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MULTIMORBIDITY PATTERNS  
OF THE FRAGILITY PHENOTYPE IN OSTEOPOROSIS

Abstract. It was highlighted that the osteoporosis and co-morbidities can lead to the worse of the frailty nursing homes elderlies through the various aspects. An association was observed between FRAX, low level of 25 OH Vitamin D and geriatric syndromes with an increased risk of falls and hip fracture at the frails group. According to the cluster analysis (k-means method), the most relevant indicators that separated the clusters were: age category, gender, clinical scale of frailty, comorbidities, geriatric syndromes and daily drugs used. The results obtained characterize the profile of institutionalized elderlies and can be used as a basis for the development of effective strategies, aimed at reducing physical, cognitive and social frailty.  
Keywords: osteoporosis; fragility phenotype; multimorbidity patterns.
**Introduction**

Increased life expectancy and improved health records systems have resulted in an expanded population with diagnosed comorbidities and geriatric syndromes (GSs) [14, 19]. It is estimated that more than 95% of people older than 65 years in western countries will have coexisting diagnoses of two or more diseases at some point in time [13].

The combination of multimorbidity marks older peoples’ frail state by the increasing risk of cognitive, functional and mobility impairment, which are identified across five common geriatric syndromes (pressure ulcers, incontinence, falls, functional decline, and delirium), hospitalizations, polypharmacy, placing in nursing homes and worsening quality of life, translating into a substantial economic burden for public health systems [2].

GSs have been defined as multifactorial health conditions that contribute to older peoples underlying frailty, being various and prevalent among community-dwellers, they are difficult to manage clinically, and put older people at increased risk not only for developing new chronic conditions, but also for placing in nurses homes [16, 17]. Acting on these syndromes may prevent serious deterioration of existing chronic conditions, as well as the decline in activities of daily living, it is necessary for health care professionals to provide interventions not only to control diseases, but to restore or maintain physical function and prevent or reduce disability [6].

Osteoporosis, pain on low back, knee, and spinal deformity were reported to be risk factors for locomotive geriatric syndrome (LoGS) [10, 12]. Several physical performance tests such as timed up and go test, back muscle strength, gait speed, grip power, the short physical performance battery, vulnerable elders survey test, Charlson and Gröningen frailty scor, were proved to be valid for identification of LoGS [12].

A lot of studies have examined the prevalence of multimorbidity, with methods for estimation ranging from descriptive statistics of the number of diseases per individual to large-scale classification systems for the measurement of morbidity burden and case-mix [19].

A number of relevant studies have been published in the last few years, and
there is an urgent need to establish what is currently known about the determinants and prevalence of multimorbidity and the most frequent patterns observed in primary care [9].

The aim of this study was to highlight and identify the main multimorbidity patterns of the frailty phenotype in osteoporosis using statistical processing methods to identify valuable information indices and establish the associative links of frailty subtype through the cluster and correlational methods.

Material and methods

The epidemiological study was part of the Institutional Project 20.80009.8007.25 Fralty: diagnosis and prevention in relation to the medico-psycho-social problems of the vulnerable elderly, which included 47(50) elderly people between 65 and 90 years old, institutionalized at the Republican Asylum for the Disabled and Retireds.

As inclusion criteria served: 65 years and older with chronic somatic diseases and geriatric syndromes, and exclusionary: elderly older than 91 years, various forms of dementia, oncological diseases. Given that the FRAX questionnaire allows testing on patients up to 90 years of age, 3 elderly people were excluded from the examination.

All participants were examined according to the complex geriatric assessment (CGA), which included: clinical characteristics (anamnesis, clinical examination), fragility – data of the Phenotype and Fragility Index Gröningen (GFI), The Vulnerable Elders Survey (VES-13), Short Physical Performance Battery (SPPB); osteoporosis – FRAX without using bone mineral density value, sarcopenia – A Simple Questionnaire to Rapidly Diagnose Sarcopenia (SARC_F), comorbidities – Charlson Comorbidity Index (CCI); mobility – Activity Daily Living (ADL), Instrumental Activity Daily Living (IADL) and gait and balance Tinetti test; psychoneurological evaluation – Mini Mental State Examination (MMSE), Geriatric Scale of Depression (GDS) and paraclinical data (25 OH Vitamin D) in the context of osteoporosis associated with the phenotype of fragility (robust, pre-fragile, fragile) in the elderly.

The data obtained from the programed investigations were analyzed by methods of variational, correlational and cluster analysis in the STATISTICA 7.0 software package.
**Results and discussions**

According to the clinical scale of fragility, 17% of participants were robust, 13% were pre-fragile and 70% fragile. Based on the FRAX score, the mean values showed 6.21±1.06 for fracture risk and 2.27±0.31 for hip fracture in the robust elderly group, prefrailty group – 4.75±1.14 (risk of fracture) / 2.03±0.57 (hip fracture), and fragile ones - 5.03±0.50 (risk of fracture) / 1.95 ± 0.19 (hip fracture).

In the specialized works of the last years, the researchers reported the complexity of the frailty syndrome in the elderly population, mentioning the importance of CGA through certain grids, in terms of establishing subtypes of frailty: functional – ADL, IADL, GFI, SPPB, VES-13, SARC-F, gait / balance Tinetti and bio-psycho-social (CCI, MMSE, GDS) [5, 20].

Pearson's correlation analysis of geriatric scores at the robust elderlies, established positive correlations between the GDS – GFI (r = 0.90*), ADL – IADL (r = 0.79*), ADL – gait and balance Tinetti (r = 0.74*), CCI – GFI (r = 0.74*) and inverse association between VES-13 – IADL (r = -0.95*), MMSE – SARC-F (r = -0.93*) (p≤0.05), results confirmed in other specialized works [Vermeulen]. In the case of CCI positive correlation with GFI demonstrates that, the CCI being a marker of chronic comorbidities, GFI is sensitive to the process of weakening the vulnerable elderlies (fig. 1).

![Correlation analysis between the Charlson Comorbidity and the Gröningen Frailty Indexes at the robust elderlies](image_url)
The inverse association between VES-13 – IADL, demonstrates that, the IADL being a marker of frailty mobility, VES-13 is sensitive to the process of decline in physical function, or those at risk of decline the vulnerable elderly (fig. 2).

**Fig. 2. Correlation analysis between IADL and the VES-13 at the robust elderlies**

The analysis of the statistical results of a study in 2020 on a group of 140 patients showed that pre-frailty represent the most critical period of psychological well-being and cognitive decline [8]. In our work, the correlational analysis of pre-frail elderlies, established high positive correlations between SPPB – Tinetti score (r = 0,99*), CCI – GDS (r = 0,83*), and inverse high associations between GFI – IADL (r = -1,0*), IADL – GFI (r = -0,96*), VES-13 – Hamilton score (r = -0,94*), VES-13 – GDS (r = -0,84*), CCI – risk of fracture by FRAX method (r = -0,82*) (p≤0.05), which shows that pre-frail group of elderlies represent an vulnerabil stage for worsen of quality of life, by the developing functional, cognitive, psychological frailty and chronic comorbidities (Fig. 3).
Researchers Furtado G.E. (2020), Vermeulen et al. (2011), noted that frail people from a multidimensional perspective of impairment are susceptible to a higher risk of physical frailty determined by the ADL score, fear of falling, having more systemic comorbidities, Batko-Szwaczka A. (2020), Bekić S. (2019), highlighted the phenotype of frailty through the prism of physical and mental determinants in the risk of frailty [3, 4, 8, 18].

The correlational analysis Pearson of frail elderlies, established positive correlations between hip fracture – risc of fracture by FRAX method (r = 0,93*), SPPB – 25-OH Vitamin D (r = 0,89*), ADL – IADL (r = 0,65*), SARC_F – GFI (r = 0,61*), and negative associations between risc of falls – 25(OH) Vitamin D level (r = -0,74*), SARC_F – MMSE (r = -0,64*) (p≤0.05). Falls are a major cause of mortality and morbidity in older adults [1]. Our study have shown that low 25(OH) Vitamin D levels was associated with an increased risk of falls and hip fracture (fig. 4).
Cluster analysis is a useful method for identifying profiles associated with multifactorial aspects. The authors Fried L. et al (2001) and Rockwood K. et al. (2005) who are the pillars of the concept of frailty, highlighted through this method the main aspects of the frailty phenotype model and the frailty index model [7, 15].

The method of building dendrograms is widely used in medicine, but this is appropriate for relatively small batches of patients [11]. In our case, (fig. 5) it is seen that the patients in the researched groups have differed pronounced in clusters and subclusters, however, their relatively large number makes the interpretation of the results quite necessary.

**Fig. 4. Correlation analysis between the risk of falls and 25-OH Vitamin D level at the frail elderlies**
Fig. 5. Dendrograma distribution of the frailty elders in clusters

The \( k \)-means method is convenient in that the user determines the number of clusters in which patients are to be classified by possible categories in the diapazon: weak-strong, little-much, etc., etc. In the present study, we aimed to elucidate the frequency of relevant clinical manifestations that would serve as markers of the evolution of subtype frailty status depending on osteoporosis and geriatric syndromes (fig. 6).

Fig. 6. Cluster analysis of the phenotype of fragility depending on osteoporosis and geriatric syndromes
At the same time, applying the \( k \)-means cluster analysis, elderlies was divided into 3 sublots according to frailty phenotype, using 47 different parameters, the most relevant indicators was: age category, gender, fragility subtype, number of chronic polypathologies and daily polymedications used, which can be easily applied in trials clinics by the clinicians (Tab.1).

**Table 1**

Cluster analysis of the subtype frailty status depending by category of age, gender, comorbidities and drugs.

| Frequent indices in clusters | Cluster I, \( n=11 \) | Cluster II, \( n=19 \) | Cluster III, \( n=17 \) |
|-----------------------------|-----------------------|------------------------|------------------------|
| **Subtype of frailty**      | Robust                | 63.63                  | 0.52                   | 0.0                    |
|                             | Prefrail              | 18.18                  | 0.52                   | 82.35                  |
|                             | Frail                 | 18.18                  | 89.47                  | 17.64                  |
| **Gender**                  | Male                  | 45.45                  | 42.10                  | 30.0                   |
|                             | Female                | 54.54                  | 57.90                  | 70.0                   |
| **Age category**            | 65-74 years           | 36.36                  | 47.36                  | 35.30                  |
|                             | 75-84 years           | 63.63                  | 42.10                  | 17.64                  |
|                             | 85-90 years           | 0.0                    | 10.50                  | 47.36                  |
| **Polypathologies**         | Pectoral angina       | 18.18                  | 26.31                  | 58.88                  |
|                             | Primary hipertension  | 36.36                  | 100                    | 82.35                  |
|                             | Chronic obstructive pulmonary disease | 63.63 | 84.21 | 52.94 |
|                             | Cerebrovascular disease | 27.27 | 31.57 | 41.11 |
|                             | History of stroke     | -                      | 26.31                  | 58.88                  |
|                             | Lombar radiculopathy  | 54.54                  | 63.15                  | 82.35                  |
|                             | Osteoarthritis        |                        |                        |                        |
| **Geriatric syndromes**     | Urinary incontinence  | 36.36                  | 57.89                  | 94.11                  |
|                             | Sarcopenia            | 27.27                  | 42.10                  | 100                    |
|                             | Immobilisation        | -                      | -                      | 64.70                  |
|                             | Pain                  | 36.36                  | 89.47                  | 94.11                  |
|                             | Falls                 | 27.27                  | 68.42                  | 100                    |
|                             | Risk of falls         | 18.18                  | 89.47                  | 100                    |
|                             | Causes of falls:      |                        |                        |                        |
|                             | Extrinsic             | -                      | 36.84                  | 29.41                  |
|                             | Cardiovascular        | -                      | 36.84                  | 88.23                  |
|                             | Neurological          | -                      | 42.10                  | 88.23                  |
|                             | Osteoarthritis        | -                      | 63.15                  | 76.47                  |
|                             | Consequence of falls: |                        |                        |                        |
|                             | Trauma                | -                      | -                      | 94.11                  |
|                             | Psychological         | -                      | 42.10                  | 88.23                  |
|                             | Loss of autonomy resulting from falls | - | 10.52 | 70.58 |
|                             | Dependency of degree: |                        |                        |                        |
|                             | II A                  | -                      | 10.52                  | 58.88                  |
|                             | II C                  | -                      | 31.57                  | -                      |
|                             | IIIA                  | 18.18                  | 42.10                  | 29.41                  |
|                             | IIIB                  | 63.63                  | -                      | -                      |
| **Number of drugs administered** | More than 3 | 45.45 | 15.78 | 17.64 |
|                             | More than 4           | 27.27                  | 31.57                  | 41.11                  |
|                             | More than 5           | -                      | 26.31                  | 41.11                  |
The cluster analysis by the centroid method of $k$-means established that the groups of elderly, separated into 3 clusters, differed according to the level and variability of the researched parameters. Cluster I was predominant by robust elderly (63.63%) from 75-84 adult age group (63.63%), who presented moderate prevalence of comorbidities more than 50%, such as: cerebrovascular disease (63.63%), osteoarthritis (54.54%), with less geriatric syndromes and dependence of degree being IIIB, that means that autonomy being not affected. Cluster II was composed entirely of frail subtype (89.47%), young elderly persons of the 65-74 age group, but more vulnerable in terms of polipathologies and GSs. Cluster 3 consisted mainly of prefrail subtype with old elderly people (85-90 years), with the highest number of metabolic, degenerative chronic diseases and GSs. The number of daily drug administration in the clusters was less than 50%, robust frail used 3 drugs daily (45.45%) and prefrail more than 4-5 daily use for each was 41.11%.

**Conclusions**

Following a multilateral research, it was highlighted that the osteoporosis and co-morbidities can lead to the worse of the frailty nursing homes elderlies through the various aspects. To our knowledge, this is the first study to describe a strong association between multimorbidity with osteoporosis in fragility phenotype. The robust, prefrail and frail elderlies groups, positive and negative associated correlates of poor physical performance, mental disorders, chronic health problems, which suggest the need for early detection and prevention measures in order to control frailty. An association was observed between FRAX, low level of 25 OH Vitamin D and geriatric syndromes with an increased risk of falls and hip fracture at the frails group. According to the cluster analysis ($k$-means method), the most relevant indicators that separated the clusters were: age category, gender, clinical scale of frailty, comorbidities, geriatric syndromes and daily drugs used. The results obtained characterize the profile of institutionalized elderlies and can be used as a basis for the development of effective strategies, aimed at reducing physical, cognitive and social frailty. The current geriatric medicine protocols of the Republic of Moldova should be revisited to address these problems using a holistic approach to health care, focusing not only on a specific disease, but on the multidimensional assessment.
INTERNATIONAL SCIENTIFIC DISCUSSION: PROBLEMS, TASKS AND PROSPECTS

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