shows their diversity in the case of the existence of a pandemic impact.

Tab. II Correlation of subjective accusations and distress created by pandemic

Correlations

		CovidAffected	SujectiveAccusartions
CovidAffected	Pearson Correlation	1	-.144*
	Sig. (2-tailed)		.042
	N	199	199
SujectiveAccusations	Pearson Correlation	-.144*	1
	Sig. (2-tailed)	.042	
	N	199	199

*. Correlation is significant at the 0.05 level (2-tailed).

In the case of people who feel an impact of the pandemic, 73.26% associate this impact with mixed, cognitive and emotional accusations, insomnia, somatic accusations and restless. It can be noted, compared to people who do not validate the existence of an impact of the pandemic, the presence of especially somatic accusations and insomnia (Fig. 6).

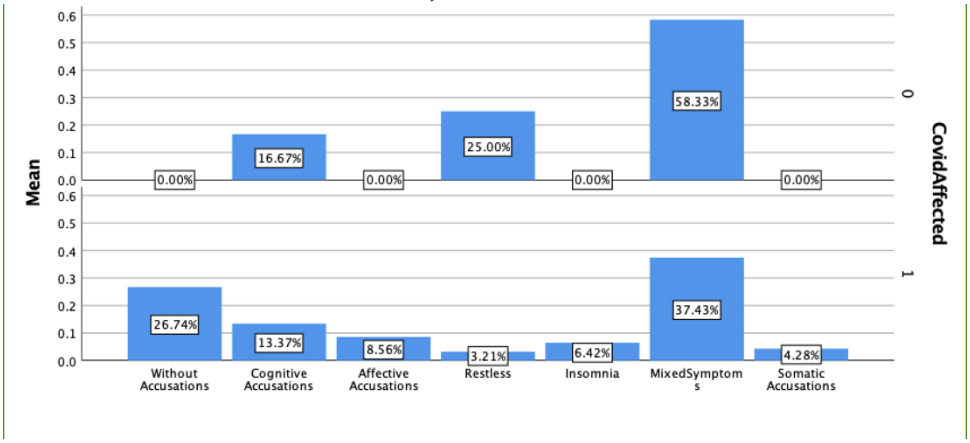

Fig. 6 Subjective accusations and distress created by pandemic

From this point of view, there is congruence between the presence of the affective accusations, cognitive accusations, insomnia and the results of objective evaluation with psychometrics tests, which indicates a critique of present condition.

A high percentage of sleep disorders was observed among those interviewed. There were 87.2% (n=163) subjects who experienced initiation insomnia during this period, only 11.2% (n=21) did not notice difficulty falling asleep (Tab. III).

Tab. III Sleep quality distribution of pandemic affected respondents

Insomnia		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No insomnia	21	11.2	11.2	11.2
	initiation	163	87.2	87.2	98.4
	wakening	2	1.1	1.1	99.5
	No answer	1	.5	.5	100.0
	Total	187	100.0	100.0	

Applying the Short Disposition Scale 99.5% of patients described manifestations specific to anxious and depressive mood as agitation, worry, irritability, insomnia, headache and dizziness, apathy, loss of hope and confidence, loss of appetite, nausea (Fig. 7).

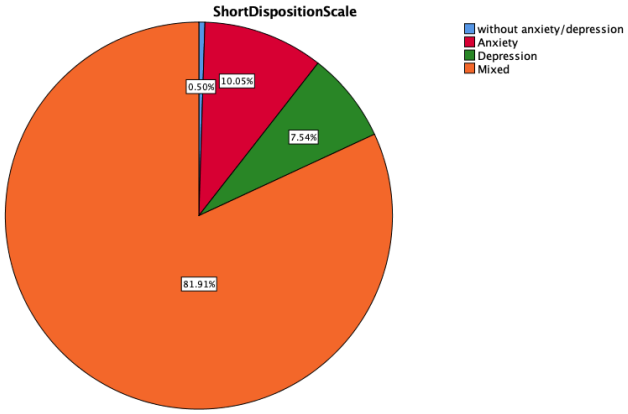

Fig. 7 The Short Disposition Scale results distribution

According to their statements, the lack of socialization, of the simple walks, the reduction of the habits they had before the pandemic, had a long-term setback. They noticed changes in attention, concentration, acquisition of fresh information. Data collected at the cognitive screening indicate an important percentage of people 44.72% (n=84) which obtained a law score at MMSE-2 (SV) indicating mild cognitive impairment (Fig. 8).

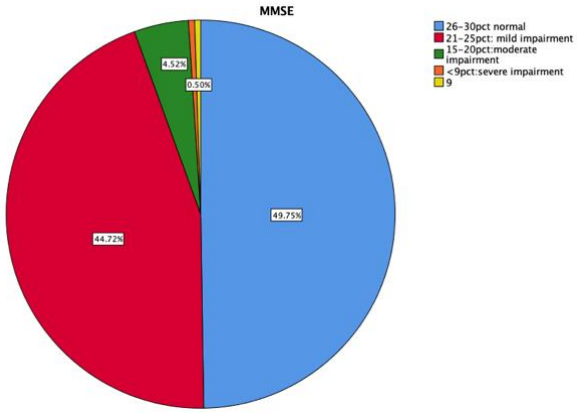

Fig. 8 The Mini-Mental State Examination (MMSE–2 VS) results distribution

After the complex neuropsychological evaluation at cognitive level, the Covid impact variable is associated in a high proportion 29.95% with a mild cognitive impairment (Fig. 9).

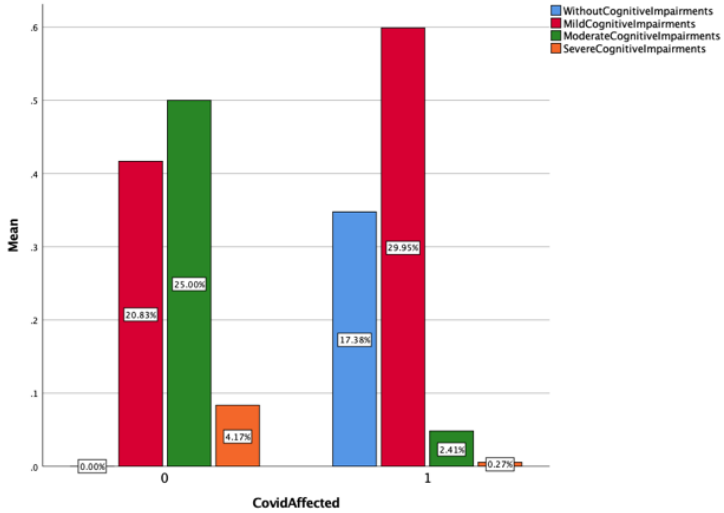

Fig. 9 Level of Cognitive Impairment and pandemic affected

The correlation was considered as statistically significant level p<0001 (Tab. IV)

Tab. IV Correlations of pandemic affected and Cognitive Impairments

Correlations

Double-click to activate

		CovidAffected	CognitiveImpairments
CovidAffected	Pearson Correlation	1	-.365**
	Sig. (2-tailed)		.000
	N	199	199
CognitiveImpairments	Pearson Correlation	-.365**	1
	Sig. (2-tailed)	.000	
	N	199	199

**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSIONS

Surprisingly, those in the 75-84 age group were not as affected as those in the 50-64 age group, which answered most often with yes. The explanation could be given by the fact that those in the 50-74 age group are mostly professionally active or that they interacted frequently with their social group before the lockdown was imposed.

There have been described situations in which families did not meet until the restrictions were lifted, holidays spent without children and grandchildren, all because of the fright of being infected. A good mechanism to get through this pandemic more easily was to live with your partner or child's family. One explanation would be that grandparents continued to have concerns and responsibilities with their grandchildren. There were situations in which they stayed with them because they couldn't return to their homes in another city.

People living with their families reported a low pandemic impact, but due to specific habitual conditions, they were associated with acute stress. In relation to the type of

associated stress, the existence of the pandemic generated a high acute and equal stress in case of variable living with the partner and living with the child and his family.

The loss of physical contact with those they used to meet before, the restriction of shopping or replacing them with online orders, has led to an increase in anxiety and depression. Most of patients described manifestations specific to anxious and depressive mood as agitation, worry, irritability, insomnia, headache and dizziness, apathy, loss of hope and confidence, loss of appetite, nausea. Difficulty falling asleep was common, 87.2% said they had initiation insomnia.

The data obtained after application of cognitive tests, highlighted a personal underestimation. This may be due to lack of social contact, lack of intellectual and physical effort. They complained changes in attention, concentration, acquisition of fresh information and in the objective evaluation a rather mild cognitive impairment was noticed.

CONCLUSIONS

People in the 50-64 age group struggled to cope, being the most physically and professionally active age group.

People who lived with their partner or child's family went through this period more easily. The daily organized activity, the fact that they helped their children and grandchildren, the simple presence of a family member counted in facing more easily lockdown period.

The majority of patients interviewed (99,5%) described mood swings specific to anxiety and depression during lockdown as agitation, worry, irritability, insomnia, headache and dizziness, apathy, loss of hope and confidence, loss of appetite, nausea.

Regarding the cognitive level, there is a personal underestimation; they accused the loss of the ability to record fresh information, concentration difficulties and organization capacity, a process refuted by the results obtained in the psychological evaluation.

People who managed to maintain a physical and mental balance during the lockdown period, explained how they planned each day, activity, did physical exercises and specific neurofitness exercises (exercises for optimal brain function).

Conflicts of interest

The authors declare no conflicts of interest.

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PSYCHIATRIC COMPLICATIONS OF SOCIAL ISOLATION DURING COVID-19 PANDEMIC IN ELDERLY INPATIENTS

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Abstract. The lifelong perceived social isolation may have an impact on a person's physical and mental health. Because of the COVID-19 pandemic, the authorities were forced to implement social distancing and isolation measures that impacted our lives. Previously there were some evidence in the specialty literature that correlated the perceived social isolation with depression, poor sleep quality, impaired executive function, cognitive impairment, maladaptive cardiovascular function, and reduced immunity (statistically significant at every stage of life). In elderly, loneliness is associated with a 40% increase in the risk of dementia. Knowing these data, our objective was to assess how the Covid-19 pandemic impacted our practice and patients in 2020, compared to 2019. From the quantitative point of view the number on inpatients was reduced by 3 quarters but the number of outpatients doubled. Hospitalized patients presented significantly more somatic and psychiatric comorbidities compared to the previous year (79.6% with 3 and over 3 diagnostics, p=0.043). From the diagnosis point of view, most of them had associated affective disorders and circadian rhythm disorders. The main symptoms for which they referred to our services were depressive symptoms, sleep problems, anxiety, memory losses and vertigo. Other common symptoms registered were sadness, numbness, confusion, fury, symptoms of post-traumatic, alternated mood, perceived stress, emotional disbalances, irritability or emotional exhaustion. It also seems there is a bidirectional link between psychiatric afflictions and Covid-19 cases.
Key words: social isolation, COVID-19 pandemic, psychiatric consequences, elderly patients

Rezumat. Perceperea izolării sociale poate avea un impact asupra sănătății fizice, mentale şi cognitive a unei persoane. Din cauza pandemiei de Covid-19, autoritățile au fost forțate să pună în aplicare măsuri de izolare și distanțare socială, care ne-au afectat viața. Există date în literatura de specialitate, ce corelează perceperea izolării sociale cu depresia, calitatea slabă a somnului, afectarea funcției executive, afectare cognitivă, funcție cardiovasculară inadaptată sau imunitatea redusă (date semnificative statistic în fiecare etapă a vieții). De exemplu, la vârstnici, singurătatea percepută este asociată cu o creștere cu 40% a riscului de demență. Cunoscând aceste date, obiectivul nostru a fost de a evalua modul în care pandemia Covid-19 a influențat practica noastră și pacienții în 2020, comparativ cu anul 2019. Din punct de vedere cantitativ, numărul pacienților internați a fost redus cu 3 sferturi, dar numărul pacienților consultați în regim ambulatoriu s-a dublat. Pacienții spitalizați au prezentat semnificativ mai multe comorbidități somatice și psihice comparativ cu anul precedent (79,6% cu 3 și peste 3 diagnostice, p = 0,043). Din punct de vedere al diagnosticului, cei mai mulți dintre ei au suferit de tulburări afective și tulburări de ritm circadian. Principalele simptome pentru care s-au prezentat au fost dispoziția depresivă, tulburări de somn, anxietate, pierderi de memorie și vertij. Alte simptome frecvente înregistrate au fost tristețe, parestezii, confuzie, furie, simptomele posttraumatice, anhedonia, perceperea stresului, dezechilibrele emoționale, iritabilitatea sau epuizarea emoțională. Se pare, de asemenea, că există o legătură bidirecțională între afecțiunile psihiatrice și cazurile COVID -19.
Cuvinte cheie: izolare sociala, pandemie de COVID -19, complicații psihiatrice, pacienți vârstnici

INTRODUCTION

Isolation had an ambivalent effect on humans because it has attracted and frightened us since the beginning of civilization. However, until a couple years ago, its consequences have not been fully and scientifically explored.

A meta-analysis published 5 years ago by Hawkley L.C. and Capitanio J.P. [1], unequivocally demonstrated that the effects of lifelong perceived social isolation (more specifically on loneliness) can wreak havoc on a person's physical, mental, and cognitive health. Hawkley presents clear evidence that correlates perceived social isolation with depression, poor sleep quality, impaired executive function, cognitive impairment, maladaptive cardiovascular function, and

reduced immunity (statistically significant at every stage of life) [1].
Moreover, a study published in 2019 by Alcaraz K.I. et al. [2], a public health researcher at the American Society for the Study of Cancer (which analyzed data from more than 580,000 people), found that social isolation increases the risk of premature death from any cause regardless of race. According to Alcaraz, social isolation doubled the risk of early death in Afro-American population, while in Caucasians the risk increased by 60% to 84% [2].
Other recent research shows that the magnitude of the risk of social isolation is remarkably similar to the risk of people with conditions such as obesity, nicotine addiction or lack of access to health care and physical inactivity. In this study, researchers evaluated many variables and found that, in general, race appeared to be a stronger predictor of social isolation than gender. Interestingly, Sutin A. et al. [3] found that loneliness is associated with a 40% increase in the risk of dementia. The study looked at data from more than 12,000 adults over the age of 50. Participants assessed their level of loneliness and social isolation and completed a cognitive battery every two years for a period of 10 years, so the relevance of longitudinal data is reliable [3].
The real challenge of social isolation was revealed globally, during the COVID-19 pandemic where it was noticed quite quickly that quarantine isolation induces a rapid increase in behavioral and psychological symptoms related to stress (in about 60% of patients with dementia). The same effects were observed in two-thirds of their caregivers. So, the health services are required to plan a post-pandemic strategy to meet these emerging needs.
The increase in the incidence of mental and behavioral symptoms was reported in [4]:

• 59.6% of patients as worsening of pre-existing symptoms
• This required medication changes in 27.6% of these cases.
• As onset in 26% of patients.

Symptoms varied depending on the profile of the patients, their gen and ethnicity, type of dementia and severity of the disease. Anxiety and depression in the context of isolation were associated with the severity of the disease (mild to moderate), female gen and the diagnosis of Alzheimer's dementia (OR 1.35, CI: 1.12-1.62) [4].
In addition, we got some interesting conclusion from a meta-analysis published in 2020 by Sepúlveda-Loyola W. et al. [5] that included the data of 20069 people from 41 studies published after the onset of the pandemic in Pubmed, Scielo and Google Scholar (with the following MeSh search terms: "COVID-19", "coronavirus", "aging", "elderly", "social isolation" and "quarantine"), in English, Spanish or Portuguese. The main symptoms reported were anxiety, depression, poor sleep quality and physical inactivity during the isolation period [5]. In these cases, the main international recommendations were to implement cognitive strategies, increasing the level of physical activity using online applications or videos and telemedicine.

OBJECTIVE

The aim of the study was to evaluate from the data of our psychiatric office from the National Institute of Geriatric and Geriatrics (NIGG) ”Ana Aslan”, gather from the 1st of January to the 31 of December 2020, the impact of the isolation caused by Covid-19 on the inpatient’s structure, symptomatology and diagnostic.

METHODS

Simple statistical analysis of the data (n=294) from the inpatient registry between the 1st of January to the 31st of December 2020 of the psychiatric office from the NIGG ”Ana Aslan”, Bucharest, Romania. The diagnostics system used was

International Classification of Diseases 10th edition (ICD 10), and the severity of the afflictions was also estimated by ICD standards.

RESULTS

From all registered inpatients prevailing diagnostics was: major depressive disorder (MDD), sleep disorder (SD), vascular dementia, anxious disease, Alzheimer's disease, Mild Cognitive Impairment.

The patient's profile in the psychiatric office from the NIGG "Ana Aslan" in 2020: an average age of 69.4 years; predominant female gender (Fig. 1) and urban residences (Fig. 2)

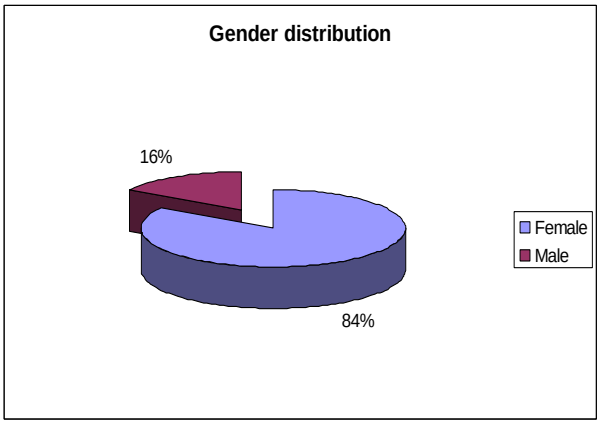

Fig. 1 Gender distribution

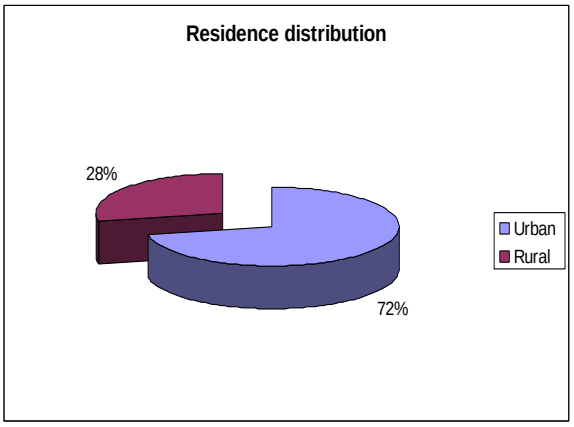

Fig. 2 Residence distribution

The outpatient activity doubled (+108%) but at the same time the number of hospitalized patients who needed specialized psychiatric services decreased by 3 quarters, compared to 2019.

Hospitalized patients presented significantly more somatic and psychiatric comorbidities compared to the previous year (79.6% with 3 and over 3 diagnostics, p=0.043).

In the psychiatric office from the NIGG "Ana Aslan" there were registered, that due to the COVID -19 pandemic, the structure of patients' symptoms modified, as follow:

• The main symptoms were more severe.

• The main symptoms for which they referred to our services were depressive symptoms, sleep problems, anxiety, memory losses and vertigo.

• Other common symptoms registered were sadness, numbness, confusion, fury, symptoms of post-traumatic, alternated mood, perceived stress, emotional disbalances, irritability or emotional exhaustion.

From the diagnosis point of view, most of them had associated affective disorders and circadian rhythm disorders. Interestingly, compared to the inpatients, most of the outpatients (84%) used and appreciated telemedicine services, although this initially created additional stress.

The most common diagnostics association was between major depressive disorders or sleep disorder as first diagnostic, with (Tab. I):

Tab. I The most common association between the first and the second diagnostic

The most frequent diagnostics association	
MDD (321) with Vascular Dementia (299)	14,81%
MDD (321) with Vertigo (438)	32,74%
MDD (321) with SD (332)	35,30%
MDD (321) with Anxious Disease (325)	22,28%
MDD (321) with Mild Cognitive Impairment (303)	20,96%

MDD (321) with Alzheimer's Dementia (368)	7,54%
SD (332) with Mild Cognitive Impairment (303)	28,47%
SD (332) with Vertigo (438)	31,50%
SD (332) with MDD (321)	74,55%
SD (332) with Anxious Disease (325)	36,59%
SD (332) with Vascular Dementia (299)	14,00%
SD (332) with Alzheimer's disease (368)	8,76%

DISCUSSIONS

A metanalysis published last year by Taquet M. and his collaborators that included the data from the electronic health record network from 69 million US individuals, 62 354 of whom had a diagnosis of COVID-19, revealed that whether a diagnosis of COVID-19 (compared with other health events) was associated with increased rates of subsequent psychiatric diagnoses and a psychiatric diagnosis in the previous year was associated with a higher incidence of COVID-19 diagnosis (relative risk 1·65, 95% CI 1·59–1·71; p<0·0001). Moreover, this risk was independent of known physical health risk factors for COVID-19, but we cannot exclude possible residual confounding by socioeconomic factors [6]. Interestingly, the HR was greatest for anxiety disorders, insomnia, and dementia. It was observed some similar findings, although with smaller HRs, when relapses and new diagnoses were measured. The incidence of any psychiatric diagnosis in the 14 to 90 days after COVID-19 diagnosis was 18·1% (95% CI 17·6–18·6), including 5·8% (5·2–6·4) that were a first diagnosis. The incidence of a first diagnosis of dementia in the 14 to 90 days after COVID-19 diagnosis was 1·6% (95% CI 1·2–2·1) in people older than 65 years [6]. So, our results are in the line with other big study results.

CONCLUSIONS

From the literature [7, 8] and our own experience, we can synthesize some practical advices for the patients to better cope with isolation and prevent to some degree the consequences of isolation:

1. Stay connected with your family, entourage and doctors by phone, online virtual meetings, or other channels.
2. Create a structured plan with your psychiatrist, psychologist, or social worker to stay busy. Set at least one specific goal or goal for each day. This will help your internal clock work smoothly, which will help stabilize your condition even if you suffer from depression or anxiety. Follow the treatment plan.
3. Eat healthy, avoid snacks as much as possible. By eating regularly, you will have a stable blood sugar level, which can also have a positive impact on your mood.
4. Try to move more, because exercise has been shown to help reduce depressive symptoms and emotional disorders.
5. Engage in those healthy behaviors and hobbies that do you well, such as listening to music, spending time with pets, reading a book, making art, and the like.
6. Stay informed, but limits exposure around bedtime.
7. Try to wake up and sleep at the same hours to keep a regular circadian activity that will improve your mood. Melatonin may also be a first therapeutic attempt if sleep disturbances or circadian rhythms occur.
8. Remember that this situation is temporary and will pass.

Limitations

The research is simple by designed and do not establish correlations, cause-effects, scales measurements or analyze post/pre COVID-19 effects in a complex way. Moreover, the results may be biased by the health laws enforced in 2020.

Disclosures and conflict of interest statements

There are no potential financial or personal conflicts of interests with other organizations or people that could influence the conduct or biased study results.

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INSTRUCTIONS FOR AUTHORS

MANUSCRIPTS. Manuscripts must be written in English and is necessary to contain genuine material. All manuscripts are submitted online, Word Doc, with all figures, references, figure legends and tables in the same document. Will be used Times New Roman font 12 and 1.0 spacing throughout. Acceptable formats for pictures, photos, and figures are JPG or TIF.

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