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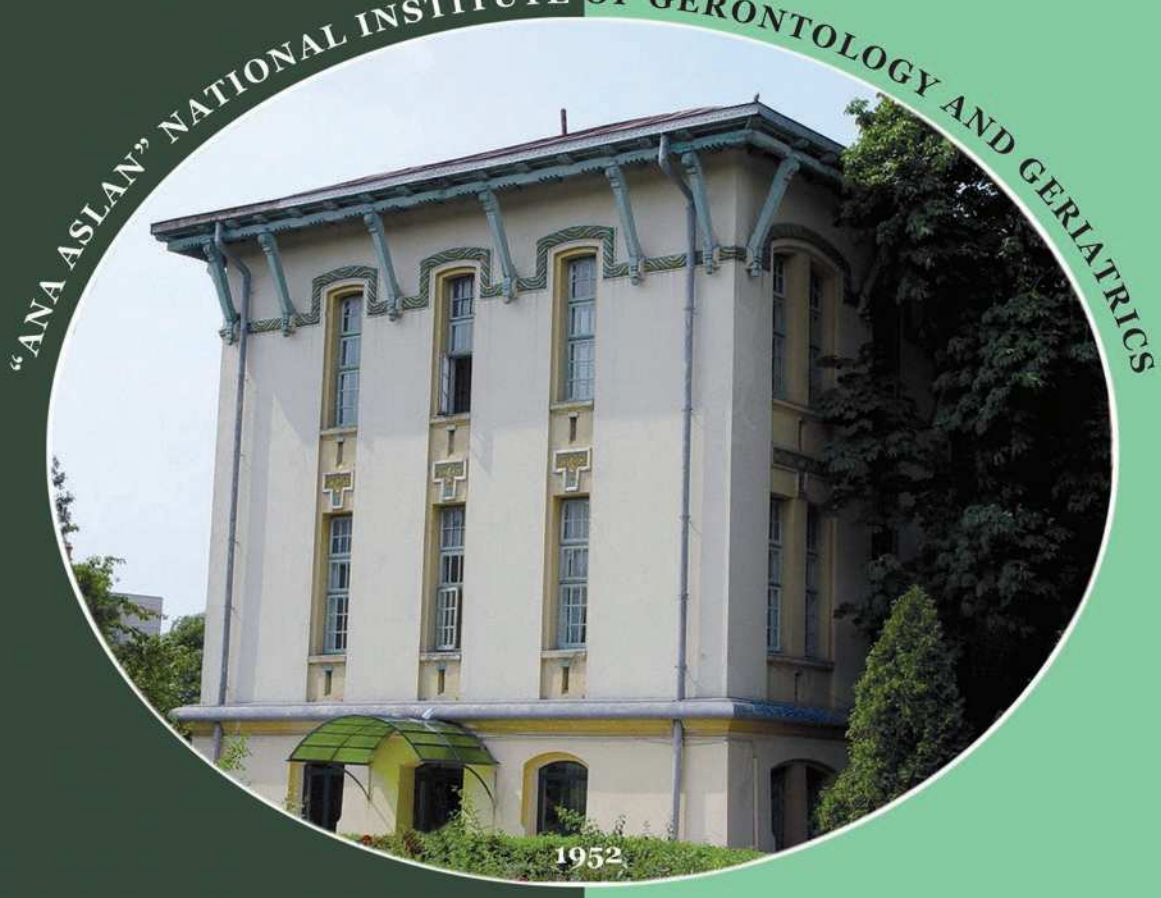


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# Contents

# Cuprins

# SCREENING OF FRAILTY SYNDROME IN A SELECTED GROUP OF ROMANIAN OLDER PEOPLE

*Cătălina **Pena**[1], Rozeta **Drăghici**[1], Anna Marie **Herghelegiu**[1,2], Doina **Roditis**[1], Anca Elena **Ștefan**[1], Gabriel Ioan **Prada**[1,2], Ileana **Jugurică**[1], Gianina **Constantin**[1]*

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*
[2] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

*Corresponding author: rozetadraghici@ana-aslan.ro*

**Abstract.** The purpose of this study was to use a population-based survey to identify the actual prevalence of frailty in older Romanian adults and to compare it with the prevalence of frailty in the elderly in other European countries. This is a cross-sectional, observational single center study of 2328 patients aged 65 years and over (mean age 73.136± 6.126 years), conducted in Bucharest and the group evaluated was selected from patients admitted to "Ana Aslan" National Institute of Gerontology and Geriatrics from January to March 2019. The screening of frailty was interfaced with a medical electronic data sheet to calculate the index of frailty in the first day of admission, using a modified Morley scale, an instrument that assesses 5 items, each question scored with 0 or 1, the resulting scores being summed and classified as "not frail" for 0, "pre-frail" for 1 or 2 and "frail" for 3 to 5. The frailty proportion between women and men was almost 3 to 1 (74.4% female and 25.26% for male). The overall prevalence of frailty was 60.26%, being not-frail 39.4%, pre-frail 39.04% and frail 21.22%. In conclusion, early identification of frailty is important, which is why international guidelines recommend routine identification of frail older people in health services. Also, it is extremely necessary a unanimous acceptance and standardization of the definition of frailty. This will enable an assessment and operationalization using unanimous accepted criteria and tools.
**Key words**: frailty, prevalence, older adults, elderly

**Rezumat.** Obiectivul acestui studiu a fost utilizarea unui sondaj pe un eșantion populațional pentru a identifica prevalența actuală a fragilității la adulții români în vârstă și pentru a o compara cu prevalența fragilității la vârstnicii din alte țări europene. Acesta este un studiu transversal, observațional, derulat într-un singur centru, cu 2328 de pacienți cu vârsta de 65 de ani și peste (vârsta medie de 73,136 ± 6,126 ani), realizat la București, iar grupul evaluat a fost selectat dintre pacienții internați la Institutul Național de Gerontologie și Geriatrie „Ana Aslan", în perioada ianuarie - martie 2019. Screeningul fragilității a fost asociat cu o fișă medicală electronică pentru a calcula indicele de fragilitate în prima zi de internare, folosind o scară Morley modificată, un instrument care evaluează 5 itemi, fiecare întrebare fiind notată cu 0 sau 1. Scorurile evaluate au fost însumate și clasificate drept „not-fragil" pentru 0, „pre-fragil" pentru 1 sau 2 și „fragil" pentru 3 până la 5. Proporția dintre femei și bărbați pentru fragilitate a fost de aproape 3:1 (74,74% femei și 25,26% pentru bărbați). Prevalența generală a fragilității a fost de 60,26% (not-fragili 39,74%, pre-fragili 39,04% și fragili 21,22%). În concluzie, identificarea timpurie a fragilității este importantă, motiv pentru care ghidurile internaționale recomandă identificarea de rutină a persoanelor în vârstă fragile din serviciile de sănătate. De asemenea, este extrem de necesară o acceptare și standardizare unanimă a definiției fragilității. Acest lucru va permite o evaluare și operaționalizare folosind criterii și instrumente unanim acceptate.
**Cuvinte cheie**: fragilitate, prevalenţă, adulţi în vârstă, vârstnici

## INTRODUCTION

Frailty among older adults is confirmed as a major concern of public health systems because of two main reasons: quality of life became a central issue of health care along with the fact that worldwide it is recording a global phenomenon of increasing life expectancy and aging population. By default, the frailty of older adults also became a major topic in human aging research.

While in the past infectious diseases were the leading cause of death, nowadays begins to shape the idea that the increasingly frequent degenerative diseases associated mortality occurs with age. And this pathology occurs frequently in frailty, which can result in important pathological and functional limitations.

According to Fried LP et al. [1], frailty of older adults has been designed as a state with increased vulnerability and an age-associated decline in function across multiple organ systems, so the ability to cope with every day or acute stressors is compromised. In other words "is a consequence of accumulated age-related defects in different physiological systems [2]" resulting in a diminished resistance to different stressors.

Frailty does not have a definition accepted by all experts in the field. Consequently, assessment tools and methods are different. As expected, the prevalence of frailty is characterized by significant variations from one study to another. In many occasions it has been highlighted that it is imperative to standardize the measurement of this syndrome, so that we can have an accurate and universally recognized evaluation of frailty.

As pointed out Collard RM et al. [3] in a systematic review published in the American Journal of Geriatric Society, prevalence of frailty in the communities varies widely, from 4.0 to 59.1%. As can be seen in Tab. I, this high variability is determined by several factors: pathophysiological, socioeconomic, geographical, methodological approaches.

Tab. I Factors influencing prevalence rates of frailty at elderly population level

| **Nr. crt.** | **Factors** | | **Rate of prevalence** | **References** |
|---|---|---|---|---|
| 1. | Population characteristics | Grater age: | 2% aged ≥50 years<br>60% aged ≥100 years | 4<br>5 |
| | | Gender (female): Females-males (Hungary)<br>Females-males (Slovenia) | 11.4%//5.4%<br>6.1%//2.3% | 6 |
| | | Diseases | | 7 |
| 2. | Socioeconomic status | Educational level-Lower education<br>Living situation(together/single)<br>Financial status-Less wealth | | 8 |
| 3. | Geographical area | *Country/continent*<br>Southern Europe<br>Northern Europe<br>USA<br>France<br>UK | <br>9,3%--21%<br><9%<br>6.9%<br>7%<br>8.5% male & 4.1% female | 9 |
| 4. | Tools used (methodological approaches) ; estimated only for community studies | Fried frailty phenotype | 57% | 10 |
| | | SHARE FI-Survey of Health, Ageing and Retirement in Europe Frailty Instrument | 18% | 11 |
| | | FI - Rockwood and Mitnitski's Frailty Index | 4% | |
| | | FRAIL-fatigue, resistance, ambulation, illnesses, loss of weight scale | 16% | |
| | | CFS-Clinical Frailty Scale | 41.5% | 12 |
| | | GFI-Groningen Frailty Indicator | 39% | 13 |
| | | SOF-Study of Osteoporotic Fractures Index | 13% | 14 |
| | | TFI-Tilburg Frailty Indicator | 20.2% | 15 |
| 5. | Healthcare settings | Primary care | 30% | 16<br>17 |
| | | Hospital inpatients | 54% | 18 |
| | | Outpatients geriatric clinics | 30% | 18 |
| | | Long term care (nursing home) | 62.1%<br>68.8%<br>75.6% | 18<br>19<br>20 |
| | | Community-based samples | 9-42% | 11 |

ADVANTAGE was a well-designed population based study with partners from 22 European countries. Its aim was to develop a strategic framework for the management and prevention of frailty at European level. Using data from this project they were calculated the prevalence rates of frailty in elderly persons in different parameters (Tab. I).

The results showed (Tab. I) that the prevalence of frailty only including community-based studies had the lowest rates in the UK, France and Germany, being 9% for each of the three countries. The highest rates were found in Portugal (38%) and Poland (42%).

Also, values of prevalence varied depending on tests and working tools used for evaluation. In studies conducted in Europe, to evaluate the prevalence of frailty among the elderly people, have been used more frequently like assessment the following instruments: the Fried frailty phenotype, SHARE-FI, the Groningen Frailty Indicator and the Clinical Frailty Scale.

## PURPOSE OF THE STUDY

The present study aimed to determine the prevalence of frailty in a sample of older inpatients (2328 subjects, screened for frailty) in Ana Aslan National Institute of Gerontology and Geriatrics (NIGG) between January-March 2019 and to compare it with the prevalence of frailty in the elderly in other European countries

## ETHICAL APPROVAL AND RESEARCH ETHICS

The NIGG Ethical Committee approved the study protocol. Before study participating, each subject signed an Informed Consent Form. All procedures performed in this study were in accordance with the ethical standards of the National Research Committee and with the Helsinki declaration and its latter amendments.

## METHOD

This is a cross-sectional, observational single center study of 2328 patients aged 65 years and over, conducted in NIGG, Bucharest. The sample evaluated was selected from patients admitted to institute between January-March 2019. Eligible patients were 65 years of age and older, with an adequate understanding of the Romanian language, able to communicate and cooperate (e.g. did not have Alzheimer's disease in advanced stage, a cognitive disease, advanced disabilities, etc.) and able to give informed consent. Exclusion criteria were taken into consideration for age less than 65 years, for elderly persons unable to communicate, with pre-existing major psychiatric and neurological problems like known dementia, or severe physical disabilities.

Subjects were selected from the center's electronic medical record (EMR) data sheet using the Hipocrate software. The screening of frailty was interfaced with a medical electronic data sheet to calculate the index of frailty in the first day of admission, using a modified Morley scale, culturally adapted for the Romanian language. This is an instrument that assesses 5 items: fatigue/weakness, poor endurance, slowness (difficulty of walking 150 meters), illnesses (more than five from ten most common diseases in elderly), and unintentional weight loss. The scale consists of 5 questions, and each question was scored with 0 or 1, the resulting scores were summed and classified as "not frail" for 0, "pre-frail" for 1 or 2 and "frail" for 3 to 5.

### Statistical analyses

Quantitative and qualitative data were used to describe the results of the study. Quantitative parameters were expressed as the mean value ± standard deviation (SD). The analysis of data was performed with Microsoft Office Excel 2003.

## RESULTS AND DISCUSSIONS

The selected subjects were elderly aged 65 years or older. The mean age of the group of 2328 subjects was 73.136± 6.126 years. The proportion between women and men was almost 3 to 1 (74.74% female and 25.26% for male), as seen in Fig. 1 and Tab. II. The overall prevalence of frailty was 60.26%, being not-frail 39.74%, pre-frail 39.04% (18.86% of subjects with score 1 and 20.18% with score 2) and frail 21.22% 14.22% of subjects with score 3; 6.40 % with score 4 and only 0.60 % of subjects with score 5).

Tab. II The percentage distribution of aging subjects depending on frailty evaluation, in the present study

| Nr. crt. | Frailty score | Total number of subjects | F/M | Percentage value (%) | | |
|---|---|---|---|---|---|---|
| 1. | 0 | 925 | 682/243 | 39.74 | 39.74 | **NOT-FRAIL** |
| 2. | 1 | 439 | 335/104 | 18.86 | 39.04 | **PRE-FRAIL** |
| 3. | 2 | 470 | 355/115 | 20.18 | | |
| 4. | 3 | 331 | 246/85 | 14.22 | 21.22 | **FRAIL** |
| 5. | 4 | 149 | 111/38 | 6.40 | | |
| 6. | 5 | 14 | 11/ 3 | 0.60 | | |

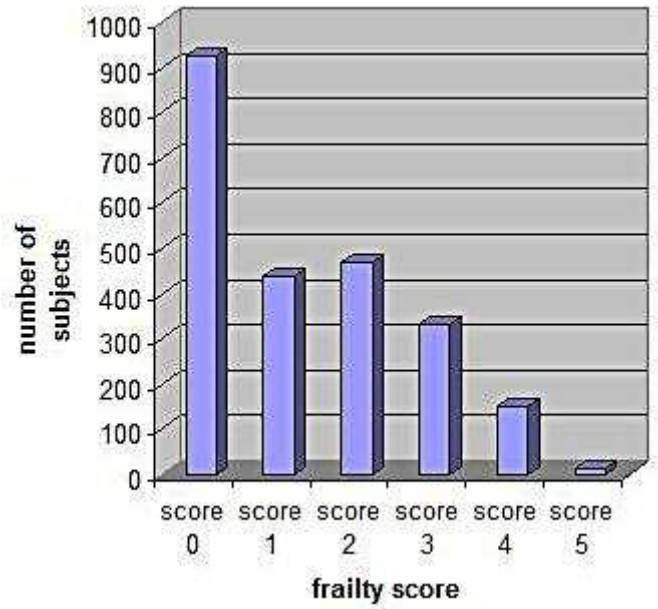


Fig. 1 Distribution of subjects based on the frailty score

Nearly 40% (i.e. 39.74%) of the 2328 subjects selected in the study were robust or not frail, and very similar proportions (39.04%) were pre-frail subjects. Increasing the frailty value score, concomitant decreases correspondingly with the number of subjects; the only exception is for score 1 of pre-frailty, where there is a slight increase from score 1 to score 2 (from 18.9% to 20.2%) (see Fig. 2, Tab. I, Tab. II).

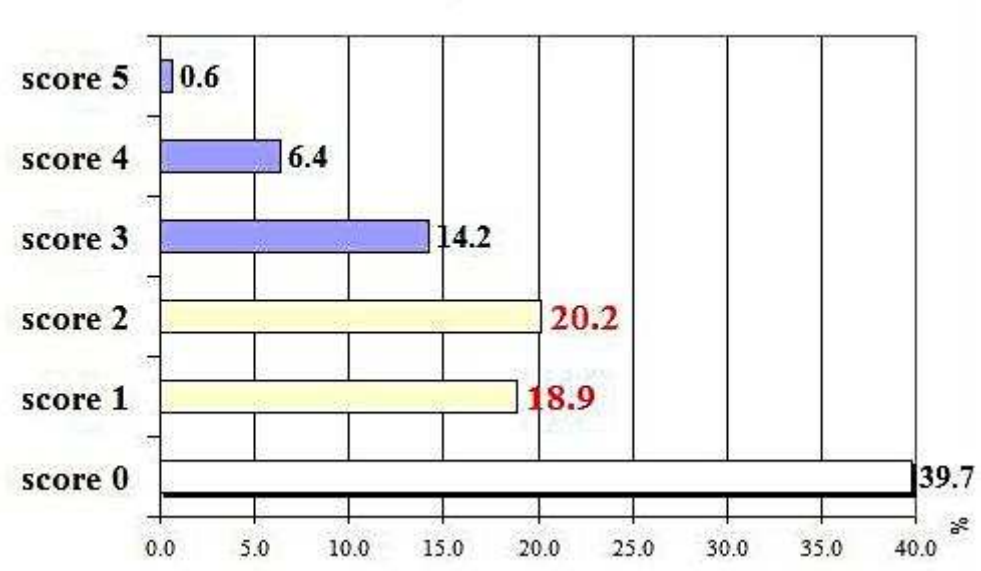


Fig. 2 Percentage distribution of subjects based on the frailty score

It is worth mentioning that (by percents) the growth trend appears only in men (slight increase from 23.69% to 24.47%), not in women, as can be seen in Tab. III and Fig. 3, where we can see that there is no significant difference in the groups established in terms of differentiated gender to study the frailty evolution.

Tab. III Percentage distribution of subjects based on the frailty score, differentiated on gender and rate women/men evolution

| Nr. Crt. | Frailty score | Percentage of women | Percentage of men | Ratio W/M |
|---|---|---|---|---|
| 1. | 0 | 73.73 | 26.27 | 2.80 |
| 2. | 1 | 76.31 | 23.69 | 3.22 |
| 3. | 2 | 75.53 | 24.47 | 3.08 |
| 4. | 3 | 74.32 | 25.68 | 2.89 |
| 5. | 4 | 74.50 | 25.50 | 2.92 |
| 6. | 5 | 78.57 | 21.42 | 3.66 |


Fig. 3 Percentage distribution of subjects based on the frailty score, differentiated on gender

Processing the data obtained into the study, we could represent and suggestively evidence, in percentage, in Fig. 4 the share of health status for the selected persons, depending on the age groups. It can be seen that the percentage values are clearly decreasing for not-fragile ones, slightly decreasing for pre-fragile and increasing for fragile.

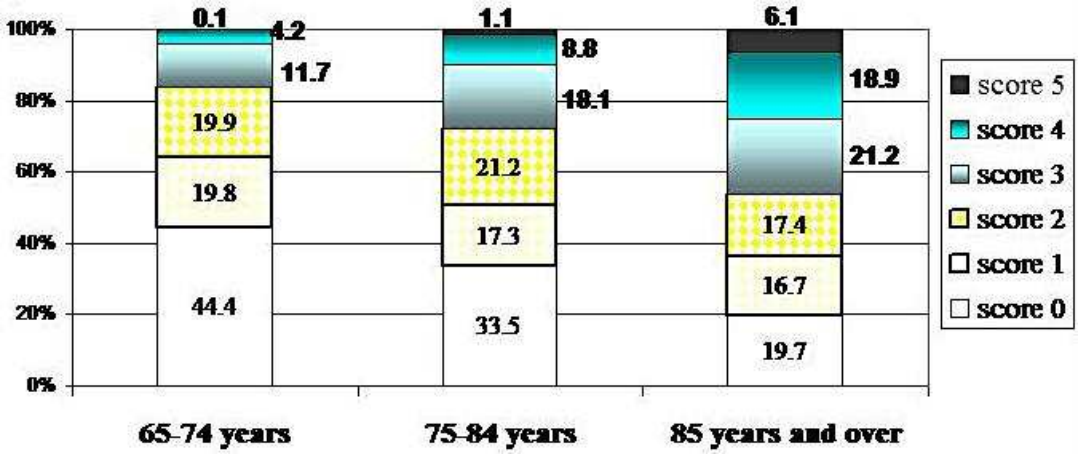


Fig. 4. Worsening the frailty syndrome presented for various age groups

The value of prevalence of frailty calculated in our study was 21.22%, a rate higher than that of other studies from USA or other European countries as we can see in Tab. IV.

Tab. IV. Prevalence of frailty in different geographical areas

| Nr. Crt. | Study | Country | Assessment tool | Number of subjects | Frailty |
|---|---|---|---|---|---|
| 1. | American Cardiovascular Health Study | USA | CHS frailty criteria | 5317 community dwelling men and women 65 yr and over | 6.9% |
| 2. | The French Three-City Study | Fr | | 6079 community dwelling men and women 65 yr and over | 7 % |
| 3. | Hertfordshire Cohort Study (CHS) | UK | CHS criteria | 648<br>64-74 yr | 8.5% W<br>4.1% M |
| 4. | The Survey of Health, Aging, and Retirement in Europe (SHARE) Study | EU | | 16.584 men and women 50 yr and older | S-EU<br>9.3-21% |
| | | | | | N-EU<br><9% |

## STRENGTHS AND LIMITATIONS OF THE STUDY

The first strength of our study is that it has relevant results because it had a representative number of older patients, but the study has also some limitations. First, data obtained are from one clinical site (single-center design) and the population sample was not entirely characteristic for Romanian population, but the sample is relevant in giving an opinion about frailty in our country. In light of this, our findings are valid, despite the fact that it is necessary to conduct a multi-center study to confirm the results.

## CONCLUSIONS

1. Early identification of frailty is important, which is why international guidelines recommend routine identification of frail older people in health services. It is extremely necessary a unanimous accep-

tance and standardization of the definition of frailty. This will enable an assessment and operationalization using unanimous accepted criteria and tools. For data obtained in epidemiologic studies it is necessary to reach a consensus on which diagnostic and assessment instrument to use.

2. It is justified an initial test screening for all hospitalized patients aged 65 years and over, at the beginning of hospitalization. Next, pre-frail and frail older people will benefit from a comprehensive geriatric evaluation. Need to the development of a frailty-screening strategy.

***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.

***Authors' contributions***

Concept and design: *Rozeta* ***Drăghici****, Anna Marie* ***Herghelegiu****, Doina* ***Roditis****, Anca Elena* ***Ștefan****, Gabriel Ioan* ***Prada***
Data collection: *Ileana* ***Jugurică***
Analysis and interpretation: *Gianina* ***Constantin***
Literature research: *Cătălina* ***Pena***
Manuscript preparation: *Cătălina* ***Pena***

## REFERENCES


[1] Fried LP, Tangen CM, Walston J, et al. *Frailty in older adults: evidence for a phenotype.* J Gerontol A Biol Sci Med Sci 2001, Mar;56(3):M146-56.

[2] Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. *Prevalence of frailty in community-dwelling older persons: a systematic review.* J Am Geriatr Soc 2012, 60(8):1487-92.

[3] Xue QL. *The fraily syndrome: definition and natural hystory*. Clin Geriatr Med,2011,27,1-15.

[4] O'Halloran AM, Finucane C, Savva GM, Robertson IH, Kenny RA. *Sustained attention and frailty in the older adult population.* J Gerontol B Psychol Sci Soc Sci 2013, 69(2), 147-56.

[5] Duarte N, Teixeira L, Ribeirto O, Paul C. *Frailty phenotype criteria in centenarians: Findings from the Oporto Centenarian Study.* Eur Geriatr Med 2014, 5(6), 371-6.

[6] Romeo-Ortuno R, Soraghan C. *A Frailty Instrument for primary care for those aged 75 years or more: findings from the Survey of Health, Ageing and Retirement in Europe, a longitudinal population-based cohort study (SHARE-FI75+).* BMJ open 2014:4(12):e006645. DOI:101136/bmjopen-2014-006645.

[7] Kojima G. *Prevalence of frailty in nursing homes: a systematic review and meta-analysis*. J Am Med Dir Assoc 2015, 16(11), 940-5.

[8] Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. *Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries*. J Gerontol A Biol Sci Med Sci 2009, 64(6), 675-81.

[9] Shimada H, Makizako H, Doi T, Yoshida D, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc 2013, Jul;14(7), 518-24.

[10] Bieniek J, Wilczyński K, Szewieczek J. *Fried frailty phenotype assessment components as applied to geriatric inpatients.* Clin Interv Aging 2016; 11: 453–459.

[11] O'Caoimh R, Galluzzo L, Rodriguez-Laso A, et al. *Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis*. Ann 1st Super Sanita 2018, 54, No.3:226-238.

[12] Kelly S, Brien IO, Smuts K, Sullivan MO, Warters A. *Prevalence of frailty among community dwelling older adults in receipt of low level home support: a cross-sectional analysis of the North Dublin Cohort.* BMC Geriatrics (2017) 17:121 DOI 10.1186/s12877-017-0508-2.

[13] Drubbel I, Bleijenberg N, Kranenburg G, et al. *Identifying frailty: do the Frailty Index and Groningen Frailty Indicator cover different clinical perspectives? a cross-sectional study*. BMC Family Practice 2013,14:64; https://doi.org/10.1186/1471-2296-14-64

[14] Ensrud KE, Ewing SK, Cawthon PM, et al. *A Comparison of Frailty Indexes for the Prediction of Falls, Disability, Fractures and Mortality in Older Men*. J Am Geriatr Soc 2009, March ; 57(3), 492–498.

[15] Goggens RJ, Schols MGA, van Assen M. *Exploring the efficiency of the Tilburg Frailty Indicator: a review*. Clin Interv Aging 2017, 12: 1739–1752.
[16] van Kempen JA, Schers HJ, Jacobs A, et al. *Development of an instrument for the identification of frail older people as a target population for integrated care*. Br J Gen Pract 2013, 63(608):e225-31. DOI:10.3399/bjgp13X664289
[17] Papiol M, Serra-Prat M, Vico J, et al. *Poor muscle strength and low physical activity are the most prevalent frailty components in community-dwelling older adults*. J Aging Phys Act 2016, 24(3), 363-8.
[18] Peters LL, Boter H, Buskens E, Slaets JP. *Measurement properties of the Groningen Frailty Indicator in home-dwelling and institutionalized elderly people.* J Am Med Dir Assoc 2012, 13(6), 546-51.
[19] Gonzalez-Vaca J, de la Rica-Escuin M, Silva-Iglesias M, et al. *Frailty in Institutionalized older adults from Albacete. The FINAL study: rationale, design, methodology, prevalence and attributes.* Maturitas 2014, 77(1), 78-84.
[20] Matusik P, Tomaszewski K, Chmielowska K, et al. *Severe frailty and cognitive impairment are related to higher mortality in 12-month follow-up of nursing home residents*. Arch Gerontol Geriatr 2012, 55(1), 22-4.

# BLOOD PRESSURE CONTROL IN HYPERTENSIVE ELDERLY PATIENTS – LIFESTYLE FACTORS AND ADHERENCE TO TREATMENT

*Maria-Cristina **Corbu**[1], Anna Marie **Herghelegiu**[1,2], Cătălina **Nuță**[1,2], Ovidiu **Bajenaru**[1,2], **Nacu** Raluca[1,2], Gabriel-Ioan **Prada**[1,2]*

[1]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2]*"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*

*Corresponding author: Cătălina Nuță, cata_deni87@yahoo.com*

**Abstract.** High blood pressure (HBP) has a major impact in healthcare, it is one of the major determinants of mortality and morbidity in older age. It is important, yet difficult to identify and modify actionable risk factors for low adherence to treatment and poor control of BP especially in elderly patients. Material and methods: This cross-sectional monocentric study, conducted in 2019, included 160 elderly hypertensive patients distributed into a study group (uncontrolled HBP) and a control group (controlled HBP), based on blood pressure at admission. Several factors potentially involved in BP control, such as socio-cultural factors, multiple comorbidities, lifestyle factors and antihypertensive medication were analyzed. Results: Education level was positively and significantly associated with BP control in older people (37.33% in the study group and 56.47% in the control group graduated from higher forms of education, the difference being significant with a p of 0.015564). Patients with higher stages of HBP and a higher number of daily administered drugs had poorer control of BP values (stage I was diagnosed in 8% of the people in the study group and in 35.29% in the control group, stage II in 29.33% and, respectively, 23.53% and stage III in 62.67% and, respectively, in 41.18%, with a p of 0.000176). The study group used an average of 2.89 hypertension drugs, compared to an average of 2.39 in the control group, the difference being significant with a p of 0.000718. Coexisting pathologies were more prevalent in the study group (diabetes 21.33% vs. 20.00%, kidney disease 38.67% vs. 29.41%, neurocognitive disorders 14.67% vs. 7.06%, depressive disorders 41.33% vs. 35.29%), but without statistical significance. The usage of a pill organiser was less frequent in the study group, but without statistical significance. Conclusions: There is a positive association between the level of education and the management of essential HBP in the elderly. Furthermore, lower stages of hypertension and avoidance of polypragmasy were significantly more likely to appear in the control group.
**Key words**: hypertension, control, factors, elderly

**Rezumat.** Hipertensiunea arterială (HTA) are un impact major în sistemul de sănătate și este un factor determinant al mortalității și morbidității în populația vârstnică. Este important, însă dificil, de identificat și de acționat asupra factorilor de risc care induc aderența scăzută la tratament și controlul scăzut al HTA, în special în rândul vârstnicilor. Materiale și metode: Acest studiu transversal, monocentric, realizat în 2019, a inclus 160 de vârstnici cu hipertensiune arterială, care au fost incluși fie în grupul de studiu (HTA necontrolată), fie în grupul de control (HTA controlată), în funcție de valorile tensionale la internare. Mai mulți factori pot influența controlul HTA, printre aceștia numărându-se factori socio-culturali, prezența de comorbidități, stilul de viață și tratamentul antihipertensiv. Rezultate: Nivelul educațional se corelează în mod pozitiv și semnificativ statistic cu un control mai bun al HTA la vârstnici (37,33% dintre pacienții din grupul de studiu și 56,47% din grupul de control au absolvit studii superioare, diferența fiind semnificativă statistic cu p 0,015564). Pacienții cu stadii avansate HTA și cu un număr ridicat de medicamente antihipertensive au un control mai slab al valorilor tensionale (stadiul I a fost diagnosticat la 8% dintre pacienții din grupul de studiu și la 35,29% în grupul de control, stadiul II la 29,33% și, respectiv, 23,53%, stadiul III la 62,67% și, respectiv, la 41,18%, p fiind 0,000176). Grupul de studiu administrează, în medie, 2,89 medicamente antihipertensive, față de 2,39 în grupul de control, diferența fiind semnificativă cu p de 0,000718. Comorbiditățile sunt mai frecvente în grupul de studiu, fără semnificație statistică (diabet zaharat 21,33% vs. 20,00%, boală renală cronică 38.67% vs. 29,41%, tulburări neurocognitive 14,67% vs. 7,06%, tulburare depresivă 41,33% vs. 35,29%). Utilizarea unui organizator de medicamente este mai rară în grupul de studiu, însă fără semnificație statistică. Concluzii: Există o asociere pozitivă între nivelul educațional și gestionarea hipertensiunii arteriale esențiale la vârstnici. În plus, stadiile avansate de HTA și polipragmazia se întâlnesc în mod semnificativ mai frecvent la pacienții cu HTA necontrolată.
**Cuvinte cheie:** hipertensiune arterială, control, factori, vârstnici

## INTRODUCTION

With recent medical advancement, including the development and implementation of innovative diagnostics and treatments, life expectancy has increased: in 2018 the elderly represented 19.7% of the people of the European Union [1]. It is estimated that the life expectancy will be over 80 in 2050, in Europe [2]. In Romania too the elderly population is well represented. The data provided by the Census of Population from 2011 shows that there are 3.247.744 persons over 65 (16.14% of the population) [3].

High blood pressure (HBP) is a widely diagnosed pathology in the elderly and it leads to complications with a high risk of mortality and morbidity. According to the SEPHAR III study, HBP is highly prevalent (75.1% in people over 65). Even if 69.8% of the elderly with HBP from Romania are following medical treatment, only 17.8% manage to control their tensional values [4]. The benefits of managing HBP by medical treatment are confirmed by literature, as global mortality is lowered by 9% and cardiovascular morbidity and mortality by 28% [5]. There are a series of factors that can influence the management of essential HBP in the elderly.

The educational level seems to be a very important element in the management of essential HBP in the elderly population, because most of them do not fully understand the impact of this disease and, thus, do not follow a healthy lifestyle and the prescribed treatment [6]. Additionally, living in rural or urban areas can influence the accessibility to medical services and, also, impact the lifestyle (physical activity and diet) [7]. The adherence to treatment seems to be a very important factor influencing the degree of control over this disease. Some studies show us that the people with affected cognitive function and the ones with many daily medications tend to have suboptimal adherence to treatment, including the medication responsible for HBP [8]. In addition to these factors, there might be other actionable factors, less addressed in research, that relate to the patients attitude towards their own health: using tools to maintain treatment adherence (such as pill organizers) and understanding and following the treatment schedule.

Our working hypothesis is that specific modifiable factors (level of education, environment, the use of tobacco, alcohol, coffee and salt, the use of a dosette box (pill organizer), written drug chart and the ability to use it correctly, the presence of specific comorbidities are involved in the control of HBP in the elderly.

The main objective is to identify the relationship between these social, cultural, lifestyle and medical factors and the degree of arterial hypertension control.

## MATERIALS AND METHODS

This study represents a cross sectional, monocentric study that took place at the Institute of Gerontology and Geriatrics "Ana Aslan" Bucharest, between January and June 2019. The patients were referred by general practitioners or by other medical professionals for chronic and subacute diseases and were included in this study (respecting the inclusion and exclusion criteria) in the chronological order of hospital admission. The data was collected from the patient's medical records and by direct interview.

The selected inclusion criteria were: age over 65, the presence of essential high blood pressure and the presence of antihypertensive treatment for at least 3 months. The exclusion criteria were: secondary high blood pressure, the absence of antihypertensive treatment at current admission, newly diagnosed high blood pressure during admission, major cognitive impairment (known from the medical history of the patient or a score of maximum 17 points at the Mini Mental State Evaluation (MMSE) at admission),

high grade of disability (evaluated with the Activity of Daily Living (ADL) score).

All data was acquired from the hospital database and by direct interview with the patient, most importantly the data related to the patients' attitude towards managing hypertension: usage of dosette box/pill organizer, understanding of the drug administration routine, usage of diuretics late in the day and correct identification of antihypertensive drugs in daily routine.

The direct interview with the patient and the collection of data using a questionnaire (see Annex 1) was an important element of the study. This methodology was chosen in order to better understand the patients' attitude towards their health and their role in maintaining it. Additionally, it allowed the researcher to establish a trusting relationship with the patient and to extract more accurate data. Another advantage over relying on questionnaires filled in by patients directly is a lower risk of incorrect data, caused by hearing, visual or cognitive dysfunctions, more frequent in the elderly population. The data collected was chosen based on the clinical experience of the research team and based on the methodologies of similar studies.

The patients were distributed into two groups: a study group and a control group. The criteria were the blood pressure values from the first day of the current admission. If the values are over 130-139 mmHg for the systolic pressure and 70-79 mmHg for the diastolic pressure (targets suggested by the Guide of Management of High Blood Pressure, published by the European Society of Cardiology in 2018) the patient is included in the study group, and the control group was formed by patients with normal values of the blood pressure at admission.

**STATISTICAL ANALYSIS**

Normally distributed continuous variables were reported as "mean (SD)", while non-normally distributed variables were expressed as "median (interquartile range)". Qualitative variables were expressed as "absolute frequency (percentage of subgroup)". The differences of numeric variables between the two groups were assessed by t student test, while the differences of categorical variables between these subgroups were assessed with $\chi^2$ test. Pearson correlation was used to assess whether there is a significant relationship between tensional values and number of daily antihypertensive drugs. All tests were considered significant if $p < 0.05$ and were performed using the *Social Sciences Statistics* freeware.

**RESULTS**

The studied group comprises a total of 160 patients with a mean age of 75.82 (95% CI [74.6802, 76.9598]) with a standard deviation of 7.22. The median age is 75 years and the interquartile range (IQR) is 11, while the overall range was 30 (the age varied between 65 and 95 years).

The average age is similar in the two groups (75.73 and 75.89). A higher frequency of females was observed in the control group (75.29%, vs. 69.33% in the study group). The distribution according to the environment of origin does not differ between the control group and the study group (74.67% of patients in the study group and 75.29% from the control group were living in an urban area). The distribution according to education level was different: in the control group there were fewer patients with primary education (14.12% vs. 16.00%), fewer with secondary education (29.41% vs. 46.67%) and more with a high level of education (graduation from university or post-secondary education: 56.47% vs. 37.33%). In the control group there was a lower frequency of patients living alone (36.47% vs. 46.67%) (Tab. I).

Among the sociodemographic variables, the level of education was the only statistically significant one in this study. The higher the level of education, the greater the likelihood of controlled blood pressure is. Thus, the level of education and the blood pressure control represents a positive association, with statistical

significance (p 0.042224, test value) chi-square being 6.3295 (see Tab. IV).

Tab. I Socio-demographic structure of the patient group

| | **Study group (n = 75)** | **Control group (n = 85)** |
|---|---|---|
| Average age (SD) | 75.73 (7.31) | 75.89 (7.22) |
| Female - n (%) | 52 (69.33%) | 64 (75.29%) |
| Urban area - n (%) | 56 (74.67%) | 64 (75.29%) |
| Rural area - n (%) | 19 (25.33%) | 21 (24.71%) |
| Primary education - n (%) | 12 (16.00%) | 12 (14.12%) |
| High school education (n) | 35 (46.67%) | 25 (29.41%) |
| Post-secondary, university (%) | 28 (37.33%) | 48 (56.47%) |
| Living alone - n (%) | 35 (46.67%) | 31 (36.47%) |

The mean blood pressure showed differences between the two groups: in the study group the average systolic blood pressure was 158 mmHg and the diastolic one was 83.53 mmHg. In the control group the mean values were 128.24 mmHg, and 72.59 mmHg, respectively.

Different prevalences were observed regarding the monitored comorbidities: diabetes mellitus, chronic kidney disease, neurocognitive disorder, depressive disorder affect patients in the study group to a greater extent. Patients in the study group had a higher stage of essential HBP, the difference being statistically significant. In the study group, stage I was in a smaller proportion (8.00%, compared to 35.29% in the control group), stage II in a similar proportion (29.33% and 23.53% in the control group), and stage III was found in a higher proportion (62.67%, compared to 41.18% in the control group) (Tab. II).

The higher the stage of essential HBP is, the less likely the values of the blood pressure to be well controlled are. Thus, the essential HBP stage and its control represent a negative association direction, with statistical significance (p 0.000176, the chi-square test value of 17.2939) (Tab. IV).

Tab. II Distribution of HBP stages and prevalence of studied comorbidities

| | **Study group (n = 75)** | **Control group (n = 85)** |
|---|---|---|
| Stage I HBP - n (%) | 6 (8.00%) | 30 (35.29%) |
| Stage II HBP - n (%) | 22 (29.33%) | 20 (23.53%) |
| Stage III HBP - n (%) | 47 (62.67%) | 35 (41.18%) |
| Average systolic pressure - mmHg (SD) | 158.00 (17.56) | 128.24 (9.42) |
| Average diastolic pressure - mmHg (SD) | 83.53 (9.13) | 72.59 (6.99) |
| Diabetes mellitus - n (%) | 16 (21.33%) | 17 (20.00%) |
| Chronic kidney disease - n (%) | 29 (38.67%) | 25 (29.41%) |
| Neurocognitive disorder - n (%) | 11 (14.67%) | 6 (7.06%) |
| Depressive disorder - n (%) | 31 (41.33%) | 30 (35.29%) |

Regarding the daily antihypertensive therapeutic regimen of the elderly included in the study we found a similar distribution of therapeutic classes, and the most frequently used classes of drugs were beta-blockers and diuretics (their distribution being represented in Fig. 1).

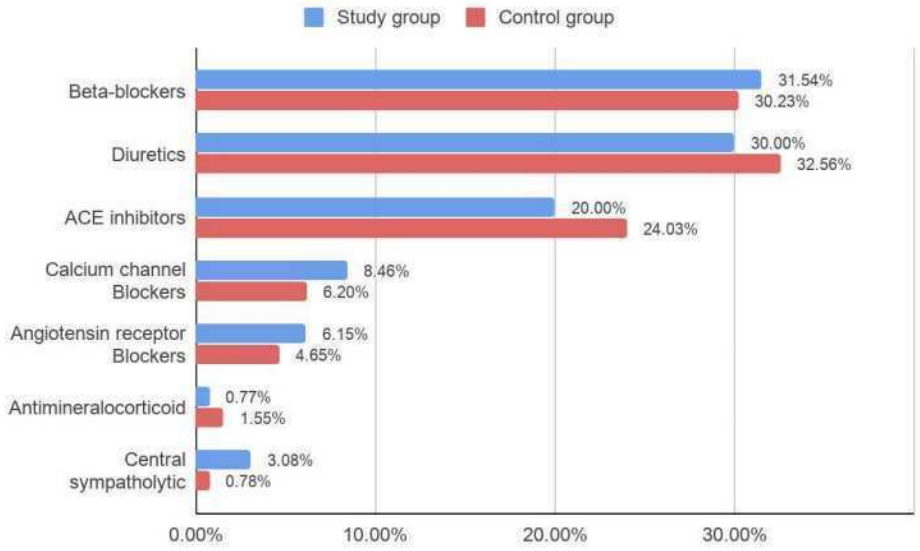


Fig. 1 Distribution of therapeutic antihypertensive molecule classes in the study and control group

An important factor that showed statistically significant differences between the two groups was the number of medicines taken daily for blood pressure control. On average, one person in the control group had 2.89 active antihypertensive substances in the daily therapeutic scheme, compared to 2.39, in the case of a person in the study group (p=0.000718). Furthermore, using Pearson's statistical correlation analysis, it was found that there is a statistically significant correlation between the number of antihypertensive drugs given daily and the systolic blood pressure at admission (p=0.000666), respectively the diastolic one (p=0.012284) and the mean blood pressure (p=0.000527).

In terms of lifestyle, 4 behaviors were evaluated: consumption of tobacco, alcohol, coffee and salt. In the study group, a higher proportion of alcohol, tobacco and coffee users were found, and the salt restriction diet was observed in the two groups in similar proportions. Regarding smoking, 14.67% of the patients in the study group were active smokers at the time of inclusion in the study, compared to 7.06% in the control group. The proportion of alcohol consumption at the time of inclusion in the study was found at 16.00% in the study group and 8.24% of the control group, and 68.00% of the people in the study group consumed daily coffee, compared to 56.47% of the control group (Tab. III).

Tab. III Lifestyle and attitude towards one's own health

| | **Study group (n = 75)** | **Control group (n = 85)** |
|---|---|---|
| Smoking- n (%) | 11 (14.67%) | 6 (7.06%) |
| Chronic alcohol consumption - n (%) | 12 (16.00%) | 7 (8.24%) |
| Chronic coffee consumption - n (%) | 51 (68.00%) | 48 (56.47%) |
| Frequent salt consumption - n (%) | 27 (36.00%) | 29 (34.12%) |
| Dosette box usage - n (%) | 34 (45.33%) | 54 (63.53%) |
| Treatment routine comprehension - n (%) | 55 (73.33%) | 79 (92.94%) |
| Correct treatment administration - n (%) | 51 (68.00%) | 58 (68.24%) |

Patients with controlled and, respectively, uncontrolled essential hypertension have presented differences regarding the attitude towards the administration of drugs, as assessed by the direct interviews performed. The people in the control group used a dosette box and understood the therapeutic scheme more than those in the study group. Correct administration of antihypertensive drugs was observed in similar proportions in the two groups (see more details in Fig. 2).

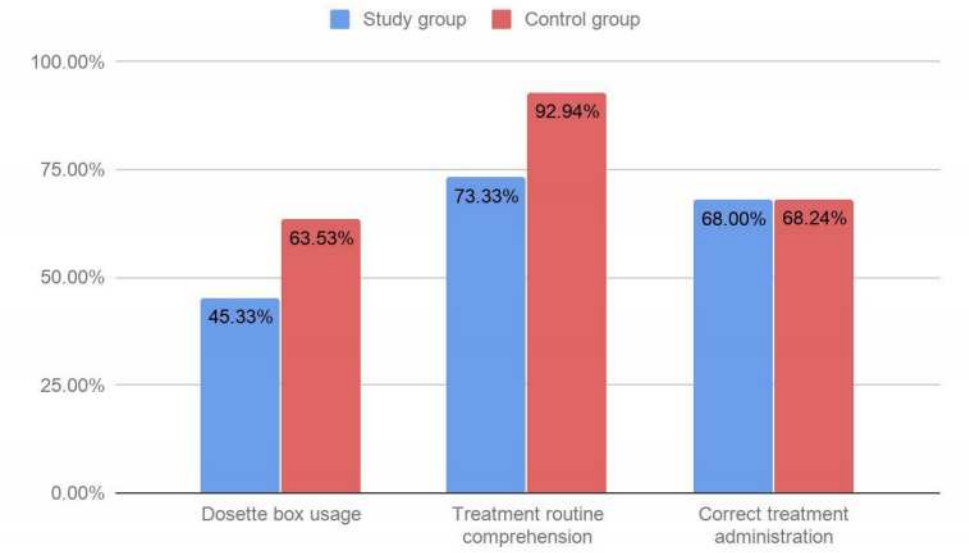


Fig. 2 Assessment of the patients' antihypertensive drugs administration: using a pill organiser, understanding and properly administering the medication routine

While most factors followed in the study were different between the two groups of controlled and uncontrolled HBP, the education level, hypertension stage and number of hypertensive drugs administered daily presented statistically significant differences (Tab. IV).

Tab. IV Statistical significance of the factors evaluated in the study, in relation to the control blood pressure in the elderly with essential hypertension. AV= average value

| **Factors** | **Study group (%/AV)** | **Control group (%/AV)** | **t/χ2 test** |
|---|---|---|---|
| Male gender | 30.67% | 24.71% | $p > 0.05$ |
| Education level (Primary/ secondary/ tertiary) | 16.00%/46.67%/ 37.33% | 14.12%/29.41%/ 56.47% | $p < 0.05$ |
| Living alone | 46.67% | 36.47% | $p > 0.05$ |
| Smoking | 14.67% | 7.06% | $p > 0.05$ |
| Chronic alcohol consumption | 16.00% | 8.24% | $p > 0.05$ |
| Chronic coffee consumption | 68.00% | 56.47% | $p > 0.05$ |
| Dosette box usage | 45.33% | 63.53% | $p > 0.05$ |
| Treatment routine comprehension | 73.33% | 92.94% | $p > 0.05$ |
| Stage of essential HBP (I/II/III) | 8.00% /29.33% /62.67% | 35.29% /23.53% /41.18% | $p < 0.05$ |
| Chronic kidney disease | 38.67% | 29.41% | $p > 0.05$ |
| Cognitive impairment | 14.67% | 7.06% | $p > 0.05$ |
| Depression | 41.33% | 35.29% | $p > 0.05$ |
| Number of daily antihypertensive drugs | 2.89 | 2.39 | $p < 0.05$ |

## DISCUSSION

The results of this study confirm that there are factors that influence the control of essential hypertension in the elderly, similar to other studies.

The male gender has been previously associated with a lower control of essential HBP in the elderly [9]. The SEPHAR III study, which followed a Romanian cohort, confirmed that HBP control is correlated with the female gender [4]. Our study has not revealed differences in the control of HBP depending on the urban or rural environment. This differed from similar studies, which included, however, a larger rural population (36.2% rural, 22% semi-urban, compared to 24.6% rural in the present study [7].

A low education level correlates with a poor disease control as well: a similar study discovered that 49.2% of patients who graduated post-secondary studies adhere to the treatment, compared to 40.2% of patients with a primary education [9]. These results were not replicated in studies which used fewer categories („< 8 grades" and „> 8 grades", as the largest differences appear in the post-secondary group) [10].

Lifestyle choices major impact HBP control, as well. Alcohol and smoking have been described as risk factors: another study has revealed a similar incidence of these habits, compared to the present study. According to it, smoking raises the risk of uncontrolled HBP 3.94 times and drinking alcohol 2.48 times [11].

Diets rich in salt have been cited as a HBP risk factor but the observation has not been replicated in our study. Non-adherence to the low-salt diet raises the uncontrolled HBP risk 1.74 times [11]. The SEPHAR III study observed a high concentration of salt in the diet of patients with uncontrolled HBP [4]. Coffee consumption has a complex relationship with HBP: several studies have led to the conclusion that coffee may lower blood pressure (a 9% decrease of HBP risk at 7 daily cups of coffee) [12]. Similarly, 3 cups daily lower the risk, compared to 1 cup daily [13]. In terms of HBP control, one cup daily raises the risk of uncontrolled HBP 1.95 times, similar to the present study (in which this correlation lacks statistical significance) [14].

Behavior towards one's health is a recognized element, which influences essential HBP control in the elderly. The present study observed more balanced proportions of adherence to antihypertensive treatment (69.86% in the study group and 68.24% in the control group), compared to other studies (16.47% among patients with uncontrolled HBP and 90.74% in the controlled HBP) [10]. The high proportion of adherence to the therapeutic scheme, together with the high adherence to the aforementioned salt restriction diet, describes a cohort of patients with a positive attitude to health, in the present study.

The behavior of HBP patients has been evaluated in several other studies, which followed variables such as the level of disease knowledge (on risk factors, complications, symptoms) and the concrete actions they perform to control the disease (medical checkups, medical therapy, physical activity, low-salt diet) [15]. As highlighted by research, direct interventions on the patient lead to better results than interventions on the medical specialists, the former including the usage of dosette boxes for pills [16]. This behavior has been evaluated in our study as well, and while there is a difference between the study and the control group, using a dosette box has not improved HBP control significantly in our cohort. The usage of tools such as the pill organizer are recommended to increase drug adherence, in hypertensive patients of any age, by the 2018 Guidelines for the management of arterial hypertension, developed by the European Society of Cardiology and the European Society of Hypertension [17].

Our study has followed two other behaviors that reflect the patient's attitude

towards their health and which may influence HBP control: the understanding of the drug administration routine and the identification of antihypertensive drugs in the routine. These factors were considered reflective of the patient's adherence to the treatment, especially in the context of a complex daily treatment routine, frequent in the case of elders, which can affect the control of individual diseases targeted by the drugs. Both behaviors were found in a moderate to high proportion in the study cohort, and while the difference in routine comprehension and correct administration were high and, respectively, low, between the two groups, the differences were not statistically significant.

The number of antihypertensive drugs taken daily is higher in patients with uncontrolled hypertension, a conclusion reached by other studies as well: administration of up to two active substances daily correlates with a controlled HBP, and administration of three or more active substances is more common among people with an uncontrolled HBP [10]. However, our cohort had a different distribution of classes of active molecules: compared to similar studies, the patients followed in the present study tend to use beta-blockers more often, and conversion enzyme inhibitors, antimineralocorticoids and calcium channel blockers less frequently [18].

Other comorbidities affect the control of high blood pressure as well, as confirmed by our study: according to another cross-sectional study, chronic kidney disease raises the risk of uncontrolled HBP 2.67 times [11]. Disorders in the depressive spectrum affect HBP control through an increased addressability of patients to healthcare services, together with a shorter time from treatment debut to controlled tension values [19]. On the other hand, depression factors in the therapeutic inertia encountered in uncontrolled HBP [20]. Neurocognitive disorders may, as well, lower treatment compliance and, thus, HBP control. All of the above disorders have been found in our study with a higher prevalence in the uncontrolled HBP group, compared with the control group, without a statistical significance. The results related to diabetes mellitus have differed in our study from the literature: according to another cross-sectional study, diabetes raises the risk of uncontrolled HBP 4.6 times, among elderly with hypertension [21]. The prevalence of diabetes was similar in the controlled and uncontrolled HBP groups in the present study.

Seniors represent a segment of the population with an increased risk of morbidity and mortality, and essential HBP is one of the most important cardiovascular risk factors. The compliance of the elderly and the adherence to treatment play a very important role in determining the prognosis and are often neglected in current medical practice. From the information received, this is the only study that evaluated the potential factors involved in blood pressure control in hypertensive elderly in Romania and one of the few of this type reported in the specialized publications [4]. Similar cross-sectional studies have followed different behaviors that influence HBP control and therapeutic adherence, such as forgetting to administer medications or not bringing it along when leaving home [22]. Additionally, studies focused on therapeutic adherence in hypertensive elderly have applied different methodologies, such as medication use estimated through automated pharmacy database captures [23], which may overestimate adherence through equating it to prescription filling.

This study has several limitations: the relatively small sample size, as well as convenience sampling method (patients were not randomly selected from the general population, so there is a possibility that the sample may not be representative of the target population). Another aspect that could influence the generalization of the conclusions is that this is a unicentric study; the patients were selected from a

population that carries out regular health checks.

## CONCLUSIONS

We can say that there is a positive relation of association and statistically significant relationship between the level of education and the management of essential HBP in the elderly. Moreover, the higher the stage of essential HBP is, the lower the management of this disease is. A large number of daily antihypertensive medications represent a factor that negatively impacts the control of essential HBP in the elderly.

The utilization of a dosette box can help the patients to take their medication in the right way and this can improve the management and for the same reason, it is also important that the patient should have a good understanding of their disease and their treatment.

The intake of alcohol, tobacco, and coffee represents a negative factor in the management of the essential HBP, but we cannot affirm that it is statistically significant from our study.

The elderly with essential HBP, males that live alone have a lower control of the blood pressure values. The presence of chronic kidney disease, mild and moderate cognitive impairment and depression are additional negative factors in the management of essential HBP, but we cannot affirm that it is statistically significant from our study.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES


[1] Eurostat. Ageing Europe. *Looking at the lives of older people in the EU*. Eurostat; 2019 Sep. Report No.: 2019 edition.

[2] World Health Organization. *World Report on Ageing and Health*. World Health Organization; 2015.

[3] *Recensământ Romania Populația Stabilă (Rezidentă) – Structura Demografică.* In: Recensământul Populației și al Locuințelor [Internet]. [cited 5 Aug 2018]. Available: recensamantromania.ro/noutati/volumul/Website

[4] Dorobantu M, Tautu O-F, Dimulescu D, et al. *Perspectives on hypertension's prevalence, treatment and control in a high cardiovascular risk East European country: data from the SEPHAR III survey*. J Hypertens 2018;36: 690–700.

[5] Musini VM, Tejani AM, Bassett K, Puil L, Wright JM. *Pharmacotherapy for hypertension in adults 60 years or older.* Cochrane Database of Systematic Reviews 2019. doi:10.1002/14651858.cd000028.pub3

[6] Chor D, Ribeiro ALP, Carvalho MS, et al. *Prevalence, Awareness, Treatment and Influence of Socioeconomic Variables on Control of High Blood Pressure: Results of the ELSA-Brasil Study.* PLOS ONE 2015. p. e0127382. doi:10.1371/journal.pone.0127382

[7] Sarfo FS, Mobula LM, Burnham G, et al. *Factors associated with uncontrolled blood pressure among Ghanaians: Evidence from a multicenter hospital-based study*. PLoS One 2018;13: e0193494.

[8] Gellad WF, Grenard JL, Marcum ZA. *A Systematic Review of Barriers to Medication Adherence in the Elderly: Looking Beyond Cost and Regimen Complexity*. The American Journal of Geriatric Pharmacotherapy 2011. pp. 11–23. doi:10.1016/j.amjopharm.2011.02.004

[9] Yang L, Xu X, Yan J, et al. *Analysis on associated factors of uncontrolled hypertension among elderly hypertensive patients in Southern China: a community-based, cross-sectional survey*. BMC Public Health 2014;14: 903.

[10] Barreto M da S, da Silva Barreto M, Matsuda LM, Marcon SS. *Factors associated with inadequate blood pressure control in patients of primary care.* Escola Anna Nery - Revista de Enfermagem 2016. doi:10.5935/1414-8145.20160016

[11] Tesfaye B, Haile D, Lake B, Belachew T, Tesfaye T, Abera H. *Uncontrolled hypertension and associated factors among adult hypertensive patients on follow-up at Jimma University Teaching and Specialized Hospital: cross-sectional study.* Research Reports in Clinical Cardiology 2017;8: 21–29.

[12] Grosso G, Micek A, Godos J, et al. *Long-Term Coffee Consumption Is Associated with Decreased Incidence of New-Onset Hypertension: A Dose–Response Meta-Analysis*. Nutrients 2017;9: 890.

[13] Chei C-L, Loh JK, Soh A, Yuan J-M, Koh W-P. *Coffee, tea, caffeine, and risk of hypertension: The Singapore Chinese Health Study*. Eur J Nutr 2018;57: 1333–1342.

[14] Lopez-Garcia E, Orozco-Arbeláez E, Leon-Muñoz LM, et al. *Habitual coffee consumption and 24-h blood pressure control in older adults with hypertension*. Clin Nutr 2016;35: 1457–1463.
[15] Bollampally M, Chandershekhar P, Kumar KP, Surakasula A, Srikanth S, Rama Mohan Reddy T. *Assessment of patient's knowledge, attitude and practice regarding hypertension*. International Journal of Research in Medical Sciences 2017;4: 3299–3304.
[16] Conn VS, Ruppar TM, Chase J-AD, Enriquez M, Cooper PS. *Interventions to Improve Medication Adherence in Hypertensive Patients: Systematic Review and Meta-analysis*. Curr Hypertens Rep 2015;17: 94.
[17] Williams B, Mancia G, Spiering W, et al. *ESC/ESH Guidelines for the management of arterial hypertension*. Eur Heart J 2018;39: 3021–3104.
[18] Sarfo FS, Mobula LM, Burnham G, et al. *Factors associated with uncontrolled blood pressure among Ghanaians: Evidence from a multicenter hospital-based study*. PLoS One 2018;13: e0193494.
[19] Ho AK, Thorpe CT, Pandhi N, Palta M, Smith MA, Johnson HM. *Association of anxiety and depression with hypertension control.* Journal of Hypertension 2015, pp. 2215–2222. doi:10.1097/ hjh.0000000000000693
[20] Moise N, Davidson KW, Chaplin W, Shea S, Kronish I. *Depression and clinical inertia in patients with uncontrolled hypertension*. JAMA Intern Med 2014;174: 818–819.
[21] Rodríguez Roca GC, Artigao Ródenas LM, Llisterri Caro JL, et al. *[Control of hypertension in elderly patients receiving primary care in Spain]*. Rev Esp Cardiol 2005;58: 359–366.
[22] Ezeala-Adikaibe BA. *Factors Associated with Medication Adherence among hypertensive Patients in a Tertiary Health Center: A Cross-Sectional Study*. Archives of Community Medicine and Public Health 2017, pp. 024–031. doi:10.17352/2455-5479.000021
[23] Siegel D, Lopez J, Meier J. *Antihypertensive Medication Adherence in the Department of Veterans Affairs.* The American Journal of Medicine 2007, pp. 26–32. doi:10.1016/j.amjmed.2006.06.028

## Annex 1.
## Patient questionnaire to assess the attitude towards personal health and the management of arterial hypertension

**Questionnaire no._____** **Date_____** **Name Initials_____**
Gender ☐ Female ☐ Male Age_____
Origin ☐ Rural ☐ Urban
Studies ☐Primary (4 years) ☐Secondary (4-10 years) ☐Higher/Vocational education (>10yrs)
Living conditions ☐ with someone ☐ alone

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Arterial Hypertension staging ☐ I ☐ II ☐ III
Level of risk ☐ average ☐ high ☐ very high
Blood pressure at admission Systolic BP _____ Diastolic BP _____
Daily number of antihypertensive medicine _____

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Total number of coexisting pathologies_____
Diabetes Mellitus ☐
Chronic Kidney Disease, > stage 3 ☐ Stage _____
Neurocognitive disorders (mild and moderate) ☐ MMSE _____
Depressive disorder ☐ GDS _____

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Smoking ☐ never ☐ quit ☐ currently
Alcohol ☐ occasionally ☐ quit ☐ actual<1/sp ☐ actual>1/sp
Coffee ☐ never ☐ occasionally ☐ weekly or more often
Dietary salt ☐ normal ☐ low-salt diet

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**Usage of dosette box/pill organiser** **☐ yes** **☐ no**
**Understanding of the drug administration routine** **☐ yes** **☐ no**
**Correct administration of antihypertensive drugs** **☐ yes** **☐ no**

# EARLY DECLINE OF INTRINSIC CAPACITY - POSSIBLE PREDICTOR OF FRAILTY SYNDROME

*Doina **Roditis**[1], Elena **Lupeanu**[1]*

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*

*Corresponding author: Doina Roditis, elena.roditis@gmail.com*

**Abstract**. The intrinsic capacity concept (IC) was introduced by WHO in 2015 to overcome traditional medical paradigms centered on the concept of disease and not on person's functional status. From a life course perspective, the World Health Organization (WHO) Healthy Ageing model shows a decline of functional capacity at early ages. For this reason, the first step of the **I**ntegrated **C**are for **O**lder **P**eople (ICOPE) Program focuses on "maintaining functioning and increasing IC reserves in the age group 45-70 years". Present transversal study is pointing out some examples of vulnerability manifested at these ages, in four IC domains. The lot of 182 NIGG patients was divided in two groups: "45-70 years" and "71 years +". The tests assessed: physical functioning (Stand on One Leg Test, Five-Repetition Sit-to-Stand Test, sensory, vitality (Brief Fatigue Inventory), and depression (GDS). Here are some percentage assessments of IC decline, in the "45-70 years"group: 34.3% subjects have lower muscular force according to "the Five-Repetition Sit-to-Stand Test", only 6% less than „the older"; 19.1% have balance difficulties according to "the Stand on One Leg Test"; both, hearing and visual problems appear in about 26% subjects. Regarding vitality, a high intensity for the "usual level of fatigue" has approximately the same weight, 26%, in both groups; also in the two groups; proportions for moderated/accentuated depression are close to 15%. Urinary incontinence, a "giant of geriatrics", appears in 17.1% „younger" patients. In conclusion, the ICOPE guideline can help early detection of IC declines for achieving secondary and tertiary prevention.
**Key words**: healthy aging, intrinsic capacity, functional ability

**Rezumat.** Conceptul de capacitate intrinsecă (CI) a fost introdus de OMS în 2015, dorindu-se depășirea paradigmelor medicale tradiționale, bazate pe conceptul de boală și nu pe starea de funcționalitate a persoanei. Din perspectiva cursului vieții, modelul Îmbătrânirii Sănătoase al Organizaţiei Mondiale a Sănătăţii (OMS) arată declinul capacității funcționale la vârste timpurii. Pentru acest motiv, primul pas al programului „ICOPE" se referă la „menținerea funcționalității și creșterea rezervelor CI în grupa de vârstă 45-70 ani". Studiul transversal de faţă prezintă câteva exemple de vulnerabilitate manifestate la aceste vârste, în patru domenii de funcționalitate ale CI. Lotul de 182 de pacienți ai INGG a fost împărțit în două grupe: „45-70 ani" și „71 ani +". Testele au evaluat: funcționalitatea fizică (Echilibrul stând într-un picior, Testul ridicării de cinci ori de pe scaun), senzorialitatea, vitalitatea (Scurt test privind oboseala/BFI) și depresia (Scala depresiei geriatrice). Câteva evaluări procentuale ale declinului CI în grupul „45-70 ani" sunt: 34,3% subiecți au o forță musculară mai scăzută, conform "Testului ridicării de cinci ori de pe scaun", pondere cu numai 6% mai mică decât a „celor mai în vârstă"; 19,1% au probleme de echilibru după „Testul stând într-un picior"; tulburările de auz și de vedere apar ambele, la 26% subiecți. În privința vitalității, intensitatea mare a „nivelului de oboseală zilnică" are aproximativ aceeași pondere, 26% în ambele grupe; tot în ambele grupe, proporțiile pentru depresia moderată/accentuată au valori de aproximativ 15%. „Gigant al geriatriei", incontinența urinară apare la 17,1% subiecți „mai tineri". În concluzie, Ghidul ICOPE poate ajuta diagnosticarea timpurie a declinului CI în scopul prevenției secundare și terțiare.
**Cuvinte cheie**: îmbătrânire sănătoasă, capacitate intrinsecă, abilitate funcţională

## INTRODUCTION

Active aging is defined as "the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age". The key determinants of active aging are: economic, behavioral, personal, social, medical and social services and the physical environment [1].

The concept of active longevity highlights the contribution and the merits of the elderly to the life of the community to which they belong. In 2012, the European Commission, observing the varied longevity of the EU countries, has called for socio-economic and medical scientific research to establish the ways in which the active life span could be increased with

two years until 2020. In this context, 2012 was proclaimed "The year of healthy aging and solidarity between generations [2].

The WHO developed a new vision [3] for healthy ageing in its World Report on Ageing and Health from 2015. This last concept of healthy aging replaces the previous one of active aging [3]. It is defined as the process of promoting and maintaining the functional ability of the elderly person and not as a life without diseases. The functional ability encompasses the people's attributes related to health that allow them to be/to achieve what they wish, giving value to their abilities of positively acting in the society. This concept is defined as the composite of the extrinsic capacity (the characteristics of the physical and social environment in which the person lives), the intrinsic capacity (IC) and the interaction between them. The intrinsic capacity (IC) is composed of all physical and mental capacities of the person and represents the amount of resources one can use during his life [4, 5].

Further, a comparison between IC and frailty is presented [6].

(1) As definitions: frailty results from the progressive decline of the physiological systems which leads to vulnerability after exposure to various stressors and decreased functional reserve capacities; IC consists in combining the physical and mental capacities of the person.

(2) As age of onset: the frailty is generally a geriatric condition; the intrinsic capacity is considered to start after the age corresponding to the median of the local life expectancy at birth.

(3) Referring to the temporal dimension of the assessment, although both are dynamic entities, frailty is mainly used in cross-sectional assessments; IC may be used in longitudinal approaches over time, highlighting the evolution of functional reserves.

(4) After characteristics, apparently, frailty and IC may represent the two faces of the same coin: one is presenting the deficits and abnormalities accumulated with aging; the other is defined by the individual's functional reserves and residual capacities. In reality, IC should not be seen as the mere opposite of frailty, the two concepts might be complementary: in particular, frailty may represent a state of extreme vulnerability to stressors defined by a clinically relevant reduction of IC (or functional reserves).

(5) Regarding the original purpose, generally: the monitoring of the frailty may discover the unmet clinical needs of the elderly; in the same time, the measurement of IC in frail individuals, specially, may provide additional information to build up the personalized care program centered on the person's values and priorities.

(6) Linked to the possible interventions: on one hand, complex geriatric evaluations are necessary for the diagnosis of frailty and they should be optimally performed in an integrated care network; on the other hand, the concept of IC is closely related to the integration of care and social services.

The diagnostics for both, frailty and IC are focused on promoting the development of person-centered care interventions. In other words, they detect one's impairments, needs and preferences, in order to improve the individual's capabilities (regardless of age, diseases, socio- demographic characteristics, and specific clinical phenotypes). The intrinsic capacity was defined as the summing of the person's physical and mental capacities. Aiming to establish a diagnosis methodology, WHO selected five theoretical areas of functionality assessing: cognition, locomotion, psychological, sensory and vitality and studied more literature reviews referring these domains. Such a study belonged to Stuck and colleagues (1999) [7], which strongly influenced later developments of geriatric medicine. It was a systematic review measuring the strength of links between different risk factors that could generate the transition to dependence in older persons, namely: mood, cognition, physical performance, energy expenditure and vision. Subsequent systematic reviews

have confirmed Stuck's results, even when the analysis of literature was restricted to data coming from low-and-medium-income countries [8].

Recently, more discussions have focused on the concept of vitality. It has been developed over time from one of the five domains, and defined as the energy metabolic capacity of the person, in other words, the biological reserve. From this the other four domains stem and act [6].

The scheme presented below (Fig. 1) contains elements from a Visual Analogue Scale of Frailty [9]. It is illustrative for a kind of balance between vitality and frailty and for the idea that biological reserve (vitality) generates the other four functioning domains (cognition, mood, mobility, communication functions).

| **VITALITY** / **FRAILTY** | | | |
|---|---|---|---|
| **Physiological ageing** | | | **Pathological ageing** |
| **ABSENCE** of FUNCTIONAL DECLINE | **IMINENT** FUNCTIONAL DECLINE | **ESTABLISHED** FUNCTIONAL DECLINE | |
| CLINICAL FUNCTIONAL CLASIFICATION | | | |
| ROBUST ELDERLY | RISK of FRAILTY | FRAIL ELDERLY | |
| | | **Low complex** / **Highly complex** / **Final stage of life** | |
| **DETERMINANTS** of ESTABLISHED **FUNCTIONAL DECLINE** | | | |
| COGNITION | MOOD / BEHAVIOR | MOBILITY | COMUNICATION |

Fig. 1 Some elements from the "Visual Analogue Scale of Frailty (VAS-Frailty)"

Further, the intrinsic capacity model is presented in two variants, focusing on the components of its functionality domains (Fig. 2A and Fig. 2B)

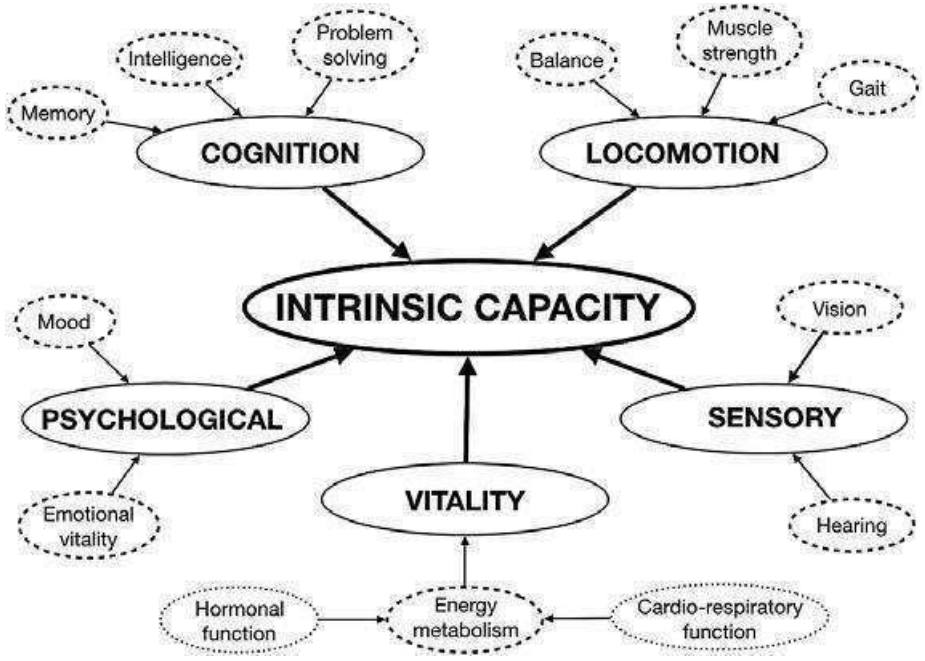



Fig. 2A Domains of intrinsic capacity, with possible subdomains [8]

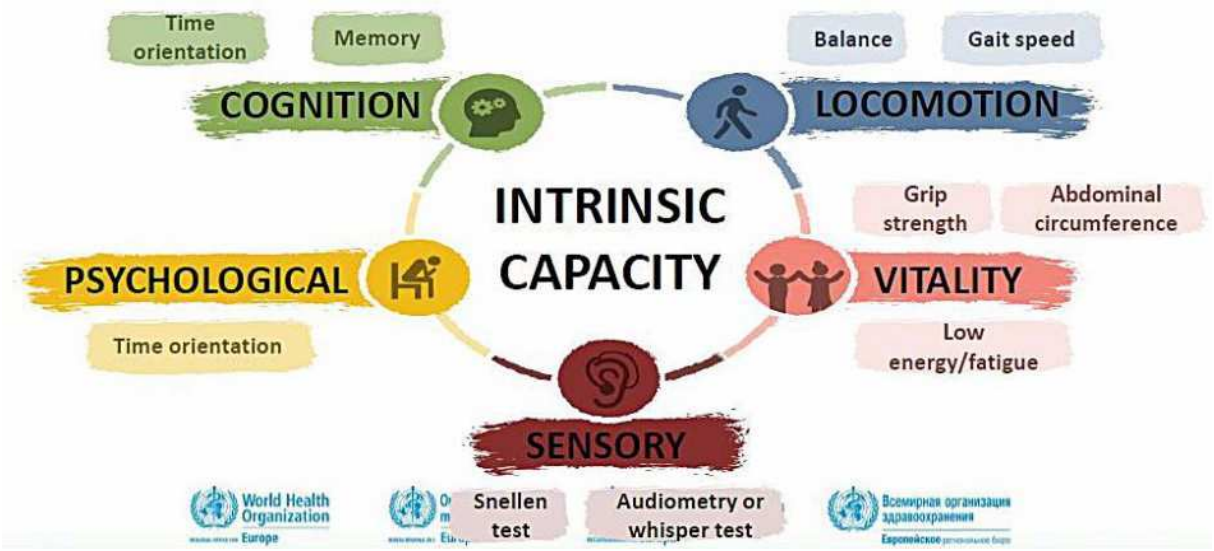



Fig. 2B Domains of intrinsic capacity [10]

A process for translating theory into practice is ongoing. WHO will provide the international validation of the operational definition of IC and the tools for measuring the five domains and objectifying one's functions for the use of the clinicians and researchers [6].

The five domains influence each other, and they are all influenced by environmental factors. Given this interrelationship, the importance of promoting integrated care becomes clearer, giving up the exclusive focus on diseases [11].

In 2015 the WHO launched the **I**ntegrated **C**are for **O**lder **P**eople (ICOPE) program.

This model proposes a shift in clinical care towards a community-level approach in the management of intrinsic capacity decline, in order to prevent the dependence of the elderly. Through this program, the WHO wants to reduce the number of dependent elderly people by 15 million until 2025. ICOPE is reorienting medical and social services towards a more coordinated and focused care model for the elderly, taking into account a longitudinal approach to the course of life [11].

ICOPE aims to optimize the functional ability through six actions:

(1) Improving motor function and vitality;

(2) Maintaining sensory functionality (sight, hearing);

(3) Prevention of cognitive impairment and promotion of psychological well-being;

Management of geriatric syndromes such as

(4) urinary incontinence,

(5) falls

(6) Supporting caregivers

The ICOPE guidelines offer evidence-based direction on:

- Comprehensive assessment of health status in older persons;
- Delivery of the integrated health care that will enable older persons to

>maintain their physical and mental capacities, and/or to

>slow or reverse any declines in these capacities

- Interventions to support caregivers.

Decreasing of the IC may begin in the middle age, before the onset of sarcopenia / or frailty.

That is why in the ICOPE strategy, the prevention starts early. The therapy approach of the functionality has 3 steps [12]:

a. Increasing IC reserves in early manifestations of aging (group 45-70 years);

b. Preservation of cognitive functions at advanced ages (71 years +);

c. Restoration of cognitive functions as needed.

**OBJECTIVES**

Our transversal study aims to highlight some examples of vulnerability manifested in the age group 45–70 years, in four of the five functional areas of IC.

**MATERIAL AND METHOD**

A group of 182 patients from INGG, consisting of 62 men and 120 women, aged between 45 and 88 years (mean age = 68.49 years), is evaluated by:

Tests linked to locomotion:

Muscular strength: The Five Times Sit to Stand Test [13] and the Hand Grip Test [14]

Balance test: Standing on one leg, open eyes, item of FICSIT-4 Scale [15]

Psycho-sensory evaluation tests for:

Depression - Geriatric Depression Scale - Short Form (GDS) [16]

Fatigue - Brief Fatigue Inventory (BFI) [17, 18]

Hearing and Sight evaluation short tests [19].

Diagnosis data are obtained from the clinic.

**RESULTS**

***Locomotion***

The balance function is present in both schemes of the IC model (Fig. 2A and Fig. 2B). Therefore, the study evaluated the subjects' locomotors function by a balance test: "standing on one foot" (item 7 of FICSIT-4). The data obtained (Fig. 3) show that half of the subjects in the 45-70 age groups have a good balance, being able to stand for 10 seconds on one foot, compared to only 14.3% of those aged 71 years +. One third of the subjects in both groups has an intermediate degree of impairment, and can stay on one leg for 5-10 seconds. In the category of those with a more affected balance (stationary for 3 seconds or less/or not at all) there are 19.1% "younger" subjects (compared to those group 71 years and over represented by 54.6%).

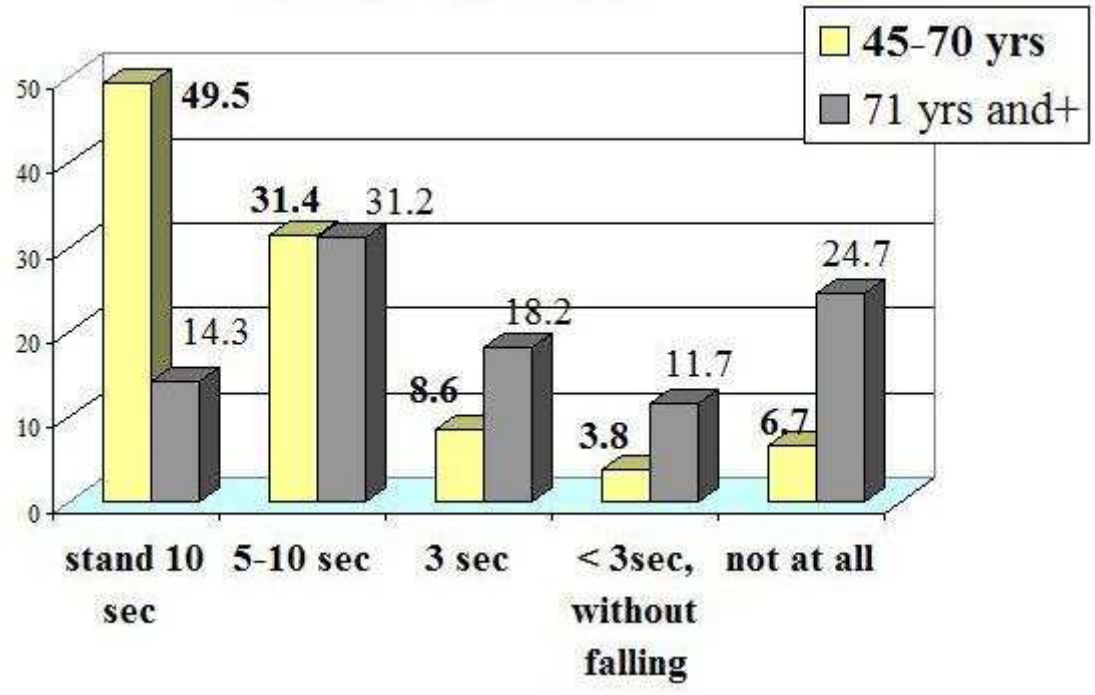



Fig. 3 Balance test, "Standing on one foot", compared the two age groups

***Vitality***

In the above figures, the muscle strength is included in the locomotors functionality (Fig. 2A) and in the vitality category (Fig 2B).

In Fig. 2A, we see the vitality influenced by energy resulted from metabolism,

linked to hormonal and cardio-respiratory functions. Fig. 2B mentions some connections of the vitality: muscle strength (handgrip), abdominal circumference (short assessment of metabolic syndrome) and fatigue.

Our study evaluated muscular force by "The five-repetition sit-to-stand test" (5R-STS), and also by "Handgrip Strength". Fig. 4 compares the data regarding the time needed by the subjects from the two age groups to perform five successive lifts. There are differences between percents of groups, but they are not very large: only 15% more "younger" subjects perform the test in less than 15 seconds, compared to the group 71 years+; and 34.3% of them exceed the normal execution time, with only 6 % less than „the older".

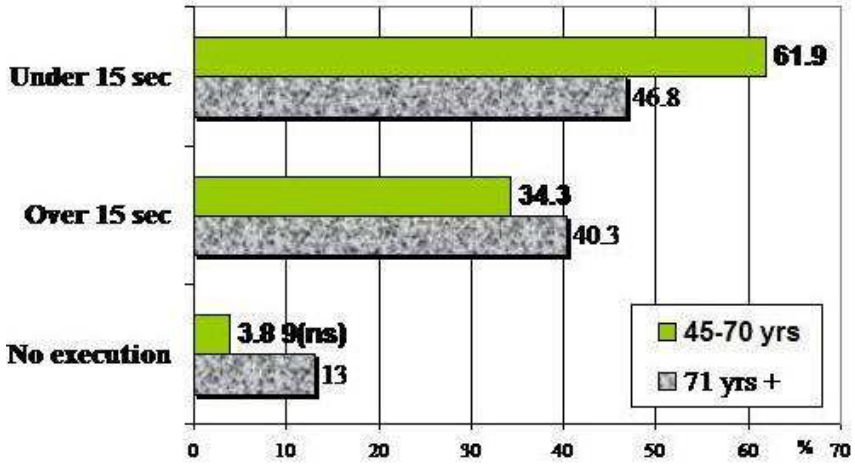



Fig. 4 The five-repetition sit-to-stand test, assessment of muscular force

The norms for strength distribution of handgrip by gender and age groups, [20] are illustrated in Fig. 5. It is seen that the maximum level of palmary compression for women is superposable with the minimum of compressive force for men, by age groups.

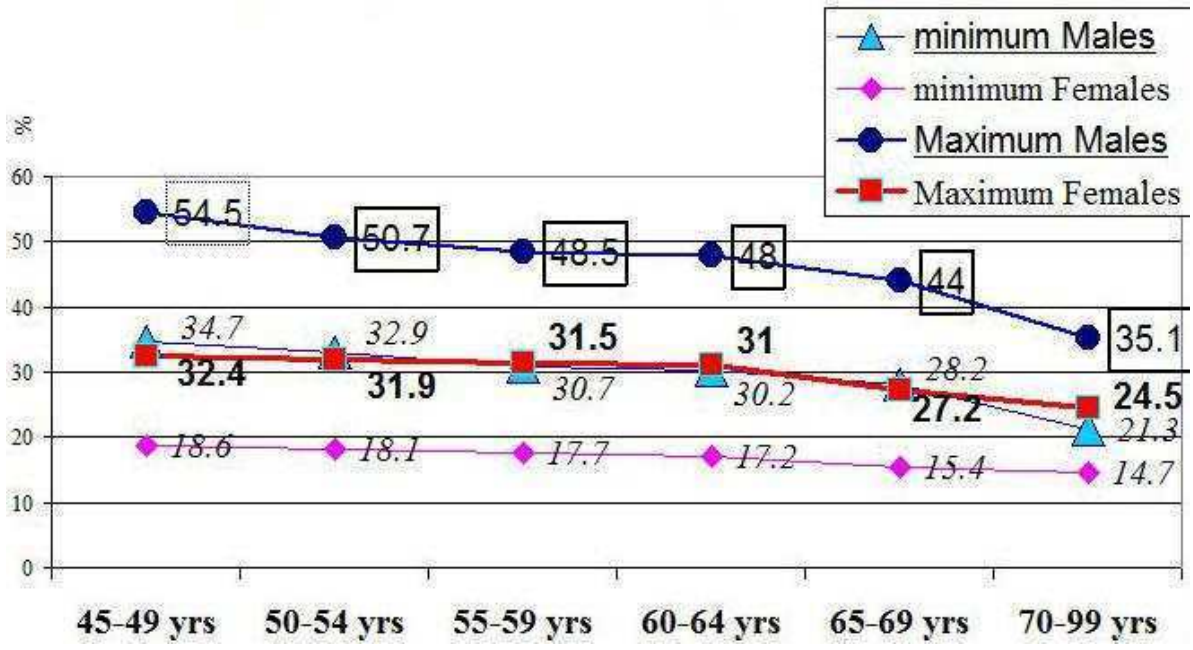



Fig. 5 Grip Strength Ratings Norms after gender and age groups

In our study (Fig. 6), the analysis of handgrip measurements reveals a weight of 57.7% subjects from the 45-70 years group with less force than the normal one, so strength deficit is higher by 5% comparative to the 71 years + group. As a result, we could say that there are more subjects in the 45-70 years age group with a lower vitality than in the group 71 years and over. The causes of this energy imbalance are suggested by the correlation analysis between some evaluations of vitality and subjects' chronic pathology.

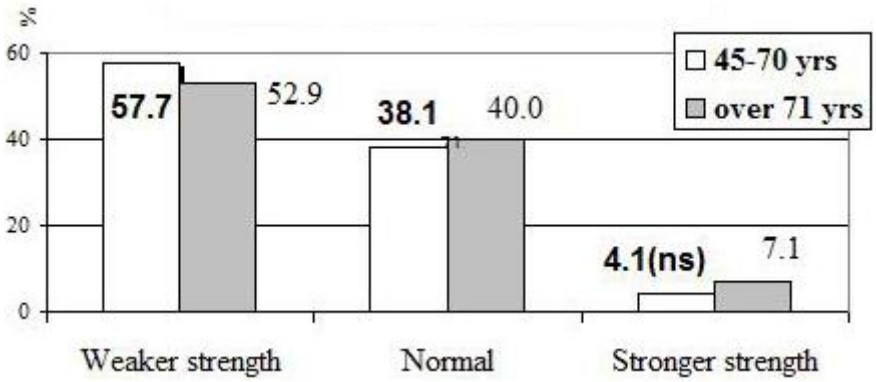



Fig. 6 Differences of grip-strength on age groups, compared with norms [13]

In the diagram from Fig. 2B, the lack of vitality is also related to abdominal circumference (AC). AC with values above normal limits can be found in both groups: 88% subjects in the 45-70 age group and 93.2% among the "older group". Abdominal obesity is the visible marker of the metabolic syndrome, a group of risk factors for cardio-vascular diseases and diabetes mellitus. In the Tab. I, we see significant correlations of AC with metabolic, hormonal and circulatory disorders. Scheme from Fig. 2B includes the fatigue (opposite of vitality). We evaluated it in our group by Brief Fatigue Inventory Scale (BFI). The proof of the link between vitality and AC is the significant correlation between abdominal obesity and commonly felt fatigue: r=0.184/ p=0.015. Tab. I contain significant correlations between AC and subjects' chronic pathology, showing the importance of metabolic syndrome for vitality.
In the group "45-70 years" we find the correlations of AC, in order of their intensity, with: cardiovascular diseases (hypertension) and endocrine-metabolic diseases (obesity, hyperuricemia, mixed dyslipidemia). In the group "71 years and over", the ranking of the correlations in descending order is with: digestive and endocrine-metabolic diseases, obesity and diabetes. There is no correlation with cardiovascular diseases because in the "older" group there are more cases of heart disease than in the "younger" group (90.7%, compared to 84% respectively).

**Tab. I Correlations between abdominal obesity (AC) and chronic pathology**

| | **Total** | | **45-70 years** | | **71 years and over** | |
|---|---|---|---|---|---|---|
| **Abdominal circumference correlated with:** | r= | p= | r= | p= | r= | p= |
| Digestive disease | | | | | -0.379 | 0.001 |
| Blood pressure | 0.281 | 0.000 | 0.464 | 0.000 | | |
| Obesity | 0.420 | 0.000 | 0.460 | 0.000 | 0.366 | 0.002 |
| Ulcerative disease of digestive tract | | | | | -0.339 | 0.004 |
| Endocrine-metabolic diseases | 0.307 | 0.000 | 0.328 | 0.001 | 0.285 | 0.016 |
| Mixed dyslipidemia | 0.166 | 0.030 | 0.230 | 0.022 | | |
| Diabetes mellitus | 0.258 | 0.001 | 0.226 | 0.024 | 0.296 | 0.012 |
| Stroke sequelae | -0.184 | 0.016 | | | | |

Next, we analyze the level of fatigue in correlation with chronic pathology (Tab. IIA and Tab. IIB). We find that only in the group 45-70 years (Tab. IIA) significant correlations appear in the first place between the usual fatigue and dysmetabolic diseases: mixed dyslipidemia (r=0.245 /p=0.012) and hypercholesterolemia (r=0.226 /p=0.021). Energy is released after the metabolism of nutrients consumed. Tab. IIA places digestive disorders (their number), ulcerative disease on the second place, and Tab. IIB on the 1st place. The third place belongs in Tab. IIA to the correlations with the cardio-circulatory function: vertebrobasilar circulatory disorders, dizziness; in the Tab. IIB, on the second place, more circulatory diseases appear (neuralgia, polyneuropathy, anemia, stroke sequelae). Last but not least, the connection with kidney diseases occurs at the oldest age (r=0.274 /p=0.017).

The fatigue assessment using Brief Fatigue Inventory (BFI) is shown in Fig. 7. An interesting fact: both the level of fatigue and its degree of interference with global functionality are higher in the case of 45-70 years age group subjects. The exception is the level of usually fatigue, which appeared in equal percentages (26.5%).

Tab. IIA Age group 45 -70 years - Correlations between chronic pathology and usual level of fatigue

| | **Daily usual level of fatigue** | | **Σ BFI items** |
|---|---|---|---|
| correlations with: | r= | p= | r= /p= |
| Mixed dyslipidemia | 0.245 | 0.012 | |
| Hypercolesterolemia | 0.226 | 0.021 | |
| Digestive diseases (nr) | | | 0.237/ 0.015 |
| Vertebrobasilar circulatory disorders, vertigo | 0.208 | 0.035 | |

Tab. IIB Age group 71 years and over -Correlations between chronic pathology and fatigue over time

| | **Intensity of fatigue from the last week** | **Intensity of daily usual fatigue** | **Σ itemi BFI** |
|---|---|---|---|
| correlations with: | r=.../ p=... | r=.../ p=... | r=.../ p=... |
| Ulcerative disease of digestive tract | 0.331/ 0.004 | 0.399/ 0.000 | |
| Digestive diseases (nr) | 0.282/ 0.014 | | |
| chronic liver disease | | | 0.234/ 0.045 |
| Neuralgia | 0.232/ 0.045 | 0.280/ 0.015 | |
| Polyneuropathy | | 0.230/ 0.047 | |
| Anemia | 0.215/ 0.063 | 0.265/ 0.021 | 0.255/ 0.029 |
| Stroke sequelae, cerebral arteriosclerosis | | 0.255/ 0.029 | |
| Kidney diseases (nr) | 0.274/ 0.017 | 0.237/ 0.041 | 0.228/ 0.050 |

Elements of BFI assessment, compared between the two age groups

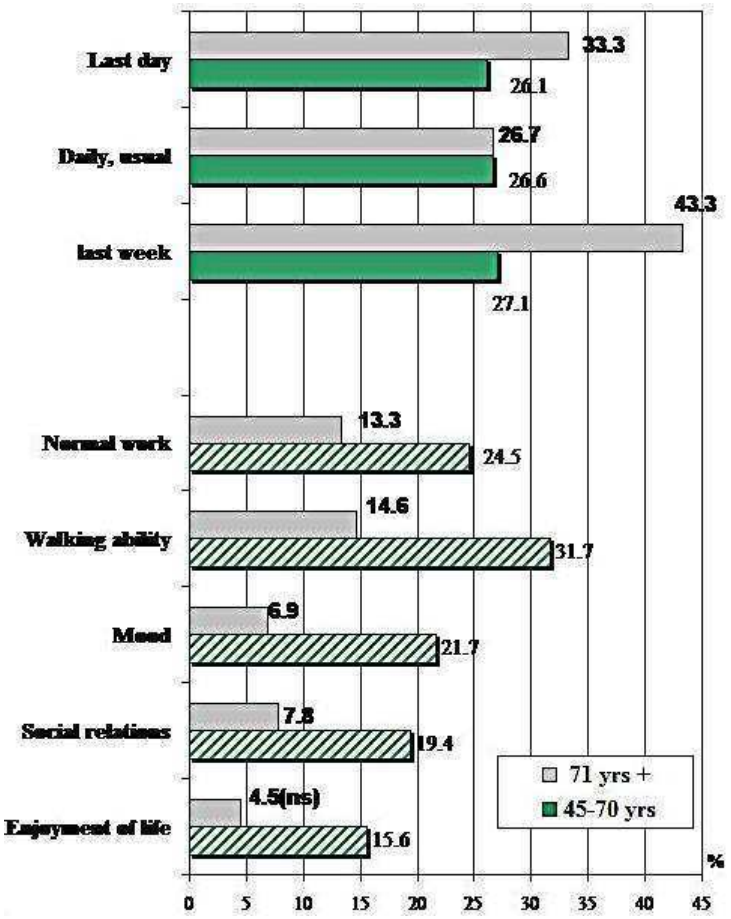



Fig. 7 Comparisons between the 2 age groups regarding
(1) the level of fatigue [last week, last 24 hours and daily / regular] and
(2) the degree of interference of fatigue with global functionality (physical, mental and social)

***Psychological domain***

In the elderly, depressive symptoms may have a strong relationship with the functional status of the individual. So, the psychological assessment may support strategies for the early identification of individuals at risk of negative outcomes [6]. The distribution by age groups of negative mood, the depression, is represented in Fig. 8. We find that in the 45-70 age groups there are as many subjects with moderate/severe depression as in the "elderly" group (namely 15%).

Correlated with this perception we find a rather higher proportion (18.8%) for dissatisfaction with own life" (GDS item 1) among those aged 45-70 years compared to the older ones (difference is 10.5%).

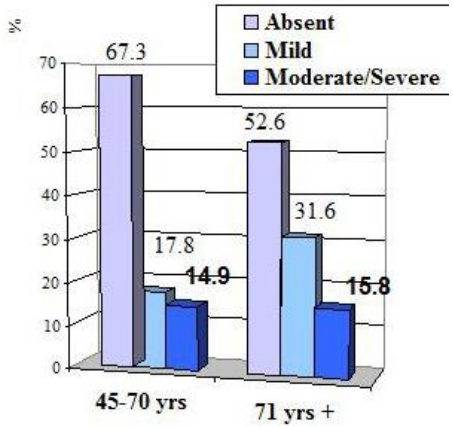



Fig. 8 The depression (GDS) distribution on age groups

The psychological field (see Fig 2A and Fig. 2B) in addition to mood also includes the emotional vitality. In our lot, self-evaluation as "full of energy" (item 13 of the GDS) appears at 78.2% subjects from "the younger" and at 61.8% from the 71 years + group (16% less subjects compared the first group).

Interestingly, a fact from the literature: secondary analyses conducted in the Women's Health and Aging Study showed that emotional vitality could be preserved in the presence of severe disability. This implies that the capacity of the individual to maintain and develop relationships may serve for differentiating health profiles and adequately contribute to a more comprehensive measure of intrinsic capacity [6]. IC is considered as focusing on the residual biological reserves of the organism (rather than on its deficits). In this context, it may be seen as sharing some commonalities with the resilience. Resilience extends well beyond the subject's biological status and spreads over its social network, cultural background, economical capacities, and living environment [7].

***Sensory impairments***

The last analyzed domain of IC is that of sensory. Fig. 9 shows comparatively the much lower share of those without hearing problems in the group 71years + (44.2%) compared to their younger homologous (73.3%). Particularly important is the presence of double sensory impairment: in the group of those under 71 years it is 10.5% -almost 4 times lower than in the group 71 years and over.

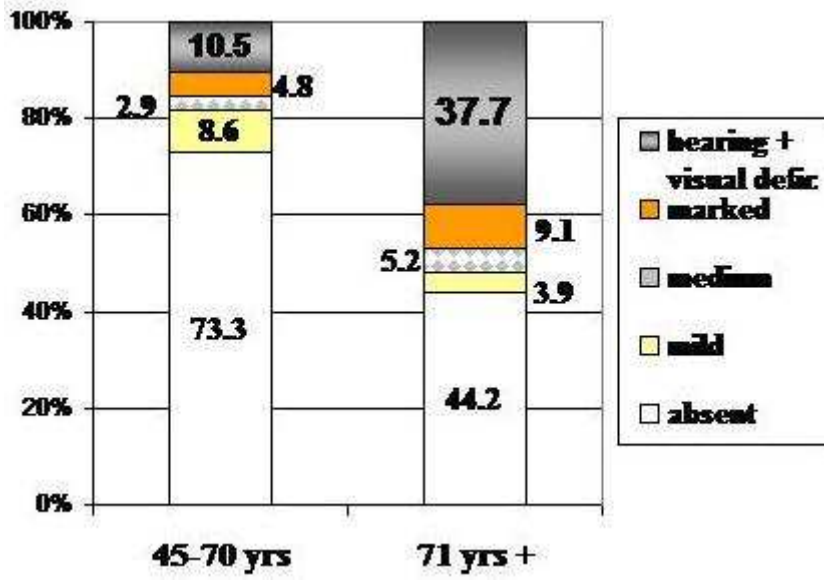
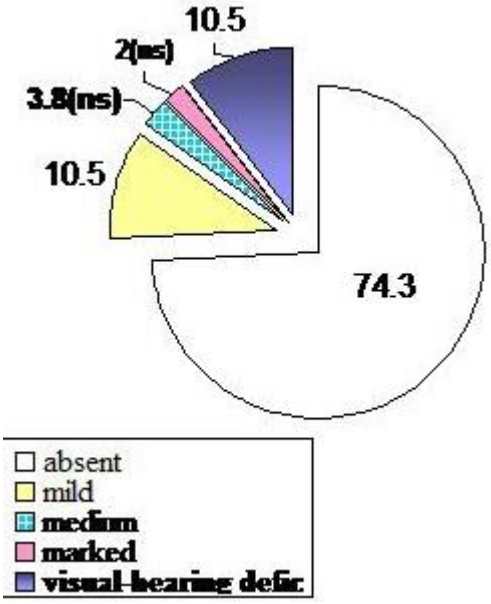



**Fig. 9 Different levels of hearing impairment compared in the two age groups**

Regarding visual disorders, in the group of "the older" there is a percent of only 36.4 subjects without any impairment (Fig. 10B), representing a half compared to that of the counterparts in the group "45-70 years" A quarter of "younger subjects" shows visual impairment of various degrees; 10.5% of them also have hearing impairment (Fig. 10A). In "the older" group, a proportion of 24.7% subjects have only visual impairment and 37.7%, visual impairments doubled by hearing.

Double sensory impairment is a major disadvantage, which can lead to an increased difficulty in the relation with physical and social environment.



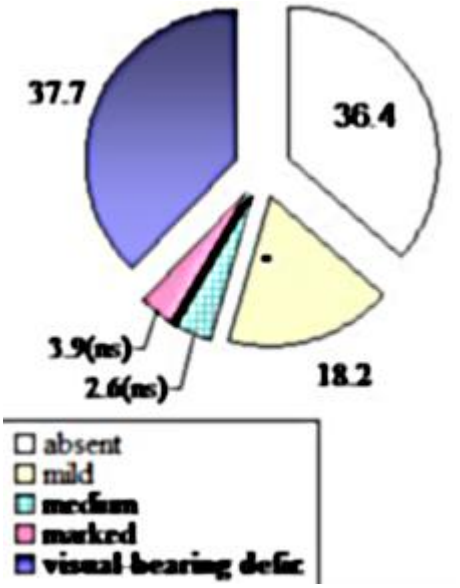




Fig. 10A: 45-70 years Fig. 10B: 71 yrs +

Fig. 10 Different levels of visual impairment compared in the two age groups

## CONCLUSIONS

Since IC includes the physical and mental functional abilities of the person, the paper analyzed dysfunctions in these areas: motor function, sensory, physical vitality and psychological functionality, related to mental state and emotional vitality. The used tests assess mobility, balance, sensory impairment, fatigue (BFI), and geriatric depression. In order to emphasize the importance of the prevention strategy developed by the ICOPE program, the study reveals the presence of vulnerabilities in the 45-70 years age group in the mentioned functional areas.

Physical, psychological and sensory impairments in the functionality of "younger" group sometimes have weights equal to those found in the "71 years and over" group.

Thus, we mention the existence of 20% "younger" subjects who perform unsatisfactorily the balance test and 30% subjects in both groups with a lower balance capacity (they can stand on one leg only 5-10 seconds).

Regarding muscle strength (handgrip), 57.7% of the subjects in the 45-70 age group have a compressive strength below the norms for age limits, compared to only 53% of those over 70 years. Also in terms of physical vitality, we remind that the percentages of daily, ordinary fatigue are equal for the two age segments, namely 26.6%. But the share of fatigue felt in the last week is higher in the 45-70 age group (43.3%) than in the older group (27.1%); a significant difference of 16.2%.

The interference of fatigue with physical, mental and social functionality is greater in the case of "younger" people: two times higher for the ability to walk, three times higher in terms of mood and almost three times in terms of social relationships.

Additionally, it is important to take into account that the share of moderate plus severe depression is almost the same in the 2 age groups (approximately 15%).

Speaking about sensory troubles in the 45-70 years group, there is a share of 8% (medium + accentuated) hearing disorders and 6% of medium + accentuated visual disorders. The double impairment (hearing plus visual one) reaches a high percentage of 10.5% representing an important aspect for elderly communication and adaptation.

ICOPE also monitors the management of geriatric syndromes such as urinary

incontinence. Our data show a relatively high share (17.1%) in the 45-70 years age group.

Considering these dysfunctions that appeared earlier in the present study, the usefulness of the WHO approach through the ICOPE program is confirmed. It is the functional capacity optimization, by maintaining higher levels of physiological reserves. In other words, it is necessary to diagnose frailty earlier in order to achieve secondary and tertiary prevention.

***Conflicts of interest***

The authors declare no conflicts of interest.

## REFERENCES


[1] WHO. *Active Aging: A Policy Framework*. Geneva 2002, p 12. https://www.who.int/ageing/publications/active_ageing/en/

[2] Coculescu M and Curaj A. *Cercetări dedicate longevităţii active în Europa*. Viata Medicala, 2011. https://www.viata-medicala.ro/opinii/cercetari-dedicate-longevitatii-active-in-europa-4319

[3] WHO. *World report on ageing and health*. Geneva 2015, p 28-30. https://www.who.int/ageing/events/world-report-2015-launch/en/

[4] WHO. *What is Healthy Ageing?* http://www.who.int/ageing/healthy-ageing/en/(accessed May 2019)

[5] Beard JR. *The World Report on Ageing and Health*. The Gerontologist, 2016, 56, S163–S166.

[6] Belloni G. and Cesari M. *Frailty and Intrinsic Capacity: Two Distinct but Related Constructs*. Front Med (Lausanne), 2019, 6, article 133. doi: 10.3389/fmed.2019.00133

[7] Stuck AE, Walthert JM et al, Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med* 1999; 48: 455-169.

[8] Cesari M. and Araujo de Carvalho I. *Evidence for the Domains Supporting the Construct of Intrinsic Capacity*. The Journals of Gerontology: Series A, 2018, 73, 12, 1653–1660.

[9] Nunes de Moraes E, Lanna FM. et al. *A New Proposal for The Clinical-Functional Categorization of the Elderly: Visual Scale of Frailty (Vs-Frailty*). Journal of Aging Research & Clinical Practice, 2016, 5, 1, 24-30.

[10] Araujo de Carvalho I, Martin F, Cesari M, et al. *Operationalising the concept of intrinsic capacity*. WHO Collaborating Center for Frailty, Clinical Research and Geriatric Training Newsletter N° 2018. https://www.who.int/ageing/health-systems/clinical-consortium/CCHA2017-backgroundpaper-1.pdf

[11] A joint FrailSafe & WHO Webinar ntrinsic capacities: How to prevent frailty and care dependence in older age. - https://www.youtube.com/watch?v=H3x4PYoc0N4

[12] WHO Clinical Consortium on Healthy Ageing 2017 Focus: Development of comprehensive assessments and care plans. https://apps.who.int/iris/bitstream/handle/10665/272375/WHO-FWC-ALC-18.1-eng.pdf

[13] Buatois S, Miljkovic D et al. *Five times sit to stand test*. J Am Geriatr Soc 2008, 56(8), 1575 - 1577.

[14] Helen C, Hayley J et al. *A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach*. Age Ageing 2011, 40 (4), 423-429.

[15] Blankevoort G. *Physical performance and cognition in older adults with and without dementia*.2015,[S.l.]:[S.n.].155p. https://www.rug.nl/research/portal/files/15799190/Chapter_3.pdf

[16] Sheikh JI, Yesavage JA. *Geriatric Depression Scale (GDS)*. Clin Gerontol 1986, June; 5(1/2):165-173.

[17] M.D Anderson Centre. *Brief Fatigue Inventory*. 1997. https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-fatigue-inventory.html

[18] Shuman-Paretsky M, Belser-Ehrlich J. *Psychometric Properties of the Brief Fatigue. Inventory in Community-Dwelling Older Adults*. Arch Phys Med Rehabil 2014, 95(8): 1533–1539.

[19] Joint Canada/United States. *Survey of Health Questionnaire Final*, 2004, 19-20.

[20] *Camry Electronic Hand Dynamometer* Instruction manual pdf, 2016 https://www.topendsports.com/testing/norms/handgrip.htm

# RISK ASSESSMENT IN OBESE OLDER PATIENTS

*Simona **Opriş**[1], Rozeta **Drăghici**[1], Alexandra **Rusu**[1]*

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*

*Corresponding author: Simona Opriş, simonaopris11@yahoo.com*

**Abstract.** The prevalence of obesity in older people is high, being one of the major risk factor of age-related diseases. Prior researches point out that atherogenic index (AI) could be used as an indicator for metabolic disturbances. Therefore, we aimed to determine if AI could be a good predictor in risk assessment in obese older patients. Observational cross-sectional study comprised 358 patients over 65 years old: 224 obese patients and 134 normal weight patients as control group. AI values are significantly higher (0.44±0.29 vs. 0.21±0.30; p<0.001) in obese compared to normal weight patients. In obese patients, 76.33% are at high risk and normal weight patients 42.53% are at high risk (hence atherogenic risk increases 1.79 times). The prevalence of dyslipidemia at obese patients rises from 31.94% in low risk AI to 75% in those at high risk. Multivariate regression analysis showed that patients with high AI had 4.35-fold risk for obesity [OR 4.35, 95% CI: 2.74-6.90, p<0.0001]. From the point of view of gender, obese women have significantly lower AI values than men (p<0.001). So even at menopause, with an estrogenic decline, women have a lower atherogenic risk. In conclusion, AI is associated with lipid changes; high risk AI leads to an increase in the prevalence of obesity, therefore AI could be a helpful marker in risk assessment of obese patients.
**Key words:** obesity, atherogenic index, risk assessment, older patients

**Rezumat.** Prevalenţa obezităţii la vârstnici este crescută, fiind unul dintre factorii de risc majori în bolile asociate vârstei a treia. Cercetări recente au arătat că indicele aterogenic (AI) ar putea fi folosit ca indicator în tulburările metabolice. Prin urmare, ne-am propus să determinăm dacă AI ar putea fi un predictor bun în evaluarea riscului la pacienţii vârstnici obezi. Studiul observaţional cross-sectional a cuprins 358 pacienţi de peste 65 ani: 224 pacienţi obezi şi 134 pacienţi normoponderali-grupul control.Valorile AI sunt semnificativ mai mari (0,44±0,29 vs. 0,21±0,30; p <0,001) la obezi faţă de normoponderali. 76,33% dintre pacienţii obezi au risc aterogenic ridicat iar normoponderalii 42,53% au risc ridicat (deci riscul aterogenic creşte de 1,79 ori). Prevalenţa dislipidemiei la obezi creşte de la 31,94% la cei cu risc scăzut AI, la 75% la cei cu risc crescut. Analiza de regresie multivariată a arătat ca pacienţii cu un AI ridicat, vor avea de 4,35 ori mai mare risc de obezitate [OR 4,35; 95% CI: 2,74-6,90; p<0,0001]. Din punct de vedere al influenţei sexului, femeile obeze au valori AI semnificativ mai mici decât bărbaţii (p<0,001). Deci chiar şi la menopauză, cu un declin estrogenic, femeile au risc aterogenic mai scăzut. În concluzie, AI este asociat cu modificările lipidice; AI cu risc ridicat conduce la o creştere a prevalenţei obezităţii, prin urmare AI ar putea fi un marker util în evaluarea riscului la pacienţii obezi.
**Cuvinte cheie**: obezitate, indice aterogenic, evaluarea riscului, pacienţi vârstnici

## INTRODUCTION

Changes in lipid profile induce metabolic disturbance, dyslipidemia and endothelium dysfunction, leading to high prevalence of obesity, hypertension and other cardiovascular diseases [1, 2, 3].

Obesity can be due to: increased fat synthesis, medication, increased energy intake and decreased physical activity. Alteration in endocrine function, changes in emotional status and impact of behavioural factors, could lead to high energy intake and therefore to obesity [3, 4, 5]. Moreover, in senescent patients, physiological and behavioural factors are implicated in ageing and age-related changes in metabolism, which can lead to obesity. Therefore, in older people, obesity can trigger a lot of consequences: cardiovascular diseases, metabolic syndrome, diabetes [2, 3].

For decades, the link between lipoprotein levels and cardiovascular diseases, respectively atherogenic risk has been studied. It was demonstrated that, in addition to cardiovascular diseases, 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 [6, 7]; good

predictor, very valuable and useful for assessing atherogenic risk. Sharaye KO [8] confirmed the statistical reliability of AI as a tool in the assessment of cardiovascular risk factors among non-obese adults.
Therefore, the aim of the study was to determine if AI could be a good predictor in risk assessment in obese older patients.

## MATERIALS AND METHODS

### Subjects

Observational cross-sectional study was conducted among 358 patients, over 65 years old, hospitalized in „Ana Aslan" National Institute of Gerontology and Geriatrics. Of these, 224 were obese and 134 normal weight patients (control group). 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.
All the patients received physical examination, laboratory tests and comprehensive psychological evaluations. We retrieved demographic information (age, sex, ethnicity and smoking) and clinical information (height, weight, body mass index, blood pressure, glucose serum levels and a lipid panel serum).
Body mass index (BMI) was calculated as weight (kg) divided by square of height ($m^2$). Obesity was defined as BMI≥30Kg/$m^2$ and the patients were classified as:

- normal weight (18.5-24.9 Kg/$m^2$)
- overweight (25-29.9 Kg/$m^2$) and
- obese (>30 Kg/$m^2$)
  - obesity class I (30-34.9 Kg/$m^2$)
  - obesity class II (35-39.9 Kg/$m^2$)
  - morbid obesity-class III (>40 Kg/$m^2$)

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

### 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. The prevalence of obesity according to AI risk categories was calculated by logistic regression model. 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 [3, 4, 7].
From a total of 358 older patients studied, we obtained the follow distribution:

- at obese patients: 16.07% male and 83.92% female;
- at normal weight patients: 22.38% male and 77.61% female.

and within obese patients, obesity class distribution is:

- obesity class I -74.10%
- obesity class II -16.51%
- morbid obesity-class III -9.37%

As seen in Tab. I, there was a significant increase in AI with increasing BMI

($p<0.001$). Pearson correlation analyses showed that at normal weight patients, AI was positively but insignificantly correlated with BMI ($r=0.159$; $p=0.064$).

Tab. I Baseline characteristics of the studied patients

| | **Obese patients (n=224)** | **Normal weight patients (n=134)** |
|---|---|---|
| Age (years) | 66.05±6.35 | 68.84±8.47 |
| Body mass index (kg/m$^2$) | 34.09±3.80* | 22.94±1.92 |
| Atherogenic index | 0.44±0.29* | 0.21±0.30 |

Results are presented as means±S.D.; p*<0.001 vs. C

If in normal weight patients group (Fig. 1) 42.53% have high risk AI, in the obese one (Fig. 2) this increase to 76.33%.

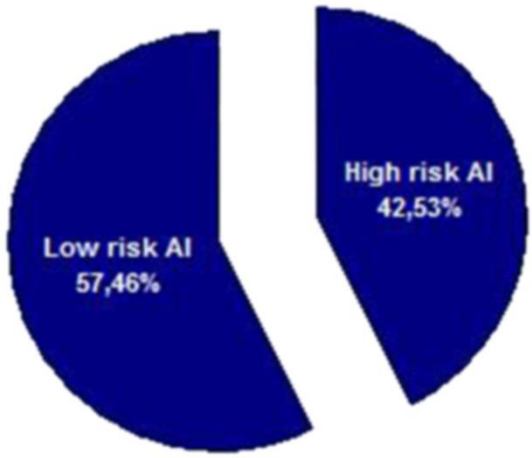



Fig. 1 High/low risk AI at normal weight patients

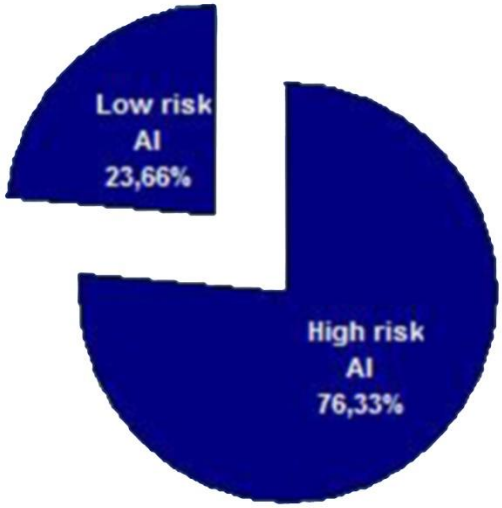



Fig. 2 High/low risk AI at obese patients

The study also reported that at obese patients group, high risk AI raise from 74.85% class I to 80.95% at class III obesity (Fig. 3).

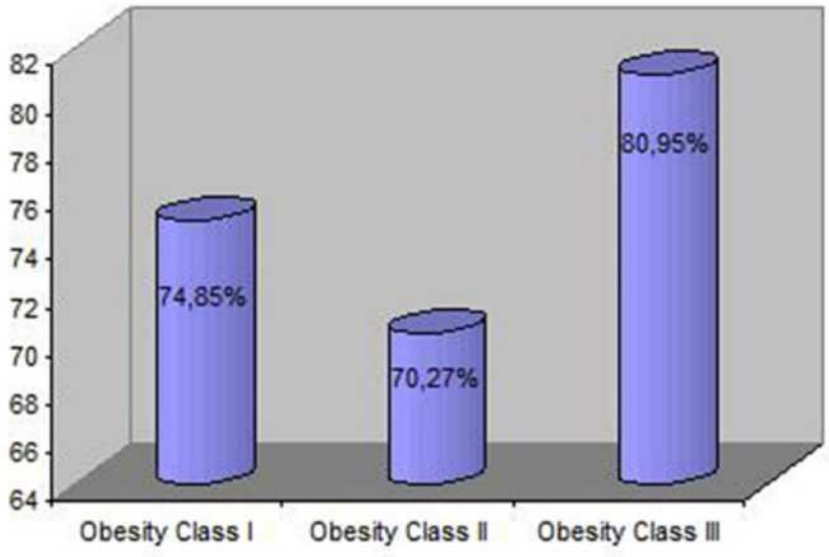



Fig. 3 High risk AI distribution at obesity classes

The prevalence of dyslipidemia is shown in Tab. II. Compared to control group, high risk atherogenic index is increased in obese patients (75% vs. 25%). Therefore, the prevalence of dyslipidemia at obese patients increased from 31.94% in the low risk AI group to 75% in the high risk AI group. So, dyslipidemia in obese patients could be an indicator of their susceptibility to cardiovascular diseases.

Tab. II Prevalence of dyslipidemia among obese patients vs. normal weight patients

| Parameters | **Obese patients (%)** | **Normal weight patients (%)** | **Total** |
|---|---|---|---|
| **Atherogenic index** | | | |
| -0.3-0.1 (low risk) | 23 (31.94) | 49 (68.05) | (72) |
| 0.11-0.24 (medium risk) | 30 (51.72) | 28 (48.27) | (58) |
| >0.24 (high risk) | 171 (75) | 57 (25) | (228) |

Multivariate logistic regression analysis showed that, compared to low risk, patients with high AI had 4.35-fold risk for obesity; the 95% confidence interval of the odds ratios [OR 4.35, 95% CI: 2.74-6.90; $p<0.0001$]. AI test has 76.34% sensibility, specificity 57.46%, prevalence of disease 62.57% and Relative Risk estimate R.R=1.84.

Regarding gender impact upon atherogenic risk (Tab. III), we found at obese women significantly low AI value then obese men ($p<0.001$).

Tab. III Comparison of main characteristics between obese men and obese women

| | **Obese men (n=36)** | **Obese women (n=188)** |
|---|---|---|
| Age (years) | 67±6.47 | 65.87±6.33 |
| Body mass index (kg/m$^2$) | 33.14±2.44$^*$ | 34.28±3.99 |
| Atherogenic index | 0.58±0.28$^{**}$ | 0.41±0.29 |

Results are presented as means±S.D.; $p^*<0.01$ vs. C; $p^{**}<0.001$ vs. C

## DISCUSSIONS

Abnormalities of blood lipids are related mainly to different dietary habits of people, lifestyle and heredity along with the other factors. Obese people seem to have an adverse pattern of plasma lipoproteins, manifested by low concentration of HDL and increased LDL-cholesterol (LDL) concentration. This could be due to increase in adipocyte mass and accompanying decrease in insulin sensitivity associated with obesity has multiple effects on lipid metabolism [1, 2, 8].

According to Flier JS [1], the abnormalities of blood lipids are related mainly to different dietary habits of people, lifestyle and heredity along with the other factors. More free fatty acids are delivered from the expanded adipose tissue to the liver where they are re-esterified in hepatocytes to form triglycerides, which are packaged into VLDL-cholesterol for secretion into the circulation. High dietary intake of simple carbohydrates also drives hepatic production of VLDL-cholesterol, leading to increase in VLDL-cholesterol and/or LDL [1]. In some obese individuals plasma HDL tends to be low in obesity [1, 7].

The positive correlations observed between the lipids/ratio lipids and BMI were in corroboration with other studies [9 -12] and reaffirmed the role of lipids in the pathophysiology of overweight and obesity as well as increasing accumulation of lipids with aging.

Hilal Y [13] reported in his study that low HDL, high LDL and high triglycerides (TG) level are positively associated with an increase in BMI. Same, Kopelman P [14] reported alteration in lipid profile associated with obesity, elevated LDL

concentrations as well as high concentrations of TG which rises the coronary heart disease risk.

In his study, Torng PL [15] determined that obesity can be strongly associated with elevated levels of lipids and significant association between BMI and HDL, TG and LDL which was similar observed in our study. Studies even revealed the adverse effect of abnormal blood lipid and lipoprotein levels in the pathogenesis and progression of atherosclerosis and cardiovascular diseases, in obese patients.

According to the results of the present study, in our previous research that we made, comparing obese patients with control, we also noticed a significant increased in AI ($p<0.005$) and find that between obesity class, AI shown a slight increase but insignificant [16].

Implication of sex hormones in lipid metabolism leads to this difference between men and women. There is a complex and still debated relationship between incidence and prevalence of cardiovascular diseases and aging, menopause, loss of estrogens; which is cause and which is consequence [17]. Till now, cross-sectional and longitudinal studies cannot clarify the distinction between lipid changes (i.e. atherogenic risk) due to mechanism of aging or to menopause pattern model or to both. But even with a decrease in estrogens levels, elderly women have a lower atherogenic risk than elderly men. Previous authors have reported: Ezeukwu AO and Agwubike EO [18] found that sedentary young males are associated with high atherogenic risk; Kanthe PS et al. [7] found that adult women significant increase in AI with BMI; Wu TT et al. [19] found that AI is useful risk factor in postmenopausal women; Nwagha U et al. [20] found a significant increases ($p<0.0001$) of AI in postmenopausal women in Nigeria and also they concluded that AI can significantly add value when assessing the risk of developing atherosclerosis.

Our results is consistent with other researchers [19-21] who also found that in women, menopause is associated with a more atherogenic risk but with less effect than men. In elderly women, decreased levels of estrogens determine low anti-atherogenic effect, thus resulting changes in lipid profiles. But, even at menopause, women have a less atherogenic risk than men.

Some limitations should be considered. The paper work is a cross-sectional analysis of obesity and atherogenic status, so we cannot set a causal relationship. We study only senescent patients and we used only BMI to measure obesity. Differences in 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 maintains his prognostic capacity in long term.

## CONCLUSIONS

- Obesity alters lipid profile, therefore also the atherogenic risk measured by AI.
- AI might be a strong marker in risk assessment in obese older patients.
- At obese patients and even overweight patients, it is recommended a decreased atherogenic risk by modification of diet, exercise, lifestyle, stress and other modifiable risk factors.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES

[1] Flier JS. Biology of Obesity. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. eds. *Harrison's Principles of Internal Medicine.17thed*. New York, NY: McGraw-Hill; 2008:462-464.

[2] Shi-Wei Shen, Yun Lu, Feng Li, et al. *Atherogenic index of plasma is an effective index for estimating abdominal obesity*. Lipids in Health and Disease 2018, 17:11.
[3] Amarya S, Singh K, Sabharwal M. *Health consequences of obesity in the elderly*. J of Clin Gerontol & Geriatr 2014, 5, 63-67.
[4] Klop B, Jan Willem F. Elte, Cabezas MC. *Dyslipidemia in Obesity: Mechanisms and Potential Targets*. Nutrients 2013, 5(4), 1218–1240.
[5] Un Ju Jung and Myung-Sook Choi. *Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease*. Int J Mol Sci 2014, 15(4), 6184–6223.
[6] Rasˇlova´ K, Dobia´sˇova´ M, Huba´cˇek JA, et al. *Association of metabolic and genetic factors with cholesterol esterification rate in HDL plasma and atherogenic index of plasma in a 40 years old Slovak population*. Physiol Res 2011, 60, 785–795.
[7] Kanthe PS, Patil BS, Bagali S, et al. *Atherogenic index as a predictor of cardiovascular risk among women with different grades of obesity.* Inter J Coll Res Int Med&Public Health 2012, 4, 10, 1767-1774.
[8] Sharaye KO. *Association of atherogenic indices and abdominal obesity indices among non obese adults in Zaria, Northern Nigeria*. J of Physiol and Pathol 2015, 6(1), 1-5.
[9] Ugwuja EI, Ogbonna NC, Nwibo AN, Onimawo IA. *Overweight and obesity, lipid profile and atherogenic indices among civil servants in Abakaliki, south eastern Nigeria*. Ann Med Health Sci Res 2013, 3, 1, 13-18.
[10] Santos APC, Vieira MS, Débora F. et al. *Atherogenic Indices and HDL Particle Size as Laboratory Parameters to Evaluate Cardiovascular Risk in the Presence of Dyslipidemia*. Journal of Biophysical Chemistry 2014, 5, 24-32.
[11] Khanam M, Khan AH, Rahman R, et al. *Comparison of Atherogenic Index of Plasma (AIP) Between Postmenopausal Women with Central Obesity and Postmenopausal Nonobese Women.* Chattagram Maa-O-Shishu Hospital Medical College Journal 2014, 13, 2, 47-50.
[12] Essiarab F, Hassan T, Lebrazi H et al. *Usefulness of lipid ratios and atherogenic index of plasma in obese Moroccan women with or without metabolic syndrome*. Ethnicity & Disease 2014, 24, 201-212.
[13] Hilal Y. *The association of anthropometric measurement and lipid profiles in Turkish hypertensive adults*. African Health Sciences 2011, 11(3), 407-413.
[14] Kopelman P. *Health risks associated with overweight and obesity*. Obesity Reviews 2007, 8, 1, 13-17.
[15] Torng PL. *Effect of menopause and obesity on lipid profiles in middle-aged Taiwanese women: the Chin-Shan Community Cardiovascular Cohort Study*. Atherosclerosis 2000, 153, 413-421.
[16] Opris S, Constantin G, Grigorie M, Halici F, Valuch A. *Impact of obesity on lipoprotein profile and cardiovascular risk at eldely patients.* Rom J Gerontol Geriatr 2016, 5, 1, 31-36.
[17] Palmisano BT, Zhu L, Eckel RH, Stafford JM. *Sex differences in lipid and lipoprotein metabolism*. Mol Metab 2018,15, 45–55.
[18] Ezeukwu AO, Agwubike EO. *Anthropometric measures of adiposity as correlates of atherogenic index of plasma in non-obese sedentary Nigerian males*. Libyan Journal of Medicine 2014, 9:1, 23798-23804.
[19] Wu TT, Gao Y, Zheng YY, Ma YT, Xie X. *Atherogenic index of plasma (AIP): a novel predictive indicator for the coronary artery disease in postmenopausal women.* Lipids in Health and Disease 2018, 17, 197-204.
[20] Nwagha U, Ikekpeazu EJ, Ejezie FE, Neboh EE, Maduka IC. *Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria*. African Health Sciences 2010, 10, 3, 248-252.
[21] Anagnostis P, Stevenson JC, Crook D, Jhonston DG, Godsland IF. *Effects of menopause, gender and age on lipids and high-density lipoprotein cholesterol subfractions*. Maturitaas 2015, 81, 1, 62-68.

# THE ROLE OF BIOMARKERS IN THE ASSESSMENT OF FRAILTY SYNDROME IN THE ELDERLY

*Ana **Popa**[1], Anatolie **Negară**[1], Ion **Sîrbu**[2], Gabriela **Șoric**[1], Ana **Popescu**[1]*

*[1]Geriatrics and Gerontology Laboratory, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova*
*[2]Department of Internal Medicine, Clinical Synthesis, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova*

*Corresponding author: Ana Popa, popaana2805@gmail.com*

**Abstract**. Fragility is an important concept of geriatric medicine and studying its etiology has become a fundamental aspiration of many researchers in the field of aging. Fried's model defining fragile persons has been praised for reproducibility and clinical consistency and was validated despite the negative results from large population studies. The index based on the physical parameters evaluates only one of the aspects of frailty, while frailty is probably a complex, multidimensional concept. Therefore, new strategies are needed to identify and evaluate frailty in the elderly. The use of biomarkers as new methods for diagnosing of frailty may provide greater accuracy in detection of fragile subjects in the early stages. The aim of the study was to make a synthesis of the role of biomarkers in identifying people at high risk of frailty, based on the results of scientific research from the PubMed and Cochrane databases. Conclusion**:** It is considered that biomarkers may be useful for the management of fragile patients only in combination with several biomarkers or with a clinical marker.
**Key words**: frailty, biomarkers, elderly

**Rezumat**. Fragilitatea este un concept important în medicina geriatrică și studierea etiologiei sale a devenit o aspirație fundamentală a multor cercetători în domeniul îmbătrânirii. Modelul lui Fried de definire a persoanelor fragile a fost lăudat pentru reproductibilitate și coerența clinică și a fost validat în pofida rezultatelor negative din studiile populaționale mari. Acest indice bazat pe parametrii fizici, evaluează doar unul din aspectele fragilității, în timp ce fragilitatea este, probabil, un concept complex, multidimensional. Prin urmare, sunt necesare noi strategii de identificare și evaluare a fragilității la vârstnici. Folosirea biomarkerilor ca metode noi pentru diagnosticarea fragilității ar putea asigura o mai mare precizie în detecția subiecților fragili în stadii timpurii. Scopul studiului a fost de a face o sinteză a rolului biomarkerilor în identificarea persoanelor cu risc crescut de fragilitate, pe baza rezultatelor cercetărilor ştiinţifice din bazele de date PubMed și Cochrane. Concluzie**:** se consideră că biomarkerii pot fi utili pentru managementul pacienților fragili doar în combinație a mai multor biomarkeri sau cu un marker clinic.
**Cuvinte cheie**: fragilitate, biomarkeri, vârstnic

## INTRODUCTION

The frailty in the aged is a complex syndrome characterized by vulnerability to stressors and decreased physiological reserve, which affects multiple organs and lead to diminished ability to perform regular daily activities, resulting in a progressive physiological decline at different systems and organs. This syndrome is associated with increased risk of falls and fractures, decreased quality of life, institutionalization, hospitalization, all of which contribute to increased mortality [1]. Globally, frailty can affect anyone at all stages of life, with a prevalence rate from 4% to 59.1% in accordance with different demographics or socio-economic conditions. However, the main affected age range is the elderly (65 and over) [2].

The systematic review conducted in 2012 by the Dutch researcher Collard RM et al. [3] regarding the prevalence of frailty, showed that 10.7% of adults over 65 are more fragile, this percentage increases to 15.7% and respectively 26.1%, for persons in the age groups 80-84 and above 85. Another randomized study conducted in 2017 by Italian researcher Liotta G et al. [4] on prevalence of frailty and its determinants, which used the geriatric evaluation questionnaire in the general population revealed that 14% of frail and

7.6% of those very fragile people are adults over the age of 65 years. The prevalence of frailty varies over time, depending on the changes in the socio-economic and physical conditions of the people.
Therefore, the syndrome is commonly known as a relative condition, without a well-defined threshold [5]. Many factors in different fields, such as physical, social, psychological, sensory and cognitive states, can cause frailty syndrome [6].

## FRAILTY ASSESSMENT TOOLS

Although the theoretical underpinnings of frailty syndrome are well-established in the literature, its translation into practice, especially in daily clinical life, remains controversial [7]. For this reason, many tools have been developed over the years to identify measure and evaluate frailty. At this time, there is a multitude of tools, with extreme internal variability in the score, instructions and areas evaluated [8]. From the wide range of tools used for frailty assessment, the frailty phenotype proposed by Fried LP et al. in 2001 [9] and the frailty index studied and validated by Canadian researchers Rockwood K and Mitnitski A [10] are probably the best known. Some studies in the field also report some limits on use of these indices in the practice of medical practitioners, although these two methods are the most used in frailty assessment.
Canadian researcher Howlett SE and Rockwood ME [11] in their work on evaluation of standard instrumental and laboratory tests to identify elderly people at increased risk of death, showed that the frailty phenotype does not allow differentiation of the degree of frailty severity only the relationship between the pathologies present in an individual and the total number of them evaluated. It is worth mentioning that these findings were also estimated by the German scientist Ritt M et al. [12] who found that although the frailty phenotype has proved to be a very strong predictor in identifying elderly people with an increased risk of mortality, but applying this evaluation index of multiple pathologies present in patients requires a longer period.
All the above imply the need to implement more complex frailty assessment tools. Thus, it was proposed to use biomarkers as new methods for diagnosing frailty as they could provide greater accuracy in detecting fragile subjects. Currently, there are no standardized tests, biomarkers or parameters that can be used to diagnose the frailty of patients, why the identification of frailty biomarkers is a major objective for future studies in the field.
The aim of the study was to make a synthesis of the role of biomarkers in identifying people at high risk for frailty. In order to achieve that, the results of studies were evaluated regarding the biomarkers used in the evaluation of the frailty of the PubMed and Cochrane databases. The information was systematized, highlighting the main aspects of the contemporary vision on biomarkers in the frailty syndrome management.

## NEW STRATEGIES.
## USE OF BIOMARKERS

Several biomarkers are currently used for the diagnosis, prognosis and stratification of frailty syndrome. The predictive value of these biomarkers in frailty syndrome has not yet been systematically examined. Experts note that use of a single biomarker is not sufficient for the assessment of frailty, suggesting that a combination of biomarkers or an association between biomarkers and clinical indices of frailty is necessary [13].
According to Al Saedi et al. [14] the possible usable biomarkers of frailty are:

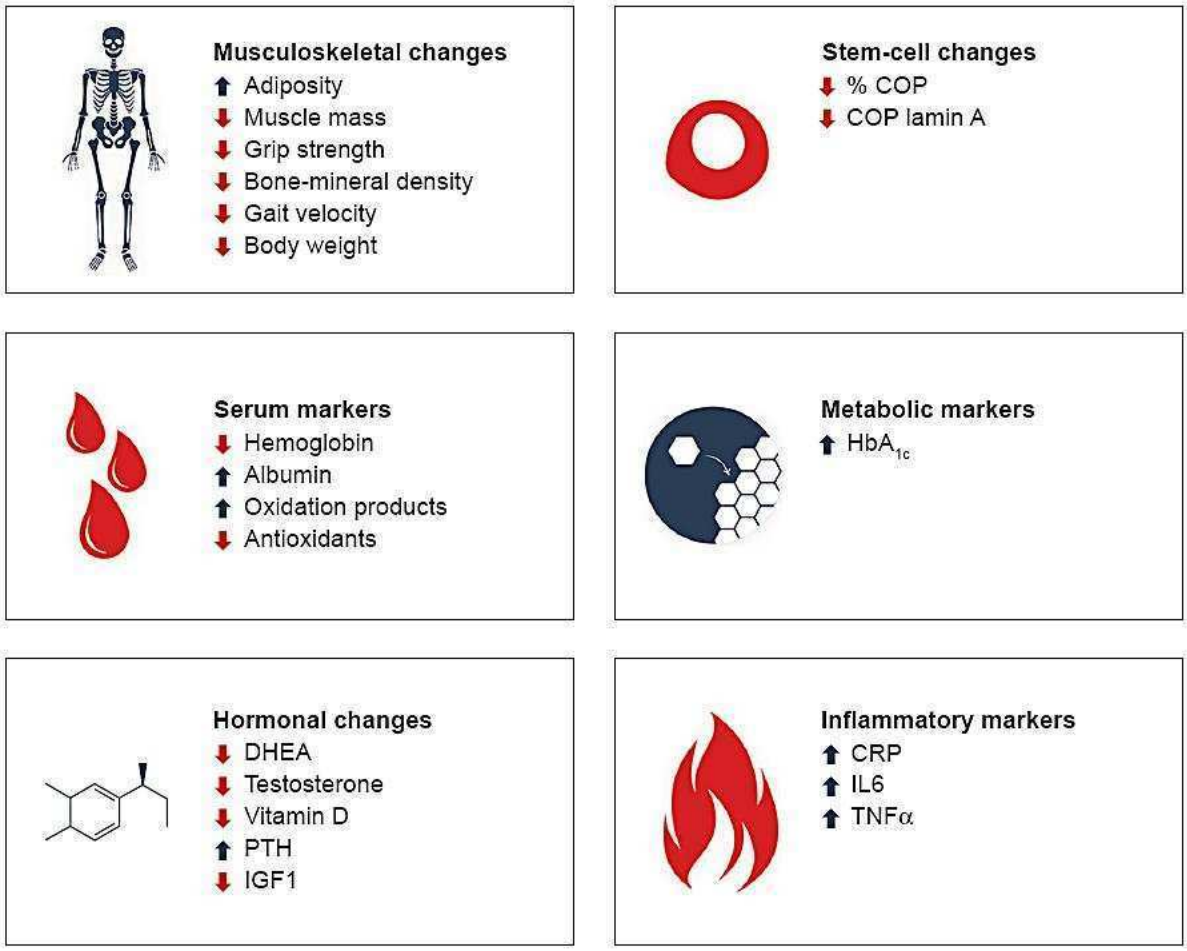



Figure 1. Current and upcoming biomarkers for frailty
*Abbreviations: COP, circulating osteoprogenitor; DHEA, dehydroepiandrosterone; PTH, parathyroid hormone; IGFI, insulin-like growth factor I; HbAIc, glycated hemoglobin; CRP, C-reactive protein; IL6, interleukin 6; TNFα, tumor necrosis factor alpha.*

Regarding the prognostic value of biomarkers in frailty, the 2015 study by Canadian scientist Mitnitski A et al. [15] who examined a laboratory frailty index based on 40 biomarkers showed that using frailty index and Fried's frailty phenotype in common with biomarkers they have a higher mortality prognosis compared to using only physical indices. These findings were previously estimated in the aforementioned study of Canadian researchers Howlett SE and Rockwood ME [11] where the evaluation of 21 biomarkers in combination with the measurement of systolic and diastolic blood pressure in the elderly showed that an index of frailty based on the laboratory data can identify the elderly persons with an increased risk of death.

Biomarkers that play a specific role in the context of frailty syndrome are considered to be related to anemia, vitamin deficiency but also inflammatory markers.

About one third of elderly people with anemia have iron deficiency, another third represent people with kidney failure or chronic inflammation as a cause of anemia. The term anemia of unknown etiology is used in the specialized literature and is used when investigations cannot suggest the cause of anemia.

InCHIANTI study, carried out by a group of American researchers who studied anemia in the elderly, showed that the hemoglobin level is closely correlated with the low physical performance and low muscle strength characteristic of the elderly [16]. In another recent study published by Gowanlock Z et al. [17] it

was demonstrated that low erythropoietin levels in the elderly play a key role in the pathogenesis of anemia of unknown etiology.

Another laboratory indicator of fragility is vitamin deficiency (vitamin B, vitamin D.) The association between vitamin D deficiency and osteo-articular pathology is well-known, but in recent years, evidence has emerged regarding its role and metabolism of a wide variety of cells [13]. Proximal muscle weakness, reduced muscle strength and increased rate of falls are attributed to vitamin D deficiency. Falls are a major problem for people over the age of 65 years, leading to significant morbidity, increased mortality, and substantial resource consumption. Meta-analysis of American researcher Murad MH et al. [18] which included 26 observational studies, selected based on empirical evidence, clinical reasons that reported that Vitamin D combined with calcium reduces the risk of falls in the elderly. These data were further found by the Spanish scientist Scheel F et al. [19] who published the results of his study on the importance of vitamin D in preventing falls in 2016, showing that the use of vitamin D does not change the risk of falls in the elderly. As such, the role of vitamin D in frailty syndrome is not fully elucidated, and large randomized studies are needed.

The link between inflammation and frailty is a topic of interest due to the multiple pathogenic effects associated with it. Thus, in the last few years, the central role of chronic inflammation in the pathogenesis of frailty has been highlighted [20]. Among inflammatory markers accompany the aging process and age related pathology, pro-inflammatory cytokines: interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- alpha) and its soluble receptors sTNF-receptorI (sTNF-RI), sTNF-receptorII (sTNF-RII) but also acute phase proteins: C-reactive protein (CRP), fibrinogen, neutrophils, red blood cell sedimentation rate (VSH) seem to play a particular role in frailty assessment [21].

Study of the English researcher Hubbard RE et al. [22], published in 2009, which included a number of 110 patients with fragility, provided additional data regarding the connection between chronic inflammation and frailty in the elderly. The research results showed a significant directly proportional correlation of the FI with CRP, IL-6 and TNF- and inversely proportional to albumin.

The same data were also found in the work of the Spanish researcher Marcos-Perez M et al. [23] who confirmed the involvement of chronic inflammation in the status of fragile in the elderly population, in particular a strong association between IL-6 and sTNF-RII. Data obtained for sTNF-RII indicated greater accuracy for predictive value of this fragility biomarker.

## CONCLUSION

Although the possible use of laboratory biomarkers in fragility assessment has been established in general, it has not yet been accepted as diagnostic tools. Studies in the field have reported that the use of a single biomarker has no prognostic or diagnostic value for fragility, requiring a combination of multiple biomarkers or with a clinical marker.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES

[1] Clegg A, Young J, Iliffe S, et al. *Frailty in elderly people*. Lancet 2013, 381, 752–762.

[2] Buckinx F, Rolland Y, Reginster JY, et al. *Burden of frailty in the elderly population: perspectives for a public health challenge.* Arch Public Health 2015; 73(1), 19.

[3] Collard RM, Boter H, Schoevers RA, et al. *Prevalence of frailty in community dwelling older persons: a systematic review*. J Am Geriatr Soc 2012; 60(8), 1487-92.
[4] Liotta G, O'Caoimh R, Gilardi F, et al. *Assessment of frailty in community-dwelling older adults residents in the Lazio region (Italy): A model to plan regional community-based services.* Arch Gerontol Geriatr 2017, 68, 1-7.
[5] Gilardi F, Capanna A, Ferraro M, et al. *Frailty screening and assessment tools: a review of characteristics and use in Public Health*. Annali di Igiene: Medicina Preventiva e di Comunita 2018, 30(2), 128-139.
[6] Labra C, Maseda A, Lorenzo-López L, et al. *Social factors and quality of life aspects on frailty syndrome in community-dwelling older adults: the VERISAÚDE study*. BMC Geriatr 2018, 18(1), 66.
[7] Clegg A, Tineri J, Iliffe S, et al. *Frailty in elderly people*. Lancet 2013, 381(9868):752-62.
[8] Cesari M, Gambassi G, Abellan van Kan G, et al. *The frailty phenotype and the frailty index: different instruments for different purposes*. Age Ageing 2014, 43(1), 10-2.
[9] Fried LP, Tangen CM, Walston J, et al. *Frailty in older adults: evidence for a phenotype.* J Gerontol A Biol Sci Med Sci 2001, 56, M146–M156.
[10] Rockwood K, Mitnitski A. *Frailty defined by deficit accumulation and geriatric medicine defined by frailty*. Clin Geriatr Med 2011, 27, 17–26.
[11] Howlett SE, Rockwood MR, Mitnitski A, et al. *Standard laboratory tests to identify older adults at increased risk of death*. BMC Med 2014, 12, 171.
[12] Ritt M, Ritt JI, Sieber CC, et al. *Comparing the predictive accuracy of frailty, comorbidity, and disability for mortality: a 1-year follow-up in patients hospitalized in geriatric wards.* Clin Interv Aging 2017, 12, 293–304.
[13] Pena MC. *Rolul parametrilor de laborator în predicția, identificarea și monitorizarea fragilității vârstnicului*. Medical Market Geriatrie 2018, vol.2018, p.18.
[14] Al Saedi A, Feehan J, Phu S, Duque G. Current and emerging biomarkers of frailty in the elderly. Clinical Interventions in Aging 2019, 14, 389–398.
[15] Mitnitski A, Collerton J, Martin-Ruiz C, et al. Age-related frailty and its association with biological markers of ageing. BMC Med 2015; 13: 161.
[16] Cesari M, Penninx BW, Lauretani FJ, et al. *Hemoglobin levels and skeletal muscle: results from the InCHIANTI study*. J Gerontol A Biol Sci Med Sci 2004, 59(3):249-54.
[17] Gowanlock Z, Sriram, S, Martin A, et al. *Erythropoietin Levels in Elderly Patients with Anemia of Unknown Etiology.* PLoS One 2016, 11(6): e0157279.
[18] Murad MH, Elamin KB, Alkatib AA, et al. *The Effect of Vitamin D on Falls: A Systematic Review and Meta-Analysis*. J Clin Endocrinol Metab 2011, (10), 2997-3006.
[19] Scheel F, Carrasco M. *Is vitamin D supplementation effective for the prevention of falls in elderly people.* Medwave 2016, Jan 26, 16 Suppl 1:e6368.
[20] Singh T, Newman A.B. *Inflammatory markers in population studies of aging*. Ageing Res Rev 2011, 10, 319–329.
[21] Varadhan R, Yao W, Matteini A, et al. *Biologically Informed Inflammatory Index of Two Serum Cytokines Predicts 10 Year All-Cause Mortality in Older Adults*. J Gerontol A Biol Sci Med Sci 2014, 69A(2), 165–173.
[22] Hubbard RE, O'Mahony MS, Savva GM, et al. *Inflammation and frailty measures in older people.* J Cell Mol Med 2009, 13, 3103–9.
[23] Marcos-Pérez D, Sánchez-Flores M, Maseda A, et al. *Frailty in Older Adults Is Associated With Plasma Concentrations of Inflammatory Mediators but Not With Lymphocyte Subpopulations*. Front Immunol 2018, 9, 1056.

# ASPECTS OF INCLUDING LIPOPROTEINS AND APOLIPOPROTEINS INTO NEW PANELS

*Cristina* ***Ionescu***[1]*, Doina Elena* ***Roditis***[1]*, Irina* ***Dumitrescu***[1]*, Elena* ***Lupeanu***[1]

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*

*Corresponding author: Cristina Ionescu, cristinaionescucristina@gmail.com*

**Abstract**. Advanced laboratory techniques added insights into lipoproteins' composition and roles as cardiovascular disease risk factors. Precipitation techniques and methods using magnetic resonance spectroscopy were developed to quantify lipoproteins but on the whole, imprecision of methods to measure lipoproteins remain a sensitive issue. Hence, LDL cholesterol calculations using equations and adjustable factors are largely used at present. Most studies have in view now that apolipoprotein B may be considered a measure of total atherogenic lipoproteins. Adding apolipoprotein B to standard lipid panels or even apolipoprotein B substituting for the lipid panel, are both now under debate. Currently, there are limitations in investigating lipid-lowering in patients with atherosclerotic cardiovascular disease. Duration of exposure elevated LDL cholesterol in patients who have developed atherosclerotic cardiovascular disease by the age of 75, remains to a large extent, unknown and also, not all increased serum LDL cholesterol phenotypes are equally atherogenic. To overcome such limitations, non-HDL cholesterol was proposed as a likely stable parameter over a 30 year period of time in cases of younger adults. However, postprandial ranges and cutoffs values for non-HDL cholesterol are not well defined. For young and middle-aged patients LDL cholesterol decrease continues to be the therapeutic target in primary and secondary prevention. Reducing number of cardiovascular events in cases of elderly was not quite evident after they were given statin treatment. In conclusion, it remains to be established if reductions in apolipoprotein B should be reported along with decreases in LDL cholesterol and triglycerides. Moreover, there is a new trend now in lipid biomarkers evaluations, namely implementation of panels of apo AI, apo CI, apo CII, apo CIII, apo B and apo (a) assays.
**Key words**: lipoproteins, LDL cholesterol, apolipoprotein B, non-HDL cholesterol

**Rezumat**. Tehnicile avansate de laborator au relevat detalii despre compoziția și rolul lipoproteinelor că factori de risc în boală cardiovasculară. Tehnicile de precipitare și spectroscopia cu rezonanță magnetică nucleară au fost dezvoltate pentru studiul lipoproteinelor, dar per ansamblu imprecizia metodelor de evaluare a lipoproteinelor rămâne o problema sensibila. Prin urmare, calculele LDL colesterol utilizând ecuații și factori de ajustare sunt larg folosite. Cele mai multe studii au acum în vedere că apolipoproteina B poate fi considerată o măsură pentru lipoproteinele aterogene totale. Adăugarea apolipoproteinei B la panelurile lipidice standard sau chiar apolipoproteina B care să substituie panelul de lipide, sunt ambele acum, în dezbatere. În prezent există limitări pentru investigarea reducerii lipidelor în cazul pacienților cu boală cardiovasculară aterosclerotica. Durata expunerii la un LDL colesterol crescut până la vârstă de 75 ani, rămâne într-o mare măsură, necunoscută, de asemenea nu toate fenotipurile de LDL colesterol crescut sunt egal aterogene. Pentru a compensa astfel de limitări, non-HDL colesterol a fost propus că parametru probabil stabil pe o perioada de timp de 30 ani, in cazurile adultilor tineri. Totusi, domeniile de valori și valorile prag postprandiale nu sunt bine definite pentru non-HDL colesterol. Pentru pacienții tineri și de vârstă mijlocie, LDL colesterol continuă a fi țintă terapeutică în prevenția primară și secundară. În cazul vârstnicilor, reducerea incidentelor cardiovasculare nu a fost atât de evidență după ce aceștia au primit tratament cu statine. În concluzie, rămâne să fie stabilit dacă reducerile de apolipoproteina B trebuie raportate împreună cu scăderile de LDL colesterol și trigliceride. Mai mult, există o nouă tendința acum, în evaluările de biomarkeri lipidici și anume, implementarea panelurilor de teste de apo AI, apo CI, apo CII, apo CIII, apo B and apo (a).
**Cuvinte cheie**: lipoproteine, LDL colesterol, apolipoproteina B, non-HDL colesterol

## INTRODUCTION

Advanced laboratory techniques added insights into lipoproteins roles as cardiovascular disease risk factors and composition. Precipitation techniques and methods using magnetic resonance spectroscopy were developed to quantify lipoproteins but on the whole, imprecision of methods to measure lipoproteins have remained a subject to address. Standard lipid panels are now considered not very helpful in diagnosing dyslipidemias, so equations and adjustable factors are still used in calculations to report lipoproteins.

Adding apolipoprotein B (apoB) to current lipid panels or even apoB substituting for the lipid panel, especially in circumstances of limited resources, are both now under debate [1].

Albers JJ et al. [2] pointed out that standard lipoprotein measures are far less specific for being predictive of cardiovascular events. Using fractionated lipoproteins as likely more specific of cardiovascular events, Albers JJ et al found out that the highest levels of fractionated high density lipoprotein (HDL-C) were associated with less cardiovascular events, low density lipoprotein (LDL)-triglyceride fraction associated low-grade inflammation and both this later fraction and small dense LDL particles failed to predict cardiovascular events in patients with vascular disease treated with statins [2]. The disadvantage of using fractionated lipoproteins is that fractions and populations of particles obtained through analytical methods are variable. However, specialized literature continues to acknowledge a phenotype A for LDL in relation to preponderance of large buoyant LDL particles, and a B phenotype for LDL characterized by preponderance of small dense LDL particles. As well, differences concerning large buoyant LDL particles and small dense LDL particles' associations with cardiovascular risk were underscored. Compared to atherogenic small dense LDL particles, large LDL particles are containing a low percentage of glycated apolipoprotein B100 and less susceptible to oxidation and glycation [3]. It is noteworthy that for estimating the cardiovascular risk, the interest is now in using number of lipoprotein particles, especially apoB particles and less data on cholesterol [4, 5].

## APOLIPOPROTEIN B

ApoB is now taken into consideration as reflecting the sum of atherogenic lipoproteins, namely LDL, very-low density lipoproteins (VLDL), and lipoprotein (a) (lp(a)). Genetic research by Ference BA et al. [6] on variants of lipoprotein lipase genes and variants of LDL receptor genes underlined that a variant of lipoprotein lipase genes was concordantly related to lowering VLDL and reduction of apoB. With regard to the LDL receptor genes, a variant in relation to decrease in number of circulating LDL particles was related as well to apoB reduction. However, magnitude of reduction in apoB due to genes variants cannot be compared to that reported after treatments with lipid lowering drugs [6, 7].

As regards these later mentioned drugs, according to a recent study [8] on apo B and triglycerides-rich lipoproteins in patients with chronic kidney disease treated with simvastatin and ezetimibe, there were reductions of apoB levels in comparison to placebo but only for patients not on dialysis. Lamprea-Montealegre JA et al. [8] noted that in chronic kidney disease, there is decreased removal of triglyceride-rich lipoproteins from plasma, so levels of triglycerides are high, whereas LDL levels are not elevated.

In a study on possible changes of LDL fractions, non-HDL cholesterol (non-HDL), apoB, triglycerides and lp(a) in relation to body weight changes, Dansinger ML et al. [3] reported associations of small dense LDL particles, LDL particle number, non-HDL, apoB and triglycerides with body weight, both in males and females. It has been highlighted for clinical practice that apoB increases can be concordant with elevations in serum LDL and a raised LDL particle number, or discordant with serum LDL, in which case, apoB higher than LDL is the parameter that associates the risk of atherosclerotic cardiovascular disease [4].

## LOWERING OF LDL CHOLESTEROL IN RELATION TO CARDIOVASCULAR RISK – MAIN GOAL OF FOLLOW-UPS

For young and middle-aged individuals LDL continues to be the therapeutic target in conventional primary and secondary

prevention. Along with statins, newer drugs such as proprotein-convertase subtilisin/kexin type 9 PCSK-9 inhibitors and ezetimibe were developed. For patients at the highest risk, namely LDL above 189 mg/dl, guidelines suggested that LDL should be decreased with no low limit established and recommended high-intensity statin treatment [9]. Use of statins to lower LDL with no low LDL limit proved to be beneficial in that it reduced the risk of developing atherosclerotic cardiovascular disease ASCVD. Results pointed out that high-intensity statin treatment to which a PCSK-9 inhibitor was added, led to decrease of LDL to levels below 70 mg/dl in less than eight weeks [10].

Reducing cardiovascular events in old individuals was not quite evident after they were given statins. Gurwitz JH et al. [11] underlined both lack of significant results as regards statins in primary prevention of cardiovascular disease for patients older than 75 years and lack of information, as patients aged 65 to 75 years who are given statins, are aging without being monitored effectively [11].

Nanna MG et al. [12] underscored that older individuals can survive to the old age if having less traditional cardiovascular risk factors except for age, sex and race. In elderly at high cardiovascular risk the need for lipid-lowering therapy must be established irrespective of their LDL values. Also, it should be noted that lipid-lowering therapies decrease LDL but do not rule out the residual cardiovascular risk resulting from inflammation and neurohormonal activation as LDL independent atherogenic pathways [13]. The AHA/ACC Cholesterol Guideline 2018 [14], suggestively entitled 'The Patient Has the Power', in view of a physician-patient shared decision, took into account both individuals younger than 40 and those older than 75 years of age. For subjects aged 40 to 75 years, without type 2 diabetes, at an intermediate 10-year atherosclerotic cardiovascular disease risk who are going to be prescribed statins, this guideline enumerated the following cardiovascular disease risk enhancers: family history of premature atherosclerotic cardiovascular disease, LDL persistently higher than 160 mg/dl, triglycerides higher than 175 mg/dl, chronic inflammatory disorders (rheumatoid arthritis, psoriasis, lupus erythematosus), high –risk ethnic groups (South Asians), chronic kidney disease, premature menopause, C-reactive protein higher than 2 mg/dl and if tested, apoB higher than 130 mg/dl [14].

Distinctly from the North-American guidelines, the European ones added psychosocial stress, vital exhaustion; major psychiatric disorders to the above cardiovascular risk enhancers [15]. Of these cardiovascular disease risk enhancers, recently [16] it was still not clear enough out of high triglycerides, triglyceride-containing apoB particles and high number of small dense LDL particles, which ones are associated with or causing atherosclerosis. Pradhan AD [16] underscored firstly that in statistical analyses associations of the above variables with vascular risk are attenuated or not found out when adjustments for confounding factors are made and secondly, that in patients with high levels of triglycerides it would be appropriate to estimate a residual cardiovascular risk.

To date, there are less clinical trial data evaluating the effectiveness of lipid-lowering therapy in older individuals without established atherosclerotic cardiovascular disease. As Brunner FJ et al. [17] highlighted, most such studies are not taking into account duration of exposure to elevations in LDL in patients who have developed ASCVD by the age of 75. To overcome above limitations, non-HDL was proposed as a likely stable parameter over a 30 year period of time in cases of younger adults and also a 30-year cardiovascular risk, based on non-HDL categories and thresholds for serum lipids [17]. For non-HDL cholesterol, the following categories were introduced: less

than 100 mg/dl; 100 to less than 143mg/dl; 143 to less than 185 mg/dl; 185 to less than 220 mg/dl and higher than 220mg/dl [17, 18].

## LIPOPROTEIN (A)

Afshar M et al. [19] reported data according to which, elevated LDL in young individuals with acute coronary syndrome was strongly associated increased lp(a). Also, Enas AE et al. [20] underscored that lp(a) is an insufficiently recognized genetic factor implicated in coronary artery disease in young Indians. Associations of LDL with lp(a) were shown at levels of LDL higher than 135 mg/dl but at levels below this value, these associations were weaker. For patients having LDL levels of 135 mg/dl, at the same time there were a strong correlation of LDL with lp(a) and a calculated low ten-year cardiovascular risk, because of which these patients could have not received statins [19].

The meta-analysis on statin trials in secondary prevention pointed out similarly that lp(a) predicted recurrent cardiovascular events in individuals with LDL values higher than 130 mg/dl. The association of lp(a) with LDL was not evidenced in patients with low LDL [21].

## LDL CHOLESTEROL CALCULATION AT PRESENT

The Friedewald equation has been considered inaccurate for extreme low or high triglyceride concentrations.

According to US data, calculated LDL loses accuracy as triglycerides increase above 400 mg/dl. Since 2013 the following equation validated by Martin SS et al. [22], replaced the Friedewald equation.

LDL cholesterol (mg/dL) = total cholesterol – HDL cholesterol – triglycerides/adjustable factor

In the equation, levels for triglycerides are from 7–49 mg/dL to 400–13975 mg/dL and levels for non-HDL are from less than 100 mg/dL to higher than 220 mg/dL [22, 23]. Along with the equation for LDL calculation, a matrix was constructed that comprises 180 adjustable factors (denominators), triglycerides and non-HDL categories. The adjustable factor is lowest for patients with very low levels of triglycerides and high levels of non-HDL, and highest for those with very high levels of triglycerides and low levels of non-HDL [23].

## CONCLUSION

In conclusion, it remains to be established if reductions in apoB concentrations should be reported along with decreases in LDL and triglycerides. Moreover, there is a new trend now in lipid biomarkers evaluations, namely implementation of panels of apo AI, apo CI, apo CII, apo CIII, apo B and apo (a) assays.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES

[1] Ruhaak LR, van der Laarse, Cobbaert CM. *Introducing serum apolipiprotein profiling for enabling precision cardiology: its time has come*. Clinical Laboratory International, Nov 2019, 6-9.

[2] Albers JJ, Slee A, Fleg JL, O'Brien KD, et al. *Relationship of baseline HDL subclasses, small dense LDL and LDL triglyceride to cardiovascular events in AIM-HIGH clinical trial*. Atherosclerosis 2016, 251, 454-459.

[3] Dansinger ML, Williams PT, Superko HR, Schaefer EJ. *Effects of weight change on apolipoprotein B-containing emerging atherosclerotic cardiovascular disease ASCVD risk factors*. Lipids in Health and Disease 2019, 18, 154.

[4] htpps://www.peterattiamd.com/ Accessed July 7, 2020.

[5] Sniderman A, Thanassoulis G, Glavinovic T, et al. *Apolipoprotein B particles and cardiovascular disease. A narrative review.* JAMA Cardiol 2019, 4, 12, 1287-1295.
[6] Ference BA, Ginsberg HN, Graham I, et al. *Low-density lipoproteins cause atherosclerotic cardiovascular disease. Evidence from genetic, epidemiologic and clinical studies. A consensus statement from the European Atherosclerosis Society consensus Panel.* Eur Heart J 2017, 38, 2459-2472.
[7] Stock J. *Triglycerides and cardiovascular risk: Apolipoprotein B holds the key*. Atherosclerosis 2019, 284, 221-222.
[8] Lamprea-Montealegre JA, Staplin N, Herrington WG, Haynes R, et al. *Apolipoprotein B, triglyceride-rich lipoproteins and risk of cardiovascular events in persons with CKD*. CJASN 2020, 15, 47-60.
[9] Michos ED, McEvoy JW, Blumenthal RS. *Lipid management for the prevention of atherosclerotic cardiovascular disease*. N Engl J Med 2019, 381, 1557-1567.
[10] Koskinas KC, Windecker S, Pedrazzini G, et al. *Evolocumab for early reduction of LDL-cholesterol levels in patients with acute coronary syndromes (EVOPACS).* J Am Coll Cardiol 2019, 74(20), 2452-2462.
[11] Gurwitz JH, Go AS and Fortmann SP. *Statins for primary prevention in older adults.* JAMA 2016, 316, 19, 1971-1972.
[12] Nanna MG, Navar AM, Woyjdyla D, Peterson ED. *The association between low-density lipoprotein cholesterol and incident atherosclerotic cardiovascular disease in older adults. Results from the national institutes of health pooled cohorts.* J American Geriatrics Society 2019, 67,12, 2560-2567.
[13] Vincent J. *Lipid lowering therapy for atherosclerotic cardiovascular disease. It is not so simple.* Clin Pharmacol Ther 2018,104, 2, 220-224.
[14] Grundy SM, Stone NJ, Bailey AL, et al. *Cholesterol clinical practice guidelines 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Circulation 2019,139, 25, e1082-e1143.
[15] Stone NJ, Blumenthal RS, Lloyd-Jones D, Grundy SM. *A focused look at United States and European guidelines on dyslipidemias.* Circulation 2020, 141, 14, 1117-1120.
[16] Pradhan AD. *Hypertriglyceridemia or the company it keeps?* Circulation 2019,140, 3, 167-169.
[17] Brunner FJ et al. *Application of non-HDL cholesterol for population based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium.* The Lancet 2019, 394, 2173-2183.
[18] Sleigh A. *Earlier screening of non-HDL cholesterol could allow education of long-term cardiovascular risk*. Clinical Laboratory International, Jan 2020, pp:3.
[19] Afshar M, Pilote L, Dufresne L, Engert JC, et al. *Lipoprotein (a) interactions with low-density lipoprotein cholesterol and other cardiovascular risk factors in premature acute coronary syndrome (ACS).* J American Heart Association 2016, 5(4):e003012.
[20] Enas AE, Varkey B, Dharmarajan TS, Pare G, et al. *Lipoprotein (a): An under recognized genetic risk factor for malignant coronary artery disease in young Indians*. Indian Heart Journal 2019, 71, 184-198.
[21] O'Donoghue ML, Sabatine MS. *Lipoprotein (a) for risk assessment in patients with established coronary artery disease*. J American College of Cardiology 2014, 63, 520-527.
[22] Martin SS, Blaha MJ, Elshazly MB, et al. *Comparison of novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile.* JAMA 2013, 310, 2061-8.
[23] O'Donnell J. *The end of the Friedewald equation?* ascls.org/Accessed April 2020

# SARCOIDOSIS-LYMPHOMA SYNDROME: A 60 YEARS CASE REPORT

*Oana-Irina **Ivănescu***[1], *Nicoleta Adriana **Neculcea***[2], *Anna-Marie **Herghelegiu***[1,3], *Gabriel-Ioan **Prada***[1,3]

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*
[2] *City Hospital Urlați, Prahova County, Romania*
[3] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

*Corresponding author: Oana-Irina Ivănescu, ivanescu.irina@yahoo.com*

**Abstract**. The association of sarcoidosis and lymphoma was first described in 1960, by Brincker and Bichel. They reported 46 cases of coexistence between sarcoidosis and another malignant lymphoproliferative disease, lymphoma being the most common. The highest risk of developing the syndrome is associated with chemotherapy for lymphoma or in one year after lymphoma treatment. This report describes a case of a 60 years old woman diagnosed with lymphoma and tonsillar onset. As the PET-CT scans showed the persistence and subsequent progression of lung and hilar lymphadenopathy, the patient underwent mediastinoscopy with a biopsy sample that indicated a histopathological appearance compatible with sarcoidosis. Due to the relatively few cases described in the literature, sarcoidosis-lymphoma syndrome remains poorly characterized and difficult to sustain through clinical trials.
**Key words**: sarcoidosis, lymphoma, tonsils, autoimmune diseases

**Rezumat**. Asocierea dintre limfom şi sarcoidoză a fost relatată în literatură încă din 1960, de către Bichel şi Brincker, care au descris 46 de cazuri de sarcoidoză coexistentă cu o altă malignitate. Ei au concluzionat că cea mai frecventă malignitate asociată sarcoidozei este limfomul. Asocierea chimioterapiei pentru limfom sau la un an post-chimioterapie poate creşte riscul de a dezvolta sindromul. Articolul prezintă cazul clinic al unei paciente în vârstă de 60 de ani diagnosticată cu limfom malign cu celula B cu debut amigdalian. Întrucât la controalele efectuate, PET-CT-urile au indicat persistența și ulterior progresia unor adenopatii hilare pulmonare, pacientei i s-a efectuat mediastinoscopie cu prelevare de biopsie care a indicat un aspect histopatologic compatibil cu sarcoidoza. Din cauza cazurilor relativ puţine descrise în literatură, sindromul sarcoidoză-limfom rămâne slab caracterizat şi greu de susţinut prin studii clinice.
**Cuvinte cheie**: sarcoidoză, limfom, amigdale, boli autoimune

## INTRODUCTION

The association between sarcoidosis and malignancy has been previously described in the literature by Bichel and Brincker in the 1960s. They reported 46 cases of coexistence between sarcoidosis and other malignant lymphoproliferative disease, lymphoma being the most common. Later, in the 1980s the association between sarcoidosis and lymphoma was referred to as sarcoidosis-lymphoma syndrome [1]. Brincker suggested that the presence of the chronic form of sarcoidosis may be a contributing factor in the development of lymphoma [1].

Sarcoidosis had usually been found to precede the lymphoma and may be a predisposing factor for the development of the lymphoid malignancy due to disturbance of the immune system [2]. However, data are suggesting that in a small number of patients, lymphoproliferative diseases preceded sarcoidosis. These patients may have an aberrant immunological reaction accompanying the immune response to the lymphoma cells [3]. Nevertheless, the diagnosis of sarcoidosis must rely upon trustworthy investigation such as a histological exam, whenever a lymphoma relapse is suspected [3]. Sarcoidosis can cause abnormal cellular immunity and the immune system`s defence against malignant tumors to fail [4].

Sarcoidosis is a chronic inflammatory granulomatous disease of unknown aetiology and pathogenesis that affects multiple organs. It is most often diagnosed

in the third and fourth decades of life [5]. The disease has diverse clinical manifestations, most frequently including pulmonary disorders [6]. Common symptoms include cough, chest tightness, and dyspnea but half of the patients with pulmonary sarcoidosis are asymptomatic especially if they are classified in the first stage of disease [7]. In severe clinical cases, sarcoidosis can lead to a failure of the internal organ functions and can determine the development of fibrosis and pulmonary hypertension [8]. The areas affected by this disease in 90% of sarcoidosis patients are the mediastinal lymph nodes, hilar lymph nodes, and the pulmonary parenchyma [9]. According to the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), the diagnosis of sarcoidosis is based on compatible clinical and radiological features, the presence of histological demonstration of non-caseating epithelioid granulomas and the exclusion of other granulomatous disorders [3].

There are three types of association between sarcoidosis and lymphoma described in the literature: the first type is the one described by Brincker and characterized by the onset of sarcoidosis several years before the diagnosis of lymphoma, the second type is in which the onset of sarcoidosis is concurrent with lymphoma, and the third type is the uncommon situation in which the onset of sarcoidosis follows the diagnosis of lymphoma by at least 1 year [10]. There are rare cases when both entities coexist and they have become a diagnostic challenge [3]. A review of 131 cases of coexistence sarcoidosis and malignancy indicated that the association is not a coincidence. The existence of a sarcoidosis appears to be responsible for an increased risk of malignant transformation of lymphoid cells [11]. Both diseases have many common presentations, including lymphadenopathy, constitutional symptoms, or hematological abnormalities [1,3]. The use of positron emission tomography with F-fluorodeoxyglucose (FDG) is very sensitive for detecting and evaluating the extent of malignant lesions [12]. However F-fluorodeoxyglucose is not accumulated only in malignant cells but also in granulomas found in sarcoidosis, and therefore could not differentiate between the two lesions. There are limitations in differentiating active inflammatory reactions from malignancies based only on F-fluorodeoxyglucose-FDG uptake [12, 13, 14]. 18F-alpha-methyltyrosine (FAMT) is an amino acid tracer for positron emission tomography and is used for tumor detection. Studies have shown that patients with sarcoidosis have an increased uptake of F-FDG in the sarcoid lesions but no increase in the accumulation of FAMT in their lymphadenopathy [14]. A combination of FDG with FAMT in PET/CT studies plays an important role in the management of sarcoidosis-lymphoma syndrome, especially in differentiating between lesions [13,14]. Tissue biopsy and a pathological diagnosis are essential before new therapies are administrated to patients where relapsed lymphoma is suspected [1,15].

Although sarcoidosis precedes lymphoma in the majority of the cases, in a small number of cases lymphoma developed first demonstrating the importance of histological confirmation. These patients usually have a mild form of sarcoidosis and a short interval between lymphoma and sarcoidosis presentation. They may also have an aberrant immunological reaction accompanying the immune response to the lymphoma cells [15].

Sarcoidosis following malignancy seems clinically and radiologically indistinguishable from idiopatic sarcoidosis. The high frequency of sarcoidosis after specific cancer (breast cancer and lymphoma) but not others, suggests a causative association between malignancy and development of sarcoidosis [16].

Due to the relatively few cases described in the literature, sarcoidosis-lymphoma syndrome remains poorly characterized and difficult to sustain through clinical trials [14, 15].

## CASE PRESENTATION

The article describes the case of 60 years-old woman referred to the „Ana Aslan" National Institute for a specialized geriatric examination.

The patient was first evaluated by the geriatrics specialist. The main complaints were asthenia, fatigue, night sweats, intermittent odynophagia, gingival bleeding, and the swelling of the cervical lymph nodes. The symptoms began a few months before the presentation to the doctor and worsened progressively. Due to oral and pharyngeal symptoms, the patient was referred to the otolaryngologist (ENT) specialist.

One month before the onset of the above symptoms, the patient reported she had an episode of acute tonsillitis for which she received several courses of oral antibiotics combined with oral anti-inflammatory, without significant improvement in her symptoms. Although treatment was followed correctly, the patient continued to feel pain in the left tonsil. The patient had no history of other diseases.

### *Clinical examination*

ENT examination revealed palpable left cervical lymph nodes, congestion, hypertrophy, and swelling of the left tonsil, inflammation and bleeding gums. Nasopharyngeal and laryngeal endoscopic examination revealed moderate hypertrophy of the lymphatic tissue in the nasopharynx and an enlarged pole of the left tonsil.

### *Investigations*

Blood tests showed normal white cells, normal antistreptolysin O antibodies but an increased fibrinogen and a slight decrease in haemoglobin (Hb) concentration. The patient also performed a cervical ultra-sound that indicated the presence of 3 lymph nodes on the left side of the neck, measuring between 1.5 and 2 cm and having inflammatory features. To exclude a suppurative infection of the left tonsil, the patient underwent tonsil needle aspiration to obtain a pus sample, but the procedure was negative (no pus in the left tonsil). Despite proper treatment, the persistence of tonsillar hypertrophy has led to the need for a biopsy. Under local anaesthesia, biopsy fragments were taken and sent for histologic and immunohisto-chemistry analysis.

After 3 weeks the results of the tests indicated a B-Cell Type Non-Hodgkin Lymphoma and the patient was referred to a haematologist for appropriate treatment. Subsequent computer tomography (CT) scans of the neck, thorax, abdomen and pelvis revealed a homogeneous mass measuring 37/20 mm with iodophilic contour situated on the left lateral wall of the left tonsil with extension to the left side of the tongue and retromolar trigone. Also, imaging of the chest identified the presence of a swollen hilar right lymph node measuring 11/13 mm. No lymphoma involvement was noted in the pelvis or abdomen.

### *Evolution and follow-up*

After hematological assessment, chemo-therapy with rituximab, cyclophosphamide doxorubicin, and vincristine was administered for 6 cycles. Chemotherapy was combined with 4 cycles of radiotherapy for better local control and overall survival. The patient had a favorable outcome and after 3 months since the last cycle of chemotherapy was ended, the ENT control showed no congestion or swelling of the left tonsil, no ulceration in the tonsilar area, no hyper-trophic masses in the nasopharynx. Neck, chest, and abdominopelvic CT scans were performed every 3 months in the first year.

A follow-up positron emission tomography (PET) scan performed 1 year after chemotherapy was ended, showed an

abnormal fluorine-18 fluorodeoxyglucose (FDG) uptake in the left tonsil thus indicating an active metabolic residual masses in this area. To control the lymphoproliferative disorder, the patient underwent autologous stem cell transplantation. She had good evolution within 14 days after transplantation.

Due to the progression of hilar lymph nodes highlighted by the follow-up chest CT and PET-CT scans the patient was referred to a thoracic surgeon where she underwent mediastinal and hilar lymphadenectomy. Histological evaluation of the biopsy specimens obtained through lymphadenectomy, revealed the presence of non-caseating granuloma suggestive of sarcoidosis. The patient complained of a dry cough and moderate chest tightness.

According to the criteria of radiological classification of sarcoidosis, the patient was placed in stage I (pulmonary lymph-adenopathy without affecting the lung parenchyma) and in the context of the existence of lymphoproliferative disease, she received only two months of cortisone therapy (of choice in this pathology).

Follow-up PET-CT performed 6 months after the diagnosis of sarcoidosis revealed a metabolically active progressive lesion in the left tonsil compared to a previous examination that had been taken 5 months before in which there was no abnormal 18 fluorodeoxyglucose (FDG) uptake in the tonsilar area.

It was initially thought that cortisone treatment, although followed for only 2 months could have reactivated lymphoma. To rule out a relapse of lymphoproliferative disease, the patient was readmitted to the ENT department for the biopsy of the left tonsil. Bucopharyngoscopic clinical examination showed scleroatrophic tonsils with a slight asymmetry, the left one being the biggest. The blood count with the leucocyte formula was within normal limits. We considered that a bilateral tonsillectomy is necessary to prevent the risk of reactivation of the tonsillar lymphoma. Under general anaesthesia, the patient underwent a bilateral tonsillectomy and the histological analysis of the collected pieces indicated a chronic inflammatory tissue without relapse of the lymphoproliferative disease. Pulmonary function tests were normal and the patient underwent regular follow-up examinations without any other treatment for sarcoidosis. Her last follow up exam was conducted in 2019 and she was symptom-free at that time.

## DISCUSSION

It might be argued that the development of sarcoidosis is related to an excessive immune response against the lymphoma cells. Sarcoidosis could also be a reaction to lymphoma treatment. The patient followed 6 cycles of chemotherapy combined with 4 cycles of radiotherapy for better local control. It is very important to be aware that sarcoidosis is an alternative diagnosis to lymphoma relapse when confronted with the reoccurrence of hypermetabolic mediastinal or hilar lymphadenopathies on PET-CT evaluation. In this case, the persistence of enlarged lymph nodes and increased metabolic reactivity evidenced by PET-CT scan examination led to further investigation of the lung and mediastinal region. Thus, having the mediastinoscopy and the mediastinal biopsy of the lymph nodes performed, there was a certainty in obtaining the diagnosis of sarcoidosis. This also emphasizes the importance of histological confirmation of lymphoma relapse suspicion to avoid unnecessary or potentially harmful treatments. As the lack of clinical manifestations delayed the diagnosis of sarcoidosis, it is difficult to specify whether sarcoidosis occurred after the onset of lymphoma or before it but in a latent form.

The association between sarcoidosis and lymphoma is important for the following reasons:

- chronic corticotherapy for advanced sarcoidosis can influence or aggravate the response to lymphoma treatment;

- on the other hand, the chemotherapy used in lymphoma can speed up the onset of symptoms in ”silent” sarcoidosis.

As this entity is less well known, the prevalence of the association syndrome between sarcoidosis and lymphoma may be much higher.

This case report has the following particular characteristics:

-The onset of tonsillar lymphoma has been confused with tonsillar phlegmon;

-The symptoms of sarcoidosis set in after the patient was diagnosed with lymphoma;

-Sarcoidosis could have been triggered by the lymphoma treatment;

-The diagnosis of sarcoidosis was difficult to establish due to lymphoma-like symptoms;

-The association between sarcoidosis and lymphoma set in an advanced age;

-The case is rare.

## CONCLUSION

Clinical presentations of sarcoidosis are divers and may mimic several other diseases specifically the lymphoproliferative diseases. Once the diagnosis is established, a systematic evaluation for the extent of the disease must be done. Sarcoidosis precedes lymphoma in the majority of cases but in this case lymphoma developed first. Another unusual aspect of this case was the occurrence of B-cell lymphoma in the tonsils and not in the spleen or bone marrow as is more common. Whenever there is a tonsillar asymmetry a biopsy must be performed to establish a definite diagnosis. The most interesting aspects of this case are the temporal evolution of these diseases and the remarkable disease control of both sarcoidosis and tonsillar lymphoma. Although both are debilitating diseases, the patient’s evolution has been uncomplicated over time. Sarcoidosis did not appear to modify the prognosis of lymphoma. The combination of FDG and FAMT in PET-CT scans may play an important role in differentiating between sarcoidosis and lymphoma lesions. Although the pathogenetic mechanisms underlying the sarcoid-lymphoma syndrome may vary, it is likely that in some cases sarcoidosis represents a systemic response to tumor antigens.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES


[1] Cho H, Yoon DH, Kim JH, Ko YB, Kwon BS, Song IH, Suh C. *Occurrence of sarcoidosis after chemotherapy for non-Hodgkin lymphoma.* Korean J Intern Med 2016 May;31(3):605-7. doi: 10.3904/kjim.2014.305. Epub 2016 Mar 12. PMID: 26968186; PMCID: PMC4855092. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855092/

[2] Shieisha A, Todd S. *Which Came First: A Rare Take on the Sarcoidosis-Lymphoma Syndrome.* American College of Chest Physicians 2015; Vol 148 (4):1378. https://journal.chestnet.org/article/S0012-3692(16)36311-5/fulltext

[3] London J, Grados A, Fermé C, et al. *Sarcoidosis occurring after lymphoma: report of 14 patients and review of the literature.* Medicine (Baltimore) 2014 Nov;93(21):e121. doi: 10.1097/MD.0000000000000121. PMID: 25380084; PMCID: PMC4616278

[4] Yamanaka T, Kanai H, Aihara N, et al. *A Case of Sarcoidosis-lymphoma Syndrome: Importance of Brain Biopsy.* NMC Case Rep J 2019; 6(2):61-64.

[5] Goswami T, Siddique S, Cohen P, et al. *The Sarcoid-lymphoma Syndrome*. Clin LymphomaMyeloma2010;10(4):241-247. https://www.medscape.com/viewarticle/729327_3

[6] Pierce TB, Margolis M, Razzuk MA. *Sarcoidosis: still a mystery?* Proc (Bayl Univ Med Cent) 2001; 14(1):8-12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1291305/

[7] Ungprasert P, Ryu JH, Matteson EL. *Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis.* Mayo Clin Proc Innov Qual Outcomes 2019;3(3):358-375. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6713839/

[8] Starshinova AA, Malkova AM, Basantsova NY, Zinchenko YS, Kudryavtsev IV, et al. *Sarcoidosis as an Autoimmune Disease*. Front Immunol 2020;10:2933. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6960207/

[9] Kahkouee S, Samadi K, Alai A, Abedini A, Rezaiian L. *Serum ACE Level in Sarcoidosis Patients with Typical and Atypical HRCT Manifestation*. Pol J Radiol 2016 Sep 23;81:458-461.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036380/

[10] Chalayer E, Bachy E, Occelli P, et al. *Sarcoidosis and lymphoma: a comparative study, QJM:* An International Journal of Medicine 2015 Volume 108, Issue 11, November 2015, Pages 871–878, https://doi.org/10.1093/qjmed/hcv039

[11] Brincker H. *Coexistence of sarcoidosis and malignant disease: causality or coincidence?* Sarcoidosis 1989;6(1):31-43.

[12] Yudistiro R, Arisaka Y, Tokue A, Nakajima T. *Differentiation of sarcoidosis-lymphoma syndrome lesions: a case report on the use of two different positron emission tomography tracers.* BMC Med Imaging 2016 Jan 8;16:1.

[13] Kaira K, Oriuchi N, Otani Y, et al. *Diagnostic usefulness of fluorine-18-alpha-methyltyrosine positron emission tomography in combination with 18-F-fluorodeoxyglucose in sarcoidosis patients.* Chest 2017; 131 (4):1019-1027.

[14] Vettiyil B, Gupta N, Kumar R. *Positron emission tomography imaging in sarcoidosis*. World J Nucl Med 2013 Sep;12(3):82-6. doi: 10.4103/1450-1147.136731.

[15] London J, Grados A, Christophe F, et al. *Sarcoidosis Occurring After Lymphoma*. Medical Journal 2014; Volume 93 - Issue 21 - p e121.

[16] Arish N, Kuint R, Sapir E, et al. *Characteristics of Sarcoidosis in Patients with Previous Malignancy: Causality or Coincidence?* Respiration 2017; 93: 247-252.

# THE CAREGIVERS AND THE DISPOSITIONAL DISORDERS. CASE STUDY

*Ioana **Găiculescu**[1]*

[1] *"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania*

*Corresponding author: Ioana Găiculescu, niknila999@yahoo.com*

**Abstract**. A caregiver is a person, often trained, to take responsibility in order to meet the physical and emotional needs of a person unable to take care of him. In reality, most of the time the caregiver is a family member who takes care of a relative or friend, a person who is not trained in this regard and who is not remunerated. Being an informal caregiver is a hard process. They put themselves on the second place and lose the benefit of spare time. A caregiver uses all his/her time in order to take care of the ill person. They have to cook for them, clean them, make exercises with them (physical or intellectual), they have to stay focused and their priority is the person that they take care of. They face dispositional changes from the ill person and try to stay calm all the time although they are overwhelmed. The data obtained from many studies revealed that it needs special attention from healthcare managers, clinicians and all of health-care personnel who deals with dementia patients regarding the caregivers of these patients. In what follows, we present the case of a 65 old caregiver, who looked after her husband diagnosed with Alzheimer disease. The main objective was to prevent the overload of the caregiver, which induced physical, emotional and psychical exhaustion. After the specific counseling techniques applied, there were noticed improvements regarding the caregiver's disposition. In conclusion the founding of support groups and brochures regarding the changes they faced could help them.
**Key words**: caregivers, disposition, information, support

**Rezumat**. Prin conceptul de aparținător se înțelege acea persoană, adesea instruită, care are grijă de nevoile fizice și emoționale ale unei persoane bolnave cronic. În realitate, în majoritatea cazurilor, aparținătorul este o persoană cunoscută care are grijă de un membru al familiei sau un prieten, o persoană care nu este instruită și nici renumerată în acest sens. A fi aparținătorul unei persoane cu probleme de sănătate presupune un proces foarte greu. Aceștia se pun în plan secund și pierd avantajele timpului liber. Aparținătorul își dedică majoritatea timpului îngrijirii persoanei cu probleme de sănătate. Trebuie să gătească, să facă exerciții cu aceștia (fizice sau intelectuale), trebuie să rămână stăpâni pe sine și să se concentreze pe cel de care au grijă. Aceștia întâmpină schimbări dispoziționale ale acestora și trebuie să își păstreze calmul deși se simt copleșiți. Datele obținute în urma derulării a multiple studii care au în vedere situația aparținătorilor indică nevoia unei abordări biopsihosociale a acestora cu luarea în considerare a efectelor fizice și emoționale apărute. Prezentăm cazul unui aparținător de 65 de ani care are grijă de soțul diagnosticat cu demență de tip Alzheimer. Principalul obiectiv a fost cel de a preveni accentuarea simptomatologiei care poate duce la epuizarea fizică, emoțională și psihică a aparținătorului. După aplicarea tehnicilor de consiliere specifice și a unor tehnici de relaxare simple, s-a constatat o îmbunătățire în ceea ce privește dispoziția aparținătorului. În concluzie, crearea unor grupuri de suport, a unor broșuri de informare cu privire la schimbările prin care trec, ar fi un proces benefic pentru aceștia.
**Cuvinte cheie**: aparținători, dispoziție, informare, suport

## INTRODUCTION

The concept of caregivers aroused scientific interest along with the development of the multidisciplinary approach of the chronically ill patients. By caregiver is meant that person, trained, to take responsibility in order to meet the physical and emotional needs of a person unable to take care of him. In reality, most of the time the caregiver is a family member who takes care of a relative or friend, a person who is not trained in this regard and who is not remunerated. This position, different from that of the formal caregiver, is associated with multiple and complex positive and negative biopsychosocial effects.

Caregivers of people with health problems (paralysis, cancer, dementia, etc.) often put their own needs in the last place. They devote all their energy and time to those who they take care for.

This done constantly, without breaks, can lead to dispositional disorders, as follows [1]:

- muscle tension,
- physical/ mental/ emotional exhaustion,
- irritability,
- concentration difficulties,
- loss of appetite,
- sleeping disorders.

Various studies indicate the existence of an increased incidence of depression in caregivers. In the United States, a study using the Patient Health Questionnaire (PHQ-9) reported that 21.6% of caregivers had symptoms of depression, with the majority having mild symptoms [2]. According to another study a cross-sectional one, conducted at Isfahan University of Medical Sciences in the year of 2015, high-level depression is found in caregivers of dementia patients. According to Beck's Depression Inventory (BDI) 69.8% (n=67 out of 96) of all caregivers had scores in the range of depression. It showed that 20.8% (n=20) of all caregivers had scores in the range of mild depression, 40.6% (n=39) had scores in the range of moderate depression, and 8.3% (n=8) had scores in the range of severe depression [3]. Often, the caregivers give up activities that they previously did with pleasure, so as not to blame themselves for not being close to those they take care for, they avoid talking with others about the situation, considering that they are victimized [4]. Most of the time the ill person is the main subject in the discussions of the caregivers with the others; they are asked how they feel, how the treatment works, if changes in the health of the ill person have occurred. The culture, the environment, the economic situation, most of the time, impose barriers regarding the option of taking a break. Many people from these situations do not benefit from material comfort to allow relaxation activities. There are cases where the caregivers benefit and accept the help of other family members, friends, specialists who can inform and advise them, these are good cases that can achieve an emotional balance [5].

But who asks, informs, advises the caregivers? The stress arising from care leads to exhaustion, sometimes even suicidal ideation [6]. This kind of data concluded it needs special attention from healthcare managers, clinicians and all of health-care personnel who deals with dementia patients and their caregivers. Caregivers should be supported more.

## MATERIAL AND METHODS

In what follows I present a case of a patient admitted to "Ana Aslan" National Institute of Gerontology and Geriatrics - Otopeni in March and October 2019. Together with her, we managed to reorganize the time devoted to the care of the husband diagnosed with Alzheimer's Dementia and the time allocated for relaxation, rest [7].

The objective of this case is to evaluate a specific model of intervention on the effects that the care of a person with Alzheimer's dementia produces.

During the clinical interview, a series of tests and scales were applied in order to identify the type of effects: Mini Mental State Examination - Second Edition, Clock Drawing Test and Short Disposition Scale are applied [7, 8, 9].

Mini Mental State Examination-2 (MMSE-2) is a clinical examination method calibrated on the Romanian population [7]. It retains clinical utility and efficiency while expanding the original's usefulness in population with milder impairment including subcortical dementia. Benefits: flexibility of administration, simplicity of scoring, portable pocket norms guide, equivalent, alternate forms, simplicity of administration, clinical relevance, expanded meta-analysis.

Clock Drawing Test by Sunderland is used for screening for cognitive impairment and dementia and as a measure of spatial dysfunction and neglect [8]. The test has a high correlation with the MMSE-2.

Short Disposition Scale is an examination scale in order to establish the subjective and objective disposition, neurovegetative reactivity and thoughts [9].

**CASE STUDY**

A., 65 years old, lives in Bucharest with her husband S. 75 years. Together they have two children and 3 grandchildren. A. is an accountant, but retired to take care of her husband, considering that no one can do it better than her.

He was diagnosed with Alzheimer's Dementia in early 2019.

He used to handle the payment of bills, purchases, housework and yard work. The children observed changes in their father's behavior, confusing their age and A. decided to go together to a specialized consultation after she found S. in the tub with cold running water, unusual behavior. He presented episodes of temporal-spatial, allopsychic and auto psychic disorientation. He left the house without announcing and he was found in the park because he did not know the way home. A. decides to stay home to supervise him permanently.

In March 2019, the spouses are admitted to ”Ana Aslan” N.I.G.G. A. is scheduled for gerontopsychological evaluation by the specialist doctor, the reason - anxious disposition and possible cognitive disorders.

Following the interview and the application of the specific tests she obtained:

- A score of 86/90 MMSE-2: EV (fixation hypomnesia),
- Clock Drawing Test by Sunderland 10/10 (fully correct drawing),
- Short Disposition Scale: Anxiety 8/9 and Depression 6/9.

The data collected indicate the presence of somatic effects: insomnia, headache, dizziness, trembled, fatigue and feeling nausea when she wakes up and the existence of an emotional impairment: permanent agitation associated with an inability to relax and an attitude of concern most of the time, loss of interest in other activities. An important effect was detected at the personality level – the loss of self-confidence. There was no significant effects on the cognitive level, the cognitive functions being, in generally, fully preserved. It was detected a slight weakening of the fixing memory.

A. explained that before she was more careful about her own person, she went to the hairdresser, to the massage; she used to read a lot, long walks. She said that now she avoids leaving her husband, afraid that it might happen something while she is not around. The children offered to help her in order for her to take a break but she refused them. At the time of the interview, A. presented proper hygiene and clothing.

From the stories, they had a beautiful marriage, full of happy events, the age difference being an advantage from her point of view, she always felt protected and loved.

The lack of professional and social activity, the short time spent outside the house, made A. develop fears, psychic and muscular tension, difficulty concentrating, insomnia, loss of appetite. Trying to take him for a short walk was refuses by him. She tries to remind him events from their life and different kinds of activities to make him smile. We establish the following meetings.

**Psychological intervention**

The following meetings were focused on free discussions in order to relax her. We managed to meet on Mondays, Wednesdays and Fridays, 6 meetings in 2 weeks; every meeting had approximate 50 minutes. For these sessions I developed an intervention model in order to reduce the identified effects at emotional and somatic level. The model includes different interventions strategies such as positive thinking (positive thoughts), laugh (recall a funny event) and outdoor walks in the institute's courtyard and different relaxation techniques: breathing exercises (inhale, exhale) and muscles contraction exercises. Another approach was to discuss

the personality in Whitehouse's vision, the scenario and the life story, in which the scenario allows the individual to project their future according to their own motivations and goals [10]. We debate the concept of the life story which allows the description and organization of the past. The two are integrated into a unified construction, named the identity of the person who is formed from the assimilation of new events and accommodation (the person undergoes an identity transformation). We chose to discuss this to help reorganize certain current segments of life. A. understood that permanent worry and lack of resting time can lead to accentuation of certain symptoms.

Another interventions strategy used was to identify some practical solutions. We discussed the possibility of hiring someone part time to help with housework and S. She explained how much time she used to stay with their grandchildren, that now when they come to visit; she is too tired to have any activity with them. She feels old and outdated.

The interventional model achieved it is purpose to relax the patient and to find some certain measures to coping more efficiently her life existence context.

## RESULTS AND DISCUSSIONS

At six months, A. returns for reassessment, obtaining:

- A score of 90/90 at MMSE-2: EV,
- Clock Drawing Test by Sunderland 10/10,
- Short Scale of Disposition, Anxiety 6/9 and Depression 5/9.

Towards de past six months, the tests result indicate an increase of 4.44% at MMSE 2, The Clock Drawing Test by Sunderland has the same score which is the highest 10/10 (perfect drawing) and for the Short Scale of Disposition we observed a decrease of 22% for Anxiety and 11% for Depression.

The results highlight a good change regarding the caregiver's disposition. The tone is better, both from an emotional and physical point of view. A. found a suitable lady to help her with S. and the house. A. started a painting course once a week, walks daily, rests, goes shopping, spends more time with their grandchildren, accepts more easily help from her children [11]. The nights became a little heavier, S. wakes up more often, became more active at night and he doesn't make the difference between day and night anymore.

Given the facts that now she understands otherwise the inherent changes in S's mood caused by dementia; it is a little easier for her to cope with the events.

Statements:

"I feel much better!"

"I have more energy, I feel like there are other ways to manage my time properly."

"I realized that I need help."

"I communicate easier with people about my situation."

## CONCLUSION

An interventional model that includes positive thinking, coping strategies, relaxation techniques and a specific approach – the concept of life story it was proven to be a successful one. The patient discovered the possibility to communicate with others and find trustworthy people, accepting she can make mistakes, reorganize her activities and time, care about self-discipline and her personal time.

Information on the steps that the caregivers go through, a recommendation from the specialist doctor, the possibility of creating support groups for caregivers, access to information should be made more intense, no one is prepared, and more should be protected.

### *Conflicts of interest*

The authors declare no conflicts of interest.

## REFERENCES

[1] DSM-5 Manual de Diagnostic şi Clasificare Statistică a Tulburărilor Mintale, Tulburarea cu simptome somatice şi tulburările înrudite. Editura Medicală Callisto 2016, 309-315.
[2] Shim RS, Baltrus P, Ye J, Rust G J. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005-2008. Am Board Fam Med. 2011 Jan-Feb; 24(1): 33-8
[3] https://humanstress.ca/stress/trick-your-stress/steps-to-instant-stress-management/, 2019
[4] Omranifard Victoria, Haghighizadeh Ebrahim and Akouchekian Shahla. Depression in Main Caregivers of Dementia Patients: Prevalence and Predictors. Advanced Biomedical Research, vol. 7, no. 1, 2018, p.34.
[5] https://www.brightfocus.org/sites/default/files/managing-stress-care-for-the-caregiver_0.pdf, 2019
[6] https://www.alz.org/alzheimers-dementia/what-is-alzheimers, 2020
[7] MMSE-2: Mini-Mental State Examination, Ed. a 2-a. Manual de utilizare a testului. GOS Romania, 2005.
[8] Agrell B, Dehlin O. The clock-drawing test. Age and ageing 1998, 27, 3, 399-403.
[9] Tudose F, Tudose C. Abordarea pacientului in Psihiatrie. Info Medica 2002, 77.
[10] https://pureadmin.qub.ac.uk/ws/files/14761610/the_ties_that_bind_us.pdf, 2020
[11] Rubin JA. Art-Terapia. Teorie şi tehnică. Editura Trei 2001, 311.

## 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.

**TITLES AND AUTHORS´ NAMES**. The manuscript will contain a page with a concise and descriptive title (12 words recommended), Times New Roman font 12, upper case, bold; in English, as well as Romanian version. This page will include also the following information: first name and name (bold) of the authors, without their professional and/or scientific degrees, including their affiliations, Times New Roman font 12, italic. Affiliations should be specified by numbers and not symbols (e.g. [1]"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania, [2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania). If all authors were main authors and so, had equal contributions to the paper, then the authors should be listed in a subtitle, in alphabetical order, followed by their contact e-mails. The corresponding author and his contact e-mail must be written just after the institutional affiliations.

**ABSTRACT**. After title and authors will insert the abstract in English, as well as Romanian version, each of them with no more than 250 words, Times New Roman font 12.

**KEY WORDS**. In the bottom of each abstract version, should be added three to five key words.

**HEADINGS**. Manuscripts that show the results of original studies must contain 2500 words maximum and include the following sections: Introduction, in which the objectives and assumptions should be clearly stated; Materials and Methods; Results; Discussions; Conclusions. In the section "Results" should be included tables, figures and figure legends.

**ILLUSTRATIONS AND TABLES**. Figures should be professionally designed. The title will be under the figure, Times New Roman font 10, and for numbering will be used Arabic numerals. If photographs of patients are used, is necessary either written permission of the patient or their pictures should not be identifiable. The title of every table should be written above, with Roman numerals for numbering, Times New Roman font 10. Place explanatory matter in footnotes. Do not repeat results of the tables as illustrations.

**ACKNOWLEDGEMENTS.** Acknowledgments should be included before "References", using 30 words maximum. Authors can express gratitude for support in the conduct of research projects.

**CONFLICT OF INTERES.** Should be included before "References".

**REFERENCES**. References will contain maximum 30 titles, representing recent publications (in the past 10 years). Old publications are accepted only if they have special importance in the respective field. References must be numbered consecutively as they are cited. List only the first three authors followed by et al. The following are sample references:

For journal articles: Shapiro A.M.J., Lakey J.R.T., Ryan E.A., et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen, N. Engl. J. Med., 2000, vol. 343, 4: 230-238.

For journal articles in electronic format: Niki E. Role of vitaminE as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence, Free Radical Biology and Medicine, 2014, 66: 3–12. http://dx.doi.org/10.1016/j.freeradbiomed.2013.03.02223557727.

For books: Goadsby P. J. Pathophysiology of headache. In: S. D. Silberstein, R.B. Lipton and D. J. Dalessio (Eds.), Wolff´s headache and other head pain 7th ed. 2001, Oxford, England: Oxford University Press (pp. 57-72).

For conference paper: Brown S. & Caste V. Integrated obstacle detection framework. Paper presented at the IEEE Intelligent Vehicles Symposium, May 2004, Detroit, MI.

For conference Paper from the Internet: Balakrishnan R. Why aren´t we using 3d user interfaces, and will we ever? Paper presented at the IEEE Symposium on 3D User Interfaces March 25-26, 2006. doi:10.1109/VR.2006.148

**ABBREVIATIONS**. The full term for which an abbreviation (acronym) stands should precede its first use in the text.

**DRUG NAMES**. Generic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the "Materials and Methods" section.

**UNITS OF MEASUREMENT**. Measurements of length, height, weight and volume should be reported in metric units (meter, kilogram, or liter or their decimal multiples). Temperatures should be given in degrees Celsius. Blood pressures should be given in mm Hg. All hematological and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units.

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Phone: +4 021 223 71 94

Fax: +4 021 223 14 80

E-mail: rjgerontog@gmail.com

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## INSTRUCȚIUNI PENTRU AUTORI

**MANUSCRISELE**. Manuscrisele trebuie redactate în limba engleză şi este necesar să conțină material original. Toate articolele se trimit în format electronic, Word Doc, cu toate figurile, tabelele, legendele şi referințele biblio¬grafice incluse în același document. Se vor folosi caractere Times New Roman 12 și spațierea la un rând a textului. JPG și TIF sunt formatele de fișier acceptate pentru figuri şi fotografii.

**TITLUL ARTICOLULUI ŞI NUMELE AUTORILOR.** Manuscrisul va conține o pagină cu un titlu concis și descriptiv al lucrării (recomandabil maxim 12 cuvinte), format Times New Roman 12, majuscule, bold; în limba engleză, precum și versiunea în limba română. Această pagină va include și următoarele informații: prenumele și numele (bold) autorilor, fără titlu profesional și/sau stiintific precum și afilierea fiecărui autor, format Times New Roman 12 italic. Afilierile autorilor vor fi specificate cu numere și nu cu simboluri (de exemplu, [1]"Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, Romania, [2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania). In situația în care toți autorii au avut contribuții egale la realizarea manuscrisului, ei vor fi menționați într-un subtitlu în ordine alfabetică împreună cu adresele lor de e-mail. Numele autorului corespondent și adresa sa de e-mail vor fi menționate imediat după enumerarea afilierilor instituționale ale autorilor.

**REZUMAT**. După titlu și autori se va insera rezumatul în limba engleză, precum și versiunea în limba română, fiecare cu un număr maxim de 250 de cuvinte, format Times New Roman 12.

**CUVINTELE CHEIE.** În partea de jos a fiecărei versiuni a rezumatului se vor include 3 până la 5 cuvinte cheie.

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**FIGURILE ŞI TABELELE**. Figurile vor fi realizate profesional. Titlul va fi scris sub figura, format Times New Roman 10, iar pentru numerotare se vor utiliza cifre arabe. Dacă sunt incluse imagini ale unor pacienți, este necesar consimțământul scris al pacientului pentru difuzare publică sau pacientul trebuie să fie neidentificabil. Titlul fiecărui tabel va fi scris deasupra, iar pentru numerotare se vor folosi cifre romane, format Times New Roman 10. Notele explicative vor fi în partea de jos a tabelului. Nu se accepta repetarea rezultatelor din tabel prin grafice.

**EXPRIMAREA MULȚUMIRILOR**. Vor fi menționate înaintea bibliografiei, utilizand maximum 30 cuvinte. Se pot exprima mulțumiri pentru sprijinul acordat în desfășurarea proiectelor de cercetare.

**CONFLICTUL DE INTERESE**. Va fi menționat înaintea bibliografiei.

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Pentru articole în format electronic: Niki E. Role of vitaminE as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence, Free Radical Biology and Medicine, 2014, 66: 3–12. http://dx.doi.org/10.1016/j.freeradbiomed. 2013.03.02223557727.

Pentru capitol sau subcapitole din monografii sau tratate: Goadsby P. J. Pathophysiology of headache. In: S. D. Silberstein, R.B. Lipton and D. J. Dalessio (Eds.), Wolff´s headache and other head pain, 7th ed. 2001, Oxford, England: Oxford University Press, pp. 57-72.

Pentru articole prezentate la conferințe: Brown S. & Caste V. Integrated obstacle detection framework. Paper presented at the IEEE Intelligent Vehicles Symposium, May 2004, Detroit, MI.

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**ABREVIERILE**. La prima utilizare in text, abrevierea (acronimul) trebuie sa fie precedat de expresia integrală.

**DENUMIREA MEDICAMENTULUI**. Se utilizează numele generic al medicamentului. Atunci când marca de proprietate a fost utilizată în articolul de cercetare, aceasta se scrie în paranteze și apare în secțiunea "Materiale și Metode" a manuscrisului.

**UNITĂȚILE DE MĂSURĂ**. Inălțimea, greutatea, volumul, lungimea vor fi exprimate în unități de măsură din sistemul internațional (centimetru, kilogram, litru, unități decimale ale litrului, metrului). Temperaturile vor fi specificate în grade Celsius. Presiunea arterială va fi precizată în mmHg. Rezultatele analizelor laboratorului clinic vor fi exprimate în unitățile de măsură din sistemul internațional SIU.

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