Clustering of Mental and Physical Comorbidity and the Risk of Frailty in Patients Aged 60 Years or More in Primary Care

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to identify the clustering of comorbidities, cognitive, and mental factors associated with increased risk of pre-frailty and frailty in patients ≥60 years in a primary healthcare setting in eastern Croatia.

Material/Methods: There were 159 patients included in the cluster analysis who were ≥60 years and who underwent four-month follow-up. The first cluster contained 50 patients, the second cluster contained 74 patients, and the third cluster contained 35 patients. Clinical parameters were identified from electronic health records and patient questionnaires. Laboratory tests, anthropometric measurements, the number of chronic diseases, the number of prescribed medications were recorded. Frailty was determined using the five criteria of Fried's phenotype model. Levels of anxiety and depression were recorded using the Geriatric Anxiety Scale (GAS) and the Geriatric Depression Scale (GDS), and the Mini-Mental State Examination (MMSE) score assessed cognitive impairment. Logistic regression models were used to identify predictors of frailty and pre-frailty.

Results: Three overlapping clusters of phenotypes predicted frailty, and included obesity (n=50), multimorbidity with mental impairment (n=74), and decline in renal function with cognitive impairment (n=35). The predictors of outcome included increasing age, number of chronic diseases, inflammation, anemia, anxiety, and cognitive impairment, and reduced muscle mass.

Conclusions: In patients ≥60 years in a primary healthcare setting, multimorbidity predictors of pre-frailty and frailty included a decline in cognitive function and renal function.

MeSH Keywords: **Cluster Analysis • Comorbidity • Frail Elderly • Kidney Failure, Chronic**

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Background

The prevalence of multimorbidity or multiple diseases in the same person increases with age and is partly due to the synergistic effects that different diseases have on each other [1]. Therefore, older people not only have complex clinical problems but may also suffer from polypharmacy and an increased risk of adverse drug reactions, resulting in increased dependence on healthcare services and increased morbidity and mortality [2]. Since the majority of consultations in the primary healthcare setting are for older patients with multimorbidity, primary care physicians are also in high demand, facing the needs of prescription integration of multiple providers and multiple medication treatments [3]. However, current clinical guidelines do not provide a practical framework for managing multimorbidity [4].

The prevalence of chronic disease varies significantly across studies and populations. However, while some conditions, such as hypertension, have a constant association with increasing age, some disease combinations show a tendency to cluster together [5]. Disease clustering is sometimes based on common pathophysiology, but in many cases, the cause is unclear [6]. However, not all patients with multimorbidity have complex care needs [7]. Factors associated with complex care have recently been identified and include certain disease patterns, decreased physical and mental function, and lower socioeconomic status [8]. Mental or cognitive disorders associated with comorbidity have been shown to significantly increase the risk of disability, poor physical function, and frailty [8,9].

Frailty is defined as a state of reduced physiological reserve in multiple systems due to the cumulative effect of aging and chronic disease [10]. Frail people are sensitive to acute illness, injury, the addition of new medication into existing prescription regimens, and can result in adverse health outcomes, including disability, falls, dependency on others, the need for long-term care, and death [11].

The Diagnostic criteria for frailty were derived from expert consensus and developed in practice to provide risk scores and predictive models. Some widely recognized frailty phenotypes include decreased muscle mass and strength, general weakness, unsteady gait, slow speed of gait, impaired balance, slowness, and reduced activity [12]. Also, cognitive impairment has been proposed as a part of the syndrome of frailty, although their relationships remain unclear [13]. Recent guidelines on the assessment and management of patients with multimorbidity recommend routine screening for patient frailty in primary care, for older people with several chronic conditions [4]. The main barrier to the implementation of these guidelines is the lack of simple evaluation and grading systems that are appropriate for use in primary care [14].

Several frailty assessment tools have been developed but they have not been sufficiently tested in different clinical settings and population groups to allow routine use for comparison of frailty [15,16]. The practical utility of these assessment tools is also limited because they are tailored to outcome measures and are not able to distinguish between different levels of frailty levels, or in response to treatment interventions [15].

There are two main models to assess frailty. The first model is based on the five criteria of Fried's phenotype model [17], which includes weight loss, grip strength, exhaustion, reduced physical activity, and reduced rate of walking. Patients with three of the Fried criteria are identified as frail, patients with one or two criteria are identified as pre-frail, and they are not frail if they have none of these criteria [17]. The second approach is more holistic and is based on a cumulative deficit model, also known as the Frailty Index, which considers medical, cognitive, psychological, and functional deficits, described with symptoms, signs, and laboratory abnormalities [18]. This construct was built using the Comprehensive Geriatric Assessment (CGA), a protocol which has been shown successfully in geriatric hospital wards, in the prevention of adverse health outcomes for geriatric patients [19]. Both frailty models were initially developed in the USA and Canada and adapted to the European population following the findings from large epidemiologic studies [20,21]. Although some validation procedures, for both models, have been performed in populations in the community, their metrics have not been sufficiently assessed to allow accurate diagnosis of frailty in primary care patients [14,22,23]. Efforts to establish simple checklists or individual physical performance tests, as modifications of the two main frailty models for use in primary care have been unsatisfactory [14]. This lack of success may also be partly because of the lack of an operational definition of frailty [24].

Mental disorders of older patients, including generalized anxiety and depression, have received increasing research attention, due to their adverse effects on the health and the quality of life of older people [25]. Since affective disorders of older people are reduced, symptoms of these disorders are usually subclinical and nonspecific and differ from those in younger people [26]. Typically, these symptoms may be similar to physical and neurologic conditions [27,28]. Therefore, mental disorders in older people are often poorly recognized by primary care physicians [29].

Previous studies have shown that multimorbidity and frailty, and depression and frailty overlap with each other, although the nature of these relationships and the temporal sequence of events are still a matter of debate [17,30]. There is evidence for a close relationship between anxiety, depression, cognitive impairment, and frailty in older people, but the effects of patterns of comorbidity remain unknown. Analysis of data

that can be routinely collected in the primary healthcare setting and the possibilities of machine-learning methods to analyze multicomponent datasets may be used to identify real-world clustering of physical frailty with mental and cognitive impairment and physical comorbidity.

Therefore, this study aimed to identify the clustering of comorbidities, cognitive, and mental factors associated with increased risk of pre-frailty and frailty in patients ≥60 years in a primary healthcare setting in eastern Croatia.

Material and Methods

Study design and patient selection

A cross-sectional retrospective study was conducted in 2018 in an academic general medicine practice in the town of Osijek (90,000 inhabitants), eastern Croatia. Older people living in the area have similar living conditions and are of a lower socioeconomic status. In Croatia, primary healthcare services have good access to the general population. An advantage of data collection from a single practice was uniformity of diagnostic criteria and terminology used [31]. The fact that this was an academic practice ensured that a skilled and knowledgeable primary care physician collected the data, which improved accuracy.

There were approximately 2,000 patients registered in this general medicine practice, and one-quarter were patients aged ≥60 years. Only community-dwelling patients and not those in institutions were included in the study. Patients were enrolled consecutively from regular attendance during a four-month follow-up study.

Study exclusion criteria included acute medical conditions, acute exacerbation of chronic diseases, patients who were actively treated with chemotherapy or biological treatments, and patients with a diagnosis of psychosis or dementia. All study participants provided written informed consent. Each clinic medical examination was performed by the primary care physician and lasted for about 40 minutes, and the primary care physician examined two or three patients per day. The initial number of study participants was 184, but after exclusion of patients without complete data, the number of patients included in the cluster analysis was 159.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, the Josip Juraj Strossmayer University of Osijek (No. 641-01/18-01/01).

Data collection

There were 46 parameters used for analysis, including data from primary care physician electronic health records, self-reported data, and data obtained by standard questionnaires (Tables 1, 2). The selection of parameters was based on knowledge and data availability.

Information on the diagnosis of chronic diseases, the total number of chronic diseases and prescribed oral medications in continuous use, anthropometric measurements, and laboratory tests, were obtained from electronic health records. In Croatia, the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) is used to classify disease. Patient self-reports obtained information on education and disability. The laboratory tests, used in the study, were only those that are being routinely collected, as a part of the chronic disease surveillance or preventive clinical examination.

Anthropometric measurements, if not updated in electronic health records, were performed at patient appointments. To identify patients with geriatric conditions not well supported with the ICD-10 diagnosis system, including mental disorders, cognitive impairment, sleep disorders, and frailty syndrome, we used the standard screening questionnaires, prepared as templates for online data collection. Patients completed questionnaires, and that included Fried's phenotype model [17], which included weight loss, grip strength, exhaustion, reduced physical activity, and reduced rate of walking. Patients with three of the Fried criteria were identified as frail, patients with one or two criteria were identified as pre-frail, and they were not frail if they had none of these criteria [17]. To assess the cluster centered values, we used the laboratory reference values, the guidelines for the management of dyslipidemias, diabetes, cardiovascular disease, and chronic kidney disease and the scoring systems of the standard screening tests for anxiety, depression, cognitive impairment, and frailty [12,32–37].

Screening for anxiety, depression, sleep disorders, cognitive impairment, and frailty

The Geriatric Anxiety Scale (GAS) and the Geriatric Depression Scale (GDS) were used to assess patient anxiety and depression [35,36]. These tests have been widely used and validated in many populations and are considered appropriate for use in the primary healthcare setting [38,39]. Two independent experts in the field performed the tests. The internal consistency was calculated with Cronbach's alpha, and for both tests, the values were high (0.897 for the GAS test and 0.875 for the GDS test). The GAS is a 25-item score, specially designed for use in the older population. The GAS allows grading of anxiety symptoms as negative, minimal, mild, modest,

Table 1. Descriptive statistics of the numerical parameters.

Parameter	Min	Max	Median (interquartile range)		Mean (standard deviation)	
Age (years)	60.00	89.00	71.00	(10.00)	71.26	(6.13)
BMI (kg/m^2)	14.33	47.05	29.75	(5.84)	30.13	(4.55)
Waist circumference (cm)	50.00	148.00	99.00	(16.20)	99.68	(12.68)
Mid arm circumference (cm)	18.00	42.00	32.00	(4.00)	31.50	(3.49)
A total number of diagnoses	0.00	10.00	3.00	(2.00)	3.01	(1.62)
A total number of medications	0.00	15.00	4.00	(3.00)	3.66	(2.15)
Fasting glucose (mmol/L)	3.90	16.20	5.50	(1.55)	6.07	(1.70)
Total cholesterol (mmol/L)	2.90	9.30	5.70	(1.73)	5.78	(1.32)
LDL cholesterol (mmol/L)	1.20	6.80	3.60	(1.52)	3.60	(1.17)
HDL cholesterol (mmol/L)	0.80	2.30	1.40	(0.40)	1.41	(0.32)
Triglycerides (mmol/L)	0.60	7.00	1.55	(0.90)	1.50	(0.90)
Glomerular filtration rate (mL/min/1.73 m^2)	18.00	191.00	86.00	(36.00)	86.97	(26.27)
Haemoglobin (g/L)	54.00	177.00	138.00	(15.00)	136.80	(14.53)
Erythrocytes (×10^{12}/L)	0.77	5.63	4.59	(0.52)	4.61	(0.41)
Haematocrit (g/L)	0.22	0.53	0.42	(0.04)	0.42	(0.04)
C-reactive protein (mg/L)	0.20	52.90	2.30	(3.87)	6.08	(12.73)

and severe, and could discriminate between physical, cognitive, and affective domains of anxiety. Scores from these domains provide the GAS [35]. The GDS is a 30-item score, appropriate for use in older people, as it uses simple yes or no responses and allows for discrimination between mild and severe depressive symptoms, even in persons with mild cognitive impairment (MCI) [36].

To assess cognitive impairment, the Mini-Mental State Examination (MMSE) was used, that has been broadly validated as a screening test, including older patients in the Croatian population [37]. A MMSE score of 24 or less (out of the maximum 30) indicates cognitive impairment. The calculated Cronbach's alpha for this test was 0.788. Sleep disorders were assessed by the standardized Pittsburgh Sleep Quality Index (PSQI) [40], in which a total score of 5 or more indicated poor sleep quality. The calculated Cronbach's alpha for this test was 0.752.

Fried's frailty phenotypic model was used to determine frailty [12,17]. We were conscious of the fact that the choice of criteria for measuring frailty may affect patient classification patterns. However, when there is no definition of frailty that meets the international consensus, nor a standard instrument to measure frailty in the primary healthcare setting, the

choice of a frailty tool is based on the purpose of the study, and the quality of the validation process [16,23,24]. Although the Fried's frailty model required the use of the Collin handgrip dynamometer (0–70 kg) for measuring grip strength and may be impractical for use in primary care, it was the best-validated measure for targeting physical aspects of frailty [10,12]. To address the concepts of multimorbidity and frailty more comprehensively, we also measured mood and cognitive impairment by using separate, objective measurement tools.

In the study population, frailty was determined using the five criteria of Fried's phenotype model [17], which by emphasizing gradation of frailty is important in clinical medicine for planning interventions [41]. The modified version of Fried's frailty model has been developed in the general older population in Europe [23]. This test discriminated between frail and nonfrail people, and a good predictive ability of the Fried's frailty model was previously confirmed for the primary health-related outcomes, including falls, hospitalization, disability, and mortality [12]. Before performing this test, participants were trained on how to use the hand grip dynamometer. They made the three attempts with each hand, under the supervision of the primary care physician, and the maximum score (in kg) was used as the grip strength score.

Table 2. Descriptive statistics of the categorical parameters.

Parameter	Values	Parameter	Values
Gender	F – 127 M – 57	Diabetes mellitus type 2	No – 141 Yes – 43
Education	Not at all – 1 Primary school – 85 Secondary school – 85 High school – 13	Chronic obstructive pulmonary disease	No – 177 Yes – 7
Geriatric Depression Scale	Severe – 8 Mild – 54 Negative – 122	Asthma	No – 166 Yes – 18
		Chronic heart disease	No – 179 Yes – 9
Geriatric Anxiety Scale Global	Minimal – 89 Mild – 58 Modest – 19 Severe – 16 Negative – 2	Coronary artery disease	No – 163 Yes – 21
		Cerebrovascular disease	No – 177 Yes – 7
Somatic	Minimal – 58 Mild – 70 Modest – 21 Severe – 32 Negative – 3	Periphery artery disease	No – 179 Yes – 5
		Gastro–intestinal disorders	No – 110 Yes – 74
Cognitive	Minimal – 47 Mild – 60 Modest – 9 Severe – 17 Negative – 52	Malignant disease	No – 164 Yes – 20
		Diagnosis of osteoporosis	No –171 Yes – 30
Affective	Minimal – 74 Mild – 41 Modest – 6 Severe – 11	Severe osteo–arthritis	No – 115 Yes – 69
		Diagnosis of low back pain	No – 118 Yes – 66
Pittsburg sleep quality index	Negative – 51 Positive – 133	Urogenital disease	No – 168 Yes – 16
Mini Mental State Examination	Negative – 86 Positive – 98	Diagnosis of thyroid gland disease	No –173 Yes – 11
Frailty index	Frailty – 24 Prefrailty – 79 Negative – 81	Incontinentio urinae	No – 172 Yes – 12
		Significant visus impairment	No – 173 Yes – 11
Hypertension	No – 34 Yes – 150	Hearing impairment	No – 25 Yes – 159
		Experienced falls	No – 130 Yes – 54
		Walk with support or visible impaired	No – 174 Yes – 10

Data analysis

Numerical data were presented as the mean and standard deviation (SD) and as the median and the interquartile range (IQR) (Table 1). Categorical data were presented as absolute numbers (Table 2). Bar diagrams were used to present the distributions of anxiety, depression, cognitive impairment, sleep disorders, and frailty in the whole study population (Figure 1) and anxiety, depression and cognitive impairment according to the grades of frailty (Figure 2). The overlapping rates between anxiety (and its domains) and depression, between each of these

mental disorders and cognitive impairment, mental disorders and pre-frailty and cognitive impairment and pre-frailty, were presented by the Venn diagrams (Figure 3). The plotted centers of the clusters are shown in Figure 4. Differences in distributions of comorbidities, between pre-frail and frail *vs.* non-frail patients and between patients in the clusters, are shown by bar diagrams (Figures 5, 6). To simplify these presentations,
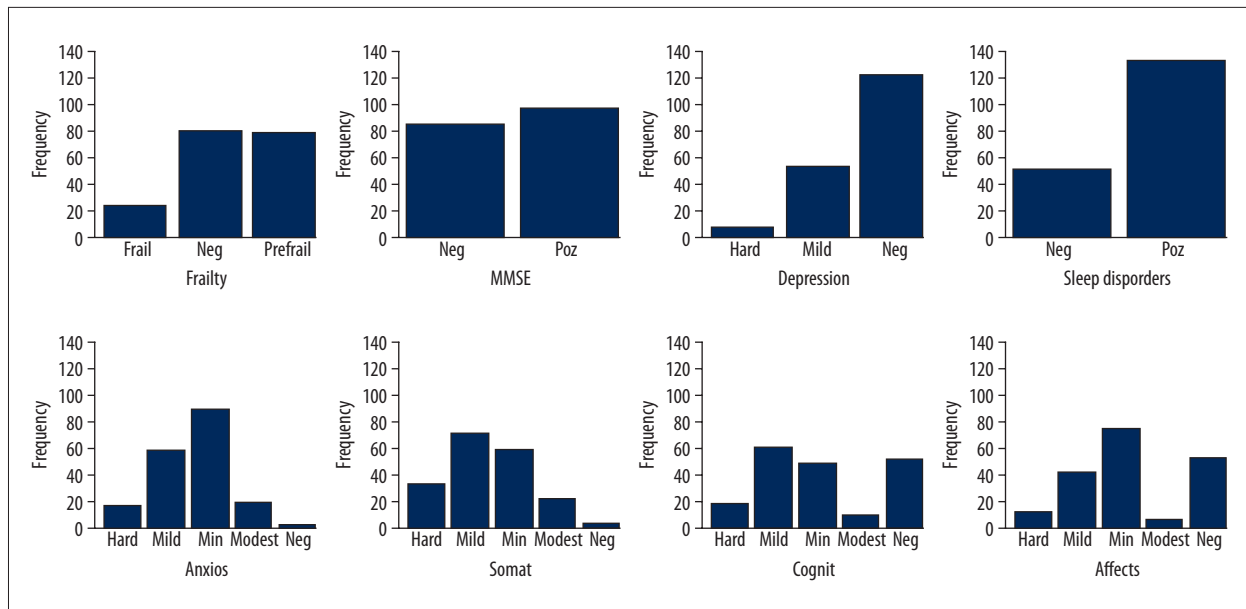
Figure 1. Bar diagrams show the distribution of pre-frailty and frailty cognitive impairment, depression, sleep disorders, and anxiety (and the domains) in the study population.

some diagnoses were combined, such as diagnoses of cardiovascular and musculoskeletal diseases. Differences between groups were assessed using the Kruskal-Wallis rank sum test. The graphical presentations of clinical phenotypes, identified by the clusters, are shown in Figure 7.

Cluster analysis

A cluster is a collection of data which describes objects similar to each other but dissimilar to objects in different clusters. Cluster analysis is one of the main methods in data analysis. In this study, the K-mean algorithm was used to identify subgroups within the sample [42]. The K-mean algorithm is a type of partitioning algorithm that uses only numerical parameters and aims to partition a set of (n) objects into (k) clusters so that the resulting intra-cluster similarity is high and the inter-cluster similarity is low. The intra-cluster similarity is measured with the mean value of distances between the objects in the cluster, which can be considered as the cluster's center.

For clustering, we used a total of 23 numerical parameters that had been previously selected. These parameters included age, frailty, anxiety (and its domains), depression, cognitive impairment, the total number of diagnoses of chronic diseases, the total number of prescribed medications, anthropometric measures, and laboratory tests indicating inflammation, anemia, metabolic status, and renal function (Table 1).

To justify distance measure scales of various numerical parameters used for clustering, we applied the scale method. This method is based on the z-score standardization and transforms

the parameters so that they acquire a mean value of 0 and a standard deviation of 1. As the cluster performance may be affected by the chosen value of (k), the second step of the analysis was the determination of the most suitable number of clusters. The search for the appropriate number of clusters, for a given dataset, is generally by trial and error. Several methods were evaluated, including the elbow and the average silhouette methods, but these did not provide unambiguous results [43,44]. We then used the Calinski-Harabasz index and, according to the maximum index value, decided to generate three clusters [45]. The R^2 value of the generated clusters was 0.19, indicating the low inter-cluster distance (Figure 4). The first cluster contained 50 patients, the second cluster contained 74 patients, and the third cluster contained 35 patients (Table 3).

To identify the most important parameters of the common prefrailty and frailty outcome, we performed logistic regression models with the odds ratio (OR) and 95% confidence interval (CI). Four models were created that included anthropometric measures (body shape), laboratory tests (hematological and biochemical), mental and cognitive tests (anxiety, depression, and cognitive impairment) and sensory impairments and disabling conditions (Tables 4–7). All these models were justified for age, the number of diagnoses of chronic diseases, and the number of prescribed medications.

Before generating the logistic regression models, we performed simple correlation analysis and checked all parameters in the input on multicollinearity, by using the variance inflation factor (VIF) [46]. Based on these criteria, some parameters were excluded from the modeling procedure. These parameters were:

Figure 2. Bar diagrams show the distribution of depression, anxiety (and the domains) and cognitive impairment according to grades of frailty.
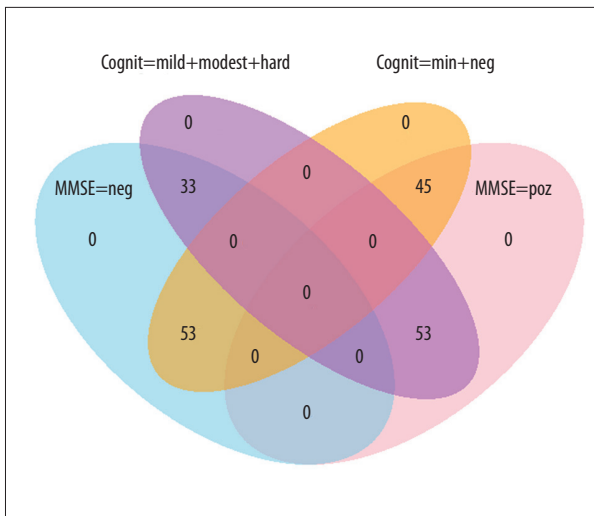
Figure 3. Venn diagram shows the overlap between the paired conditions.

BMI (model No. 1), total cholesterol and hematocrit (model No. 2) and GAS score (model No. 3). The McFadden's R2 test was used to measure the predictive ability of the generated logistic regression models, and the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to determine the inter-model quality comparison [47,48].

Results

There were 159 patients included in the cluster analysis who were ≥60 years and who underwent four-month follow-up. The first cluster contained 50 patients, the second cluster contained 74 patients, and the third cluster contained 35 patients. Participants in this study were mainly in the age range

of 60–80 years, with few being older than 80 years (Table 1). There were more women than men (Table 2). Participants varied in their anthropometric and laboratory indicators, comorbidity grades, and the number of medications prescribed (Tables 1, 2).

More than half of the study participants were positive for prefrailty and frailty and mild cognitive impairment, and the prefrailty to frailty ratio was about 4: 1. Nearly half of the study participants had symptoms of depression, which were generally of a mild grade. Sleep disorders were common, affecting about three-quarters of study participants, and the majority had some symptoms of anxiety. Physical symptoms predominated over cognitive and affective symptoms (Table 2, Figure 1).

Patients with symptoms of mental disorders, depression, and anxiety (including physical, cognitive, and affective domains), tended to have increased symptom severity according to increase in the frailty grades. A similar tendency found from the Mini-Mental State Examination (MMSE) score (an indicator of mild cognitive impairment) (Figure 2).

The assessment of paired combinations of geriatric conditions showed a disproportionate increase in the rates of overlap, compared with their proportions in the sample, and included depression and frailty, cognitive impairment and frailty, anxiety (somatic domain), pre-frailty and frailty, anxiety (cognitive domain) and depression, and anxiety (cognitive domain) and cognitive impairment (Figure 3).

The generated 3 clusters demonstrated a high degree of overlap (Figure 4) and overlapping clinical phenotypes (Table 3). The common frailty scores were higher in clusters No. 2 and No. 3, indicating pre-frailty, compared with cluster 1. Despite the marked differences between cluster No. 1 and No. 2 in
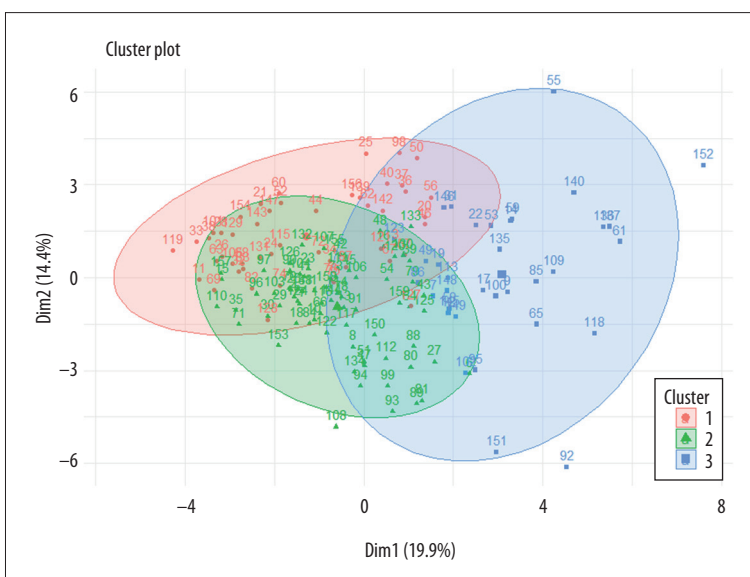
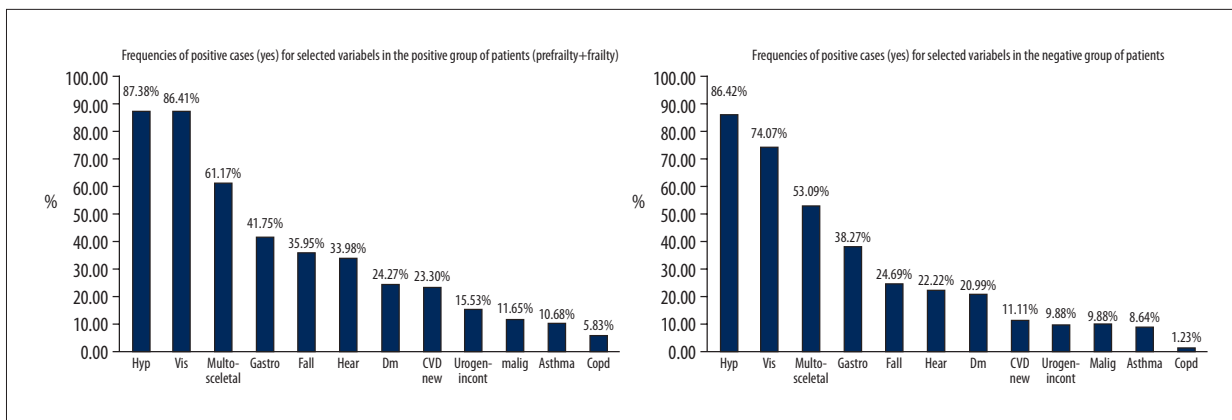**Figure 4.** Scatter plots of the three generated clusters.

Figure 5. The selected chronic medical conditions in pre-frail and frail patients compared with the non-frail individuals. Vis – visual impairment; Hyp – hypertension; Musculo-skeletal – musculo-sceletal diseases; Gastro – gastro-intestinal disease; Hear – hearing impairment; Dm – diabetes mellitus type2; Fall – experienced falls; CVD – cardiovascular disease; Malig – malignant disease; Urogenit-incont – disorders of urogenital tract and incontinentio urinae; Asthma – asthma; Copd – chronic obstructive pulmonary disease. Kruskal-Wallis test results (significance level 0.05): hyp (0.016), fall (0.025)
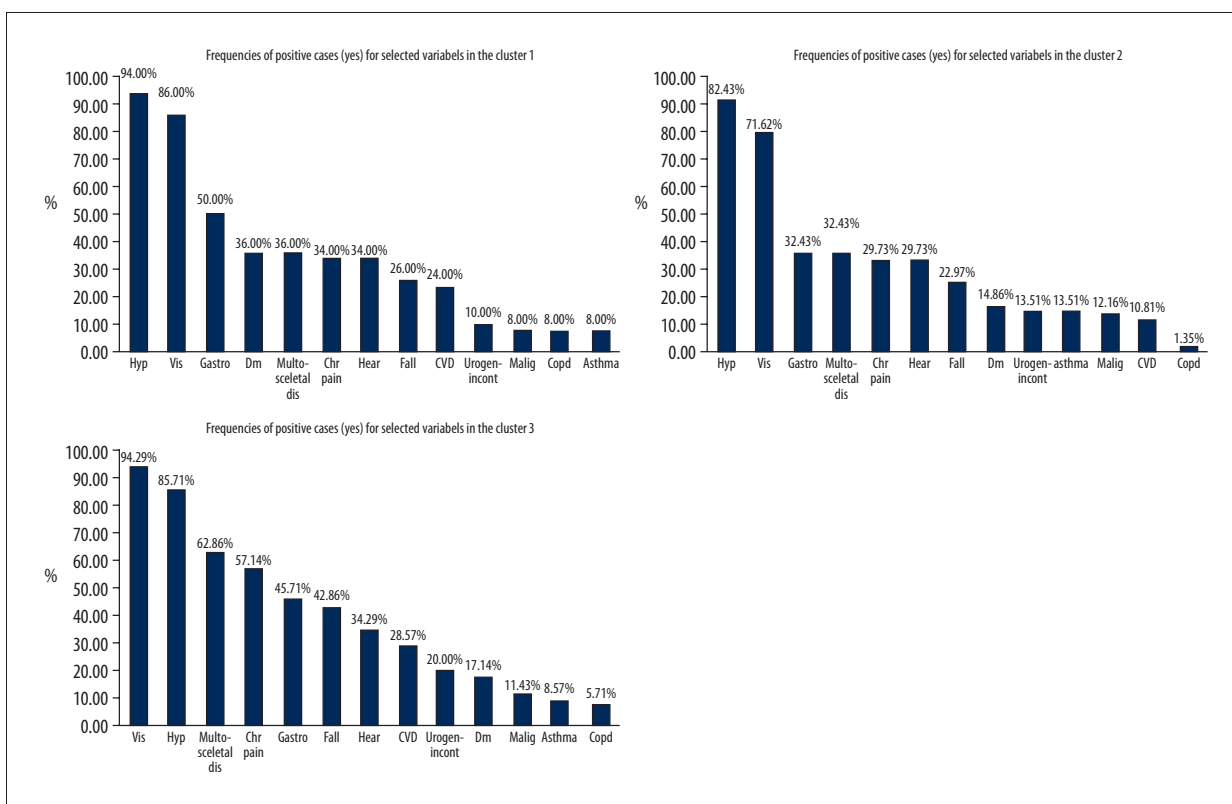

Figure 6. The selected chronic medical conditions and the differences between the clusters. Vis – visual impairment; Hyp – hypertension; Musculo-sceletal – musculo-skeletal diseases; Gastro – gastro-intestinal disease; Hear – hearing impairment; Dm – diabetes mellitus type2; Fall – experienced falls; CVD – cardiovascular disease; Malig – malignant disease; Urogenit-incont – disorders of urogenital tract and incontinentio urinae; Asthma – asthma; Copd – chronic abstructive pulmonary disease. Kruskal-Wallis test results (significance level 0.05): musculo-sceletal dis. (0.010), dm (0.016).

the frailty scores, the proportions of pre-frail and frail patients, compared with non-frail individuals, were similar and increased (found in about a half of patients) (Table 3). The highest proportions of pre-frail and frail patients were found in cluster No.3 (in about 80% of patients), with frail patients dominating the pre-frail ones.
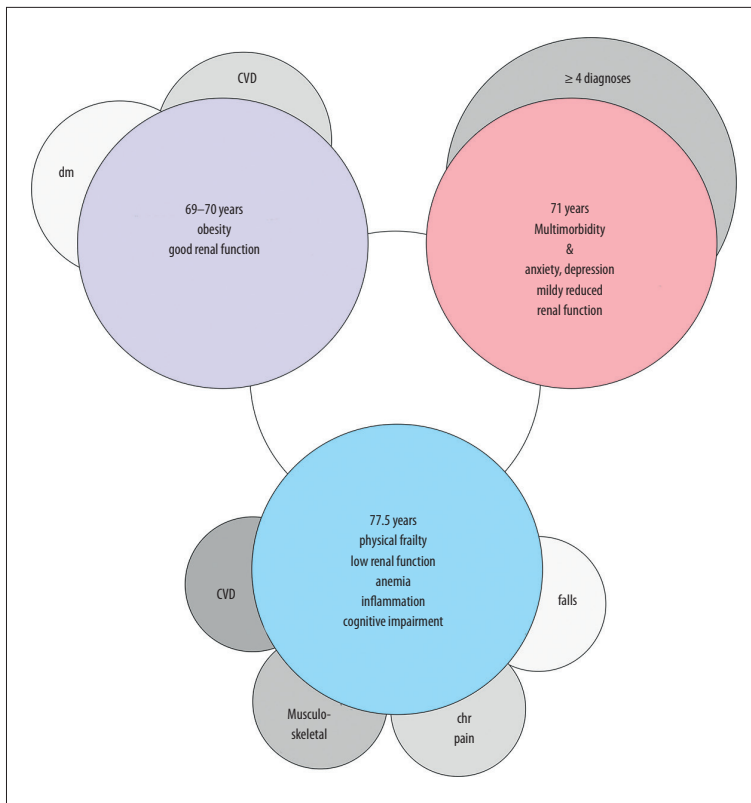
Figure 7. The main features of the three clinical phenotypes identified by the clusters.

Cluster descriptions were based on the parameters where centered values showed the greatest deviations from the reference values or where frailty was implicated. Accordingly, cluster No. 1 was associated with obesity, with a body mass index (BMI)=31.9 kg/m² and waist circumference (WC)=104.2 cm, good renal function, with a glomerular filtration rate (GFR) >90 ml/min, and good cognitive function, as indicated with a MMSE score >25. Cluster No. 2 was associated with a higher comorbidity grade and a medication prescription rate, as indicated with a total number of diagnoses of 3.5 and a total drug number of 4.7, clinical anxiety and depression, as indicated with the values of the GAS score, the SOMAT score and the GDS score, mildly decreased renal function (as indicated with a GFR <90 ml/min) and a higher frailty grade, compared with cluster No. 1. Cluster No. 3 was associated with a higher age (77.5 years), compared with the previous two clusters (69.7 and 70.9 years, respectively), markedly reduced renal function (GFR <60 ml/min), reduced muscle mass (MAC=27.7), anemia (Hb <130 gm/dL), increased inflammation (CRP=8.3 mg/L) and impaired cognitive function (MMSE score=23.4).

In the generated logistic regression models, only a part of examined parameters was significant as predictors of the pre-frailty and frailty outcome, which gave to these models a small predictive power (as indicated with low McFadden R2 index). These important parameters were: mac (Table 4), erit, and crp (borderline) (Table 5), the somat score, and the MMSE score

(borderline) (Table 6). A high level of significance of the parameter of age, demonstrated in all generated logistic regression models, means that when associations between these important parameters and the pre-frailty and frailty outcome are considered, the effect of age should be accounted for (Tables 4–6). The associations of the parameters erit and crp with the pre-frailty and frailty outcome may also be influenced by the number of chronic diseases (Table 5). No one specific parameter indicating sensory impairments/disabling conditions was found to be an independent predictor of the pre-frailty and frailty outcome (Table 7). All these conditions, taken together, as a model, have small predictive power for the pre-frailty and frailty outcome. Their appearance was strongly influenced by increasing age. All identified predictors of the pre-frailty and frailty outcome were of similar importance, as indicated by the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) of the logistic regression models.

The selected medical conditions were contrasted between pre-frail and frail and non-frail patients and visualized by the bar diagrams (Figure 5). Significant differences were found in proportions of hypertension, cardiovascular disease, and falls (Kruskal-Wallis rank sum test, p<0.05). When differences in distributions of chronic medical conditions were considered between the clusters, it was evident that in cluster No. 1, there was a higher proportion of patients with diabetes, than in cluster No. 2; that cardiovascular disease, musculoskeletal

Table 3. The clusters (k=3), input parameters (n=23), and centers of the clusters with the distributions of patients in the clusters.

Parameter	Cluster 1 (50 patients)			Cluster 2 (74 patients)			Cluster 3 (35 patients)		
No-frail, prefrail, frail	25	22	3	40	32	2	7	11	17
C-reactive protein		4.456			3.733			**8.379**	
Age		**69.769**			**70.965**			**77.478**	
BMI		**31.931**			29.497			26.401	
Waist circumference		**104.256**			97.344			92.021	
Mid arm circumference		**33.102**			31.146			**27.782**	
Number of diagnoses		2.487			**3.534**			3.434	
Number of medications		3.076			**4.689**			2.956	
Fasting glucose		3.076			6.020			5.865	
Total cholesterol		5.779			5.943			5.569	
LDL-cholesterol		3.590			3.698			3.443	
HDL-cholesterol		1.387			1.513			1.278	
Triglycerides		1.762			1.624			2.091	
Glomerular filtration rate		**96.387**			**85.891**			58.665	
Haemoglobin		140.102			136.224			128.130	
Erythrocytes		4.755			4.586			4.218	
Haematocrit		0.431			0.418			0.389	
Frailty score		**0.564**			**1.534**			**1.347**	
MMSE score		**26.282**			25.172			**23.434**	
GAS score		8.474			**23.068**			7.956	
Somatic		5.897			**11.827**			5.217	
Cognitive		1.461			5.982			1.304	
Affective		1.115			5.258			1.434	
GDS score		4.871			**13.396**			6.000	

The centred values highlighted by the bold are those that markedly deviate from the reference values of the corresponding parameters.

Table 4. The logistic regression model No. 1 with anthropometric measures as determinants of the pre-frailty and frailty outcome.

Parameter	z Value	Pr(>|z|)	OR	CI	
				5%	95%
Age	3.228	0.001**	1.118	1.056	1.184
Wc	1.509	0.131	1.029	0.997	1.061
Mac	−2.800	0.005**	0.804	0.707	0.914
Number of chronic diseases	1.195	0.232	1.166	0.943	1.442
Number of medications prescribed	0.998	0.318	1.102	0.939	1.294

Parameters with the levels of significance: **0.01. McFadden R^2 index=0.161; AIC=195.686; BIC=214.099.

Table 5. The logistic regression model No. 2 with laboratory (hematological and biochemical) measures as determinants of the pre-frailty and frailty outcome.

Parameter	z Value	Pr(>|z|)	OR	CI	
				5%	95%
Age	3.432	0.0006***	1.149	1.075	1.228
Number of chronic diseases	1.834	0.067	1.272	1.025	1.578
Number of medications prescribed	0.835	0.404	1.087	0.922	1.282
Fglu	−0.827	0.408	0.903	0.737	1.106
Ldl	0.434	0.732	1.064	0.789	1.437
Hdl	0.918	0.359	1.871	0.609	5.754
Trig	0.994	0.320	1.269	0.855	1.885
Cre	−1.193	0.233	0.992	0.982	1.003
Gfr	−0.752	0.452	0.992	0.975	1.009
Crp	1.680	0.093.	1.075	1.001	1.154
Hb	−0.373	0.709	0.994	0.966	1.022
Erit	1.857	0.063.	3.128	1.139	8.585

Parameters with the levels of significance: *** 0.001. McFadden R^2 index=0.166; AIC=208.633; BIC=248.529.

Table 6. The logistic regression model No. 3 with the scores of mental and cognitive tests as determinants of the pre-frailty and frailty outcome.

Parameter	z Value	Pr(>|z|)	OR	CI	
				5%	95%
Age	3.789	0.0001***	1.149	1.082	1.220
Number of chronic diseases	1.403	0.161	1.202	0.969	1.490
Number of medications prescribed	−0.132	0.895	0.986	0.827	1.175
Mmse score	−1.865	0.062.	0.890	0.802	0.986
Anxiety somat score	2.376	0.018*	1.135	1.040	1.239
Anxiety cognit score	0.760	0.448	1.067	0.927	1.227
Anxiety affect score	−0.194	0.846	0.979	0.815	1.175
Gds score	−0.125	0.305	0.951	0.878	1.031

Parameters with the levels of significance: *** 0.001. McFadden R^2 index=0.176; AIC=198.473; BIC=226.094.

diseases, chronic pain, and falls were more frequent in cluster No. 3, than in the other two clusters; and that cardiovascular disease were more frequent in cluster No. 1 than in cluster No. 2 (Kruskal-Wallis rank sum test, p<0.05) (Figure 6).

Descriptions of the clinical phenotypes, defined by the clusters and additional analytical methods, are shown in Figure 7.

Discussion

To our knowledge, this was the first study to address the physiological concept of frailty by using routine data from primary care electronic health records. The study used a data-driven approach, to derive clusters of the typical aging phenotypes, within which frailty was likely to develop. The identification of such patterns may be useful for directing future research and planning prevention. Therefore, primary care where there is

Table 7. The logistic regression model No. 3 with sensory impairment and disabling conditions as determinants of the pre-frailty and frailty outcome.

Parameter	z Value	Pr(>|z|)	OR	CI	
				5%	95%
Chronic pain=yes	−0.830	0.406	0.703	0.350	1.413
Urogen-incont=yes	−0.005	0.996	0.997	0.391	2.541
Vis=yes	−0.833	0.405	0.646	0.273	1.531
Hear=yes	0.506	0.613	1.228	0.630	2.391
Fall=yes	1.271	0.204	1.724	0.852	3.491
Age	3.801	0.00014***	1.135	1.074	1.199
Number of chronic diseases	1.492	0.136	1.249	0.978	1.594
Number of medications prescribed	0.522	0.601	1.054	0.892	1.243

Parameters with the levels of significance: *** 0.001. McFadden R^2 index 0.137; AIC=206.964; BIC=234.584.

access to a general patient population, and a variety of data are available, could be an ideal place for conducting such research.

Frequencies of medical conditions assessed in this study, including anxiety, depression, pre-frailty and frailty and cognitive impairment, were higher than those reported in previous epidemiologic studies (Table 2, Figure 1) [30,49]. Explanations for this discrepancy may include study bias due to the small sample size, low socioeconomic status as a characteristic of the local population, and the choice of the assessment tools.

Information provided by epidemiologic studies may only have limited value for the local healthcare providers. The reasons include the marked differences that exist in population characteristics between regions and healthcare system organizations, that may yield significant variations in the prevalence of chronic diseases and other geriatric conditions [49,50]. In this study, mental conditions in older patients were dominated by mild symptoms, and physical and cognitive symptoms were shared between certain mental conditions (Figures 2, 3) [13,25].

In the study population, frailty was determined using the five criteria of Fried's phenotype model to identify patients as frail, pre-frail, or not frail [17]. The identified clusters contained a mix of pre-frail, frail, and non-frail patients and the differences between them were observed in the proportions of frailty scores, in line with the assumption that there is a non-linear course in the frailty development (Table 3) [10]. It has also been assumed that accumulation of pathophysiology impairment in an individual, may lead to the transition from lower to higher frailty grades, or pre-frailty and frailty, where at some points of this pathway, there is the possibility of reversibility [51]. Frailty is the final pathway of aging [52]. As shown by our results, pre-frailty may be common in a non-selected

older primary care population, in particular in socioeconomically deprived areas, as it is our region, and is more prevalent than frailty (Table 3, Figure 1). Prospective clinical studies are needed to investigate the causes and rates of transition from pre-frail to frail patients in older patients.

In this study, cluster No. 1 was the obesity group, as it included increased values of anthropometric measures of body mass index (BMI) and waist circumference (WC) (Table 3). In contrast to the low common frailty score (0.56), which did not reach the threshold for pre-frailty, Cluster No. 1 contained a high proportion of pre-frail patients (22/50). This finding might be explained by the mild frailty grade of affected patients and the high percentage of non-frail people in this cluster. Obesity has been recognized as a variable determinant of frailty, as is unintended weight loss [12,53]. There is a close association between obesity and diabetes and cardiovascular disease, and these conditions are associated with frailty [54,55]. The findings of this study showed a relatively high proportion of patients with diabetes and cardiovascular disease in comorbidities associated with cluster No. 1 (Figures 6, 7). In obesity, lipid accumulation in muscle results in reduced physical performance [53]. When other features of this cluster are taken into account, including good renal function and age <70 years, then the low frailty score, found in this cluster may be explained by a short duration of diabetes and the lack of overt diabetes-related complications [56]. This assumption is supported by the fact that most of the patients in the sample were women, and diabetes and cardiovascular disease often appear in years after the menopause [57]. Therefore, the propensity for the development of diabetes and cardiovascular disease may be a factor that determines the proportions of pre-frail and frail obese patients in cluster No. 1.

In this study, clusters No. 1 and No. 2 showed a high degree of overlap with each other (Figure 4). This finding may be attributed to the similar age of study participants in these groups (69.7 years *vs.* 70.9 years) and similar proportions of pre-frail and frail *vs.* non-frail patients (25/50 *vs.* 34/74) (Table 3). However, there was a marked difference in the frailty scores (0.6 *vs.* 1.5), which may be explained by the higher comorbidity grade (4 *vs.* 3) and a medication prescription rate (5 *vs.* 3) in cluster No. 2 [10,12]. The components of comorbidities present in cluster No. 2 but not in cluster No. 1 may have influenced the higher frailty score, including mental disorders and reduced renal function (Table 3, Figure 7).

The values of the Geriatric Anxiety Scale (GAS) and the Geriatric Depression Scale (GDS) scores reached the clinical levels for general anxiety (grade, modest), anxiety somatic (grade, modest), and depression (grade, mild) (Table 3) [35,36]. Based on the logistic regression model, anxiety somatic was considered to be an independent predictor of pre-frailty and frailty (Table 6). Somatization, or conversion of mental state into physical symptoms, such as chronic pain, is more common in elderly patients with multiple comorbidities [25,28]. The association between anxiety with frailty is still a neglected area in geriatric research, and the findings of this study suggest, this association requires further investigation [58]. The results of the present study, combined with the findings from previous studies, have shown that in an elderly patient population in primary care, symptoms of anxiety, depression and cognitive impairment are challenging to separate from each other and from physical frailty (Figures 2, 3). Therefore, in older people who progress towards frailty, symptoms of physical complaints should be investigated.

In the present study, a further non-normal parameter that was found in cluster No. 2, but not in cluster No. 1, was glomerular filtration rate (GFR) (Table 3). For patients with a GFR <90 ml/min, the patients in this cluster had a mild grade of chronic renal failure [34]. Renal function declines with the development of frailty [59]. Mental disorders are common in patients with chronic kidney diseases, and there is interdependence between comorbidities over time, and the progression of reduced renal function [60,61].

In this study, in cluster No. 2, multimorbidity, chronic renal failure, and mental disorders, were integrated into a unique, recognizable clinical phenotype. The association with pre-frailty and frailty was supported by the logistic regression models, where the parameter number of chronic diseases, which indicated multimorbidity, and the parameter of somat score, which indicated mental disorders, were selected as predictors of pre-frailty and frailty (Tables 5, 6). The effect of these factors, including the progressive reduction in renal function, was strongly dependent on increasing age. The logistic regression

models suggested by the parameter of age was the strongest predictor of pre-frailty and frailty outcome (Tables 4–7). In this way, our results supported the emerging concept of frailty as unsuccessful aging [61], which is aging burdened with multimorbidity, functional deficits, and frailty, with age-related decline in renal function.

In this study, further support for the recent concepts of frailty in unsuccessful aging was from the findings in cluster No. 3 (Table 3). This cluster also indicated a clinical phenotype that was associated with reduced renal function. However, in contrast to cluster No. 2, there was an increased stage of chronic renal failure, as indicated by the GFR <60 ml/min, and increased age (77.4 *vs.* 70.9 years) (Table 3) [34]. Although the frailty scores of clusters No. 2 and No. 3 were comparable (1.53 *vs.* 1.35), cluster No. 3 contained higher proportions of pre-frail patients and frail patients, which indicated a tendency for patients in this cluster to have a frailty phenotype. These results also provided support for non-linear development of frailty [10]. Also, these results link the concept of unsuccessful aging, which emphasizes the key role of age-related renal function decline in the progression of frailty [61].

Further characteristics of cluster No. 3 support the hypothesis of unsuccessful aging, including increased C-reactive protein (CRP) (8.3 mg/L), anemia (Hb <130 gm/dL), and physical frailty, moderate values of BMI and WC, and more severe chronic renal failure [10,59]. Also, the parameter of mac, which was reduced in this cluster, indicated loss of muscle mass (sarcopenia) (Table 3) [62]. Sarcopenia is a feature of both advanced chronic renal failure and increased frailty [59,63]. The characteristics of the frailty phenotype, indicated by cluster No. 3, were identical to the core elements of frailty, as Fried and colleagues defined them. Logistic regression models were supportive, where parameters included mac, crp, and erit, were used as predictors of pre-frailty and frailty outcome (Tables 4, 5).

Further support for the assumption that the clinical phenotype presented by cluster No. 3 represented the pathway of unsuccessful aging, was shown in this study by the findings from the differences in the distribution of chronic medical conditions (Figures 5, 6). Pre-frailty and frailty status was associated with an increased prevalence of hypertension, cardiovascular disease, and falls, compared with normal non-frail condition (Figure 5). When this assessment was included in the clusters, cardiovascular disease and geriatric conditions tended to accumulate mainly in cluster No. 3 (Figures 6, 7).

The average number of chronic diseases in cluster No. 3 was similar to cluster No. 2 (3.5 *vs.* 3.4) (Table 3), which means that not only the number of chronic diseases but also information on the accumulation of integrated geriatric conditions and functional deficits are essential in identifying frail elderly

patients (Figure 7) [64]. Based on the characteristics of patients in cluster No. 3, it seems that in parallel with increasing physical frailty, there is also a progression in decline in cognitive function. The low values of the Mini-Mental State Examination (MMSE) score (23.4), reached the threshold for the diagnosis of cognitive impairment in this cluster (Table 3) [39]. The association between physical and cognitive frailty was also supported by the logistic regression model, where the MMSE score was found to be a predictor of the pre-frailty and frailty outcome (Table 6).

Therefore, the clinical phenotype in cluster No. 3, unites several lines of evidence, including on the association between frailty and cognitive impairment, and the association between chronic kidney diseases and cognitive impairment [13,65]. Also, the description of this clinical phenotype supports the dose-response effect of the decline in renal function on the increasing risk of cognitive impairment [59]. The dominant appearance of cognitive impairment at higher grades of frailty and advanced stages of chronic renal failure indicated the strong non-linear associations between these factors, which may explain the fact that, in the cluster No. 3, the parameter of the MMSE score, but not the parameter of the somat score, was not normal, despite the fact that this parameter was found to be a stronger predictor of pre-frailty and frailty outcome in the logistic regression model (Table 6).

Conclusions

This study aimed to identify the clustering of comorbidities, cognitive, and mental factors associated with increased risk of pre-frailty and frailty in patients ≥60 years in a primary healthcare setting in eastern Croatia. The findings showed that in patients ≥60 years in a primary healthcare setting, multimorbidity predictors of pre-frailty and frailty included a decline in cognitive function and renal function.

In this study, a multicomponent dataset was used with data collected in the primary healthcare setting. Clustering was used to identify clinical patterns of frailty and pre-frailty that may assist in future planning of prevention strategies. The three overlapping clusters were identified, firstly as obesity and preserved renal function, secondly as multimorbidity with mental disorders and slightly impaired renal function, and thirdly as advanced impaired renal function, cognitive impairment, and physical deficits. Within these clusters, frailty was increasingly found. Predictors of the common outcomes of pre-frailty and frailty were increased age, the number of chronic diseases, loss of the muscle mass, inflammation, anemia, anxiety somatic and cognitive impairment. Age-related decline in renal function is an important factor in the development of frailty with age.

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