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► To cite this version:

František Babič, Ljiljana Trtica Majnarić, Sanja Bekić, Andreas Holzinger. Machine Learning for Family Doctors: A Case of Cluster Analysis for Studying Aging Associated Comorbidities and Frailty. 3rd International Cross-Domain Conference for Machine Learning and Knowledge Extraction (CD-MAKE), Aug 2019, Canterbury, United Kingdom. pp.178-194, 10.1007/978-3-030-29726-8_12 . hal-02520059

HAL Id: hal-02520059

<https://inria.hal.science/hal-02520059>

Submitted on 26 Mar 2020

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Machine Learning for Family Doctors: A Case of Cluster Analysis for studying Aging Associated Comorbidities and Frailty

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Abstract. Many problems in clinical medicine are characterized by high complexity and non-linearity. Particularly, this is the case with aging diseases, chronic medical conditions that are known to tend to accumulate in the same person. This phenomenon is known as multimorbidity. In addition to the number of chronic diseases, the presence of integrated geriatric conditions and functional deficits, such as walking difficulties, of frailty (a general weakness associated with weight and muscle loss and low functioning) are important for the prediction of negative health outcomes of older people, such as hospitalization, dependency on others or pre-term mortality. In this work we identified *how* frailty is associated with clinical phenotypes, which most reliably characterize the group of older patients from our local environment: the general practice attenders. We have performed a cluster analysis, based on using a set of anthropometric and laboratory health indicators, routinely collected in electronic health records. Differences found among clusters in proportions of prefrail and frail versus non-frail patients have been explained with differences in the central values of the parameters used for clustering. Distribution patterns of chronic diseases and other geriatric conditions, found by the assessment of differences, were very useful in determining the clinical phenotypes derived by the clusters. Once more this study demonstrates the most important aspect of any machine learning task: the quality of the data!

Keywords: aging comorbidities, complexity, data-driven clustering

1 Introduction

The general trend towards an ageing population in our western society is still unbroken, and life expectancy is even rising [1]. This poses enormous future challenges for the medical profession in general and particularly for the daily practice of family doctors (general practitioners, GP's).

Aging is often associated with the burden of chronic diseases [2]. However, some older patients with chronic diseases are more vulnerable than others in the development of negative health outcomes, including hospitalization, falls, disability, low physical and mental functioning, dependency on others and most of all to pre-term mortality [3]. The clinical signs of this vulnerable state have been identified by the gerontologists and include the following features: decreased muscle mass and strength, general weakness, slow gait speed, impaired balance and generally low activity [4]. This is termed frailty and explained by the reduced reserve capacity of various physiological systems, due to the aging process and accumulation of chronic medical conditions [5]. There are numerous diagnostic criteria for assessing frailty, that can be divided into the two principal groups: tests that focus physical functions of frailty and a more comprehensive approach, based on the Cumulative Deficit Model of Frailty (the Frailty Index), which accounts for a broad range of medical, cognitive, psychological and functional deficits [6].

Frailty is a new concept, and precise theory is still missing. There are several assessment tools (or predictive models), but it may not be the best solution. One of the most widely used tests for assessing physical frailty is the Fried Phenotypic Model of Frailty [4]. It is based on the assessment of the small number of measurable components, including slow walking speed, low grip strength (measured by the hand grip dynamometer), self-reported exhaustion, unintended weight loss, and low physical activity. The credibility of this instrument relies on the fact that it has been derived from data of the large epidemiologic study. In line with the proposed evolutive and dynamic nature of frailty, this instrument includes also a prefrailty state [4, 5]. Gradation is based on disorder counting, so that 1-2 disorders indicate prefrailty and 3-5 indicate frailty [4].

In general, determinants of frailty may be divided into three groups: 1) chronic diseases and conditions associated with disability, such as falls and walking difficulties; 2) markers of physiological systems disturbance; and 3) behavioural and societal factors, such as nutrition, low socioeconomic status and low education [7]. Some chronic diseases were found in epidemiological studies as being more often associated with frailty, than some others, including: diabetes, cardio-vascular disease (CVD), malignant disease, chronic obstructive pulmonary disease (COPD) and chronic renal failure [2, 8, 9].

In the fundamental study on frailty, Fried and coll. have shown that the risks for the development of prefrailty and frailty increase in parallel with the number of chronic diseases and the number of pathophysiology disorders, described with measures of anaemia, inflammation, micronutrient deficits, metabolic regulatory factors, body composition and neuromuscular function [5]. This study has provided a

rationale for non-linearity in the development of frailty and heterogeneity of older people concerning prefrailty and frailty.

In this study, we have attempted to go a step forward and to show how prefrail and frail older people are distributed within the “naturally formed groups” or clusters, defined by the set of parameters which indicate significant pathophysiology disorders associated with frailty. We used only easily available data from General Practice (GP) electronic health records (eHRs) and patient self-reports. To identify the most important chronic diseases and geriatric disabling conditions that are associated with particular clusters, we have assessed their differences among the clusters.

Clustering methods are still rarely used in medical research and have been shown to be appropriate for grouping patients with chronic medical conditions and comorbidities, which are known to usually overlap between patients. The solving of such problems is like copying with the system’s complexity. These methods allow insights into the “natural” grouping of patients, that is, in case when theoretical assumptions of the way of their grouping (classification) are low. The main point which we have taken into account when making a decision to use the clustering or the classification methods, was “the quantity“ of theory, or how much the postulated hypothesis is convincing. The clustering methods allow a higher degree of uncertainty, than the classification methods, or take a larger, still unknown context, or may be used when we wish to reconcile the old hypothesis, to provide a new paradigm. In contrast to this, the classification methods need a strongly grounded theory and are, consequently, more predictive, than the clustering methods.

We assume that by using this methodology approach, it would be possible to identify clinical patterns that in some local population are mostly associated with frailty. The final aim is to implement the efficacious strategy for recognizing older people, GP patients, who are at increased risk for negative health outcomes. We believe that this study will add value to the requirements that screening of older people on frailty become the standard procedure in PC [10]. In general, using predictive machine learning enables the discovery of potential risk factors which provides the family doctor with information on a probable patient outcome and to react promptly and to avert likely adverse events in advance [11].

1.1 Related Work

To our knowledge, studies with similar approaches ~~to our~~ have not been published to date. The only study that we could find was based on using single measures of physical performance and cognitive function impairment tests, to identify clusters [12]. A similar paper, by ourselves, has been prepared on the smaller sample and with a larger set of parameters, is now under review in the journal devoted to analytical, clinical research, but is not in conflict with this conference paper.

Bertini et al. proposed two predictive frailty models for subjects older than 65 years old by exploiting information from 12 socio-clinical databases available in the Municipality of Bologna [13]. The authors take into account many diagnoses and functional conditions that may be impaired (decreased). They also noted that the frailty has not yet emerged as a well-defined clinical or social concept. Clegg et al. tried to

develop and validate an electronic frailty index (eFI) using routinely available primary care electronic health record data [14]. For this purpose, they used anonymized data from a total of 931 541 patients aged 65-95. The eFI enables identification of older people who are fit, and those with mild, moderate, and severe frailty.

Both presented works represent a relatively tricky and lengthy method for daily usage. By clustering methods, we can narrow this high heterogeneity of patients (based on different combinations of many diseases and disorders) and limit it to only several subgroups - these subgroups are clusters (defined according to a less number of the main features). Also, the results of some large-scale studies, such as that which include older people with multiple chronic medical conditions, may not be applied directly to the local situation, because of the large variability between populations. Thus, small datasets are appropriate for use, when there is a need that the results of research inform local healthcare providers.

2 Data Analysis

A retrospective analytical study was conducted during 2018, in the General Practice (GP) setting, in the town of Osijek, eastern Croatia, during a six-month follow-up. Only GP attenders, old 60 years and more, and not those on home care, were included in the study. Patients were assessed at their regular encounters and were recruited if they gave their written informed consent. Exclusion criteria included: acute medical conditions, worsening of chronic conditions, dementia and active chemo- or biological therapies.

Our dataset contained 261 records characterized by 10 numerical variables (89 males and 172 females). We present these variables as average and standard deviation (SD) and as median and interquartile range (Table 1).

Table 1. Descriptive statistics of the numerical variables.

Variable	Min	Max	Median (interquartile range)	Mean (standard deviation)
Age (years)	60	90	71.00 (10.00)	71.16 (6.43)
BMI (kg/m ²)	14.33	47.05	29.71 (5.78)	30.21 (4.71)
Waist circumference (cm)	50.00	148.00	99.00 (16.00)	99.88 (12.58)
Mid arm circumference (cm)	18.00	45.00	31.00 (5.00)	31.38 (3.66)
Fasting glucose (mmol/L)	3.60	16.20	5.60 (1.70)	6.24 (1.91)

Total cholesterol (mmol/L)	2.90	9.70	53.70 (1.70)	5.73 (1.33)
LDL cholesterol (mmol/L)	1.20	8.90	3.50 (1.50)	3.53 (1.18)
Glomerular filtration rate (mL/min/1.73 m ²)	24.00	191.00	86.00 (37.00)	87.25 (26.42)
Haemoglobin (g/L)	54.00	177.00	137.00 (15.00)	137.00 (13.49)
Haematocrit (g/L)	0.22	1.00	0.42 (0.04)	0.42 (0.05)

The quality of the data matters more than the selected model or the selected algorithm, therefore data-pre-processing is the most important step for all machine learning tasks.

In practice, it's rare that the number of clusters in the dataset is known at the beginning of the experiments. One possibility of how to identify the most suitable number of clusters (k value in the case of the K-Means algorithm) is Elbow method [15], [16]. This method provides a graphical visualization and uses the percentage of variance explained as a function of the number of clusters.

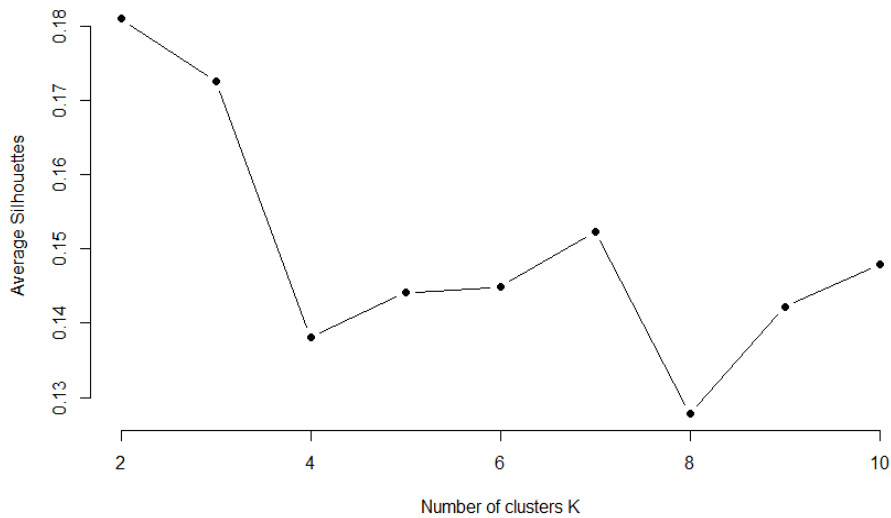


Fig. 1. The results of Average silhouette method.

The idea is to run this method on the dataset for a range of values of k (for example k from 1 to 10), and for each value of k calculate the total within-clusters sum of squared errors. On the graph, the first clusters will add much information (explain a lot of variances), but at some point the marginal gain will drop, giving an angle in the

graph [15]. This point represents the expected number of clusters. The Elbow method also has some limitation such as the elbow is not always unambiguously identified. In this case, we can use the Average silhouette method calculating how well each object lies within its cluster. The optimal number of clusters k is the one that maximizes the average silhouette over a range of possible values for k [17]. We calculated the maximal values for the 2 or 3 possible clusters (Figure 1). Based on the data characteristics, we finally choose the 3 as k -value.

For clustering we selected the K-Means algorithm as a very popular technique to partitioning data sets with numerical attributes [18]. It is an unsupervised learning algorithm constructing a partition of a data of n objects into a set of k clusters. The k -value has to be specified at the beginning. Each cluster is represented by its centre. Next, we were looking for differences among them in other features (expressed by the categorical variables – gender, diagnoses, etc.)

We applied the K-Means algorithm to pre-processed data:

- The dataset contained only numerical variables like age, bmi, waist Circumference (wc), mid-arm circumference (mac), fasting glucose (glu_f), cholesterol (chol), low-density lipoprotein (ldl), glomerular filtration rate (gfr), hemoglobin (hb) and hematocrit (htc).
- All variables were normalized based on the z-score standardization (transforms all the variables to a mean value of 0 and a standard deviation of 1).

3 Results

We constructed 3 clusters visualized in Figure 2, distinguished by the signs. The Principal Component Analysis (data points are plotting according to the first two principal components coordinates) generates the plot and an ellipse is drawn around each cluster (but not represented a boundary).

The centres of the clusters are characterized by the relevant value of each input variable, see Table 2.

Table 2. The clusters centres.

Number of cases	Clusters	age	bmi	wc	mac	glu_f	chol	ldl	gfr	hb	htc
66	1	67.560	30.950	100.154	32.467	5.619	6.798	4.469	96.275	139.835	0.437
92	2	71.113	34.641	112.968	34.145	7.900	4.650	2.556	105.758	143.161	0.435
103	3	74.213	27.031	92.134	28.875	5.806	5.455	3.306	169.028	131.129	0.402

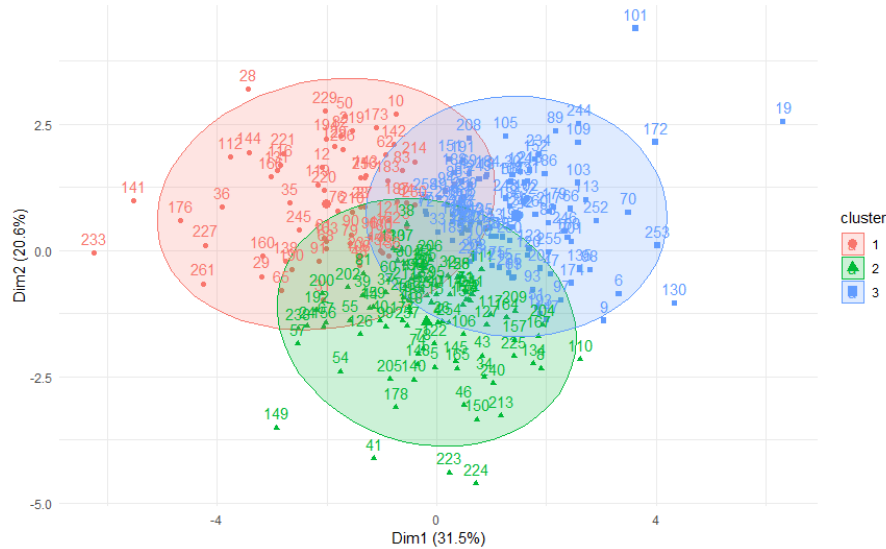


Fig. 2. The plot of 3 constructed clusters.

We evaluated the differences between clusters. We started with the proportion of prefrail and frail vs. non-frail patients in our dataset. The cluster 2 contains the highest number of non-frail patients (51). On the other hand, the numbers of prefrail or frail patients in the first and second clusters are relatively similar. The highest number of prefrail patients characterizes the third cluster. The gender ratio of cluster1 is relatively balanced (1:1); the next two have a different one 2.5:1.

The Kruskal-Wallis test by rank is a non-parametric alternative to the one-way ANOVA test when we have more than two groups [19, 20]. As the p-value is less than the significance level 0.05, we can conclude that there are significant differences between the clusters (Table 3). For this purpose we used the following list of variables:

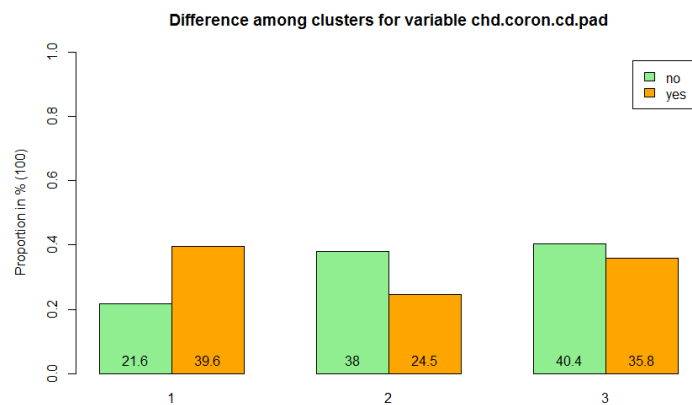
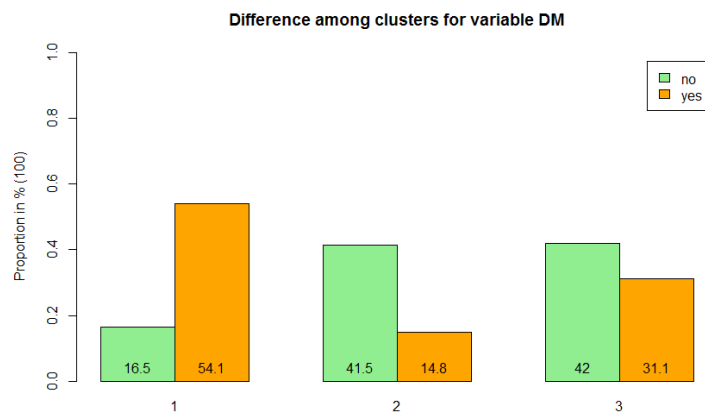
- The number of diagnoses of chronic diseases (som com).
- Selected diagnoses of chronic diseases: diabetes mellitus (dm), chronic obstructive pulmonary disease (copd) or asthma, cardio-vascular disease (cvd), including coronary heart disease (chd) or cardio-vascular disease or peripheral arterial disease (pad), malignant disease (malig), osteoporosis (osteop), low back pain (low back), osteoarthritis (oa).
- Geriatric syndromes other than frailty: urogenital disease or urinary incontinence (urogenit incont), visus impairment (visus), hearing loss (hear), falls (with or without bone fracture) (fall nf, f), walk difficulties (walk).

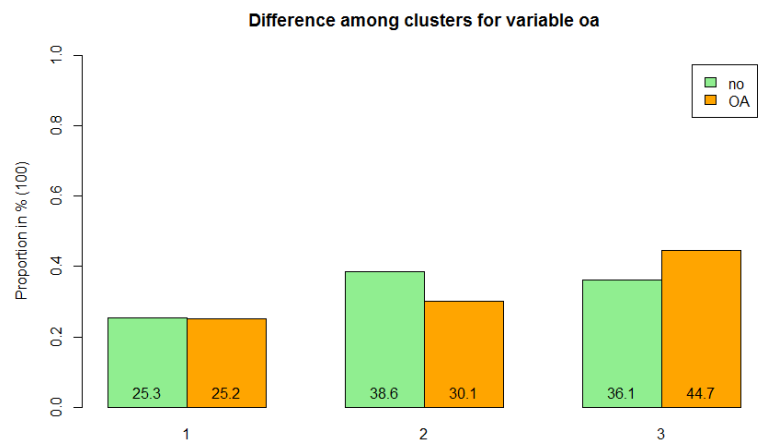
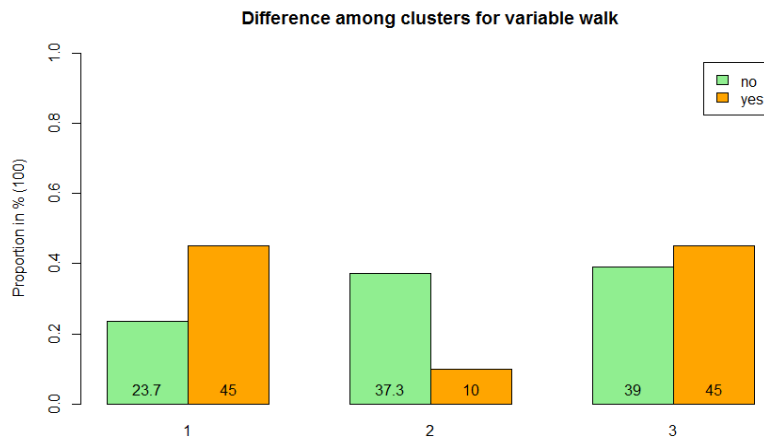
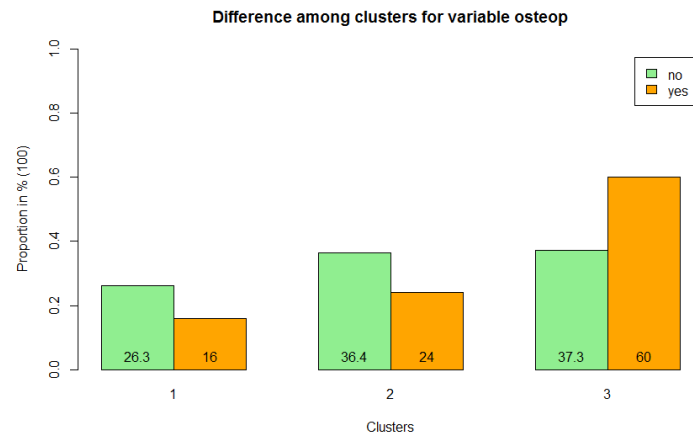
Table 3. Differences between clusters - Kruskal-Wallis test by rank.

Variable (clusters)	Kruskal-Wallis rank sum test
som com	0.003

dm	<i>0.0000001</i>
copd_asthma	0.690
chd_coron_cv_pad	<i>0.021</i>
malig	0.753
osteop	0.088
low back	0.929
oa	0.254
urogent_incont	0.449
visus	0.609
hear	<i>0.045</i>
fall	0.083
walk	<i>0.025</i>

For selected variables, we investigate the difference among the clusters in graphical form (Figure 3). The percentages were calculated on the whole 261 records.





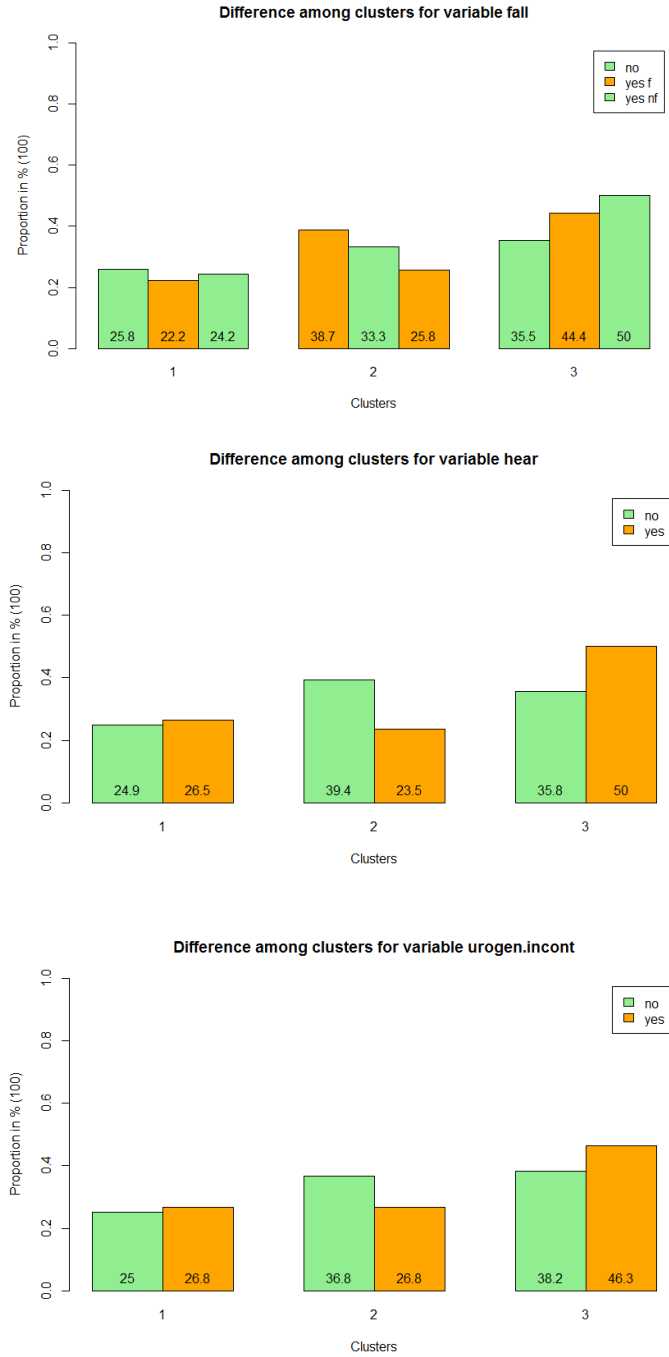


Fig. 3. Particular chronic medical conditions among clusters.

The proportion of chronic diseases and various impairments also differs among the clusters (Figure 4, Figure 5)

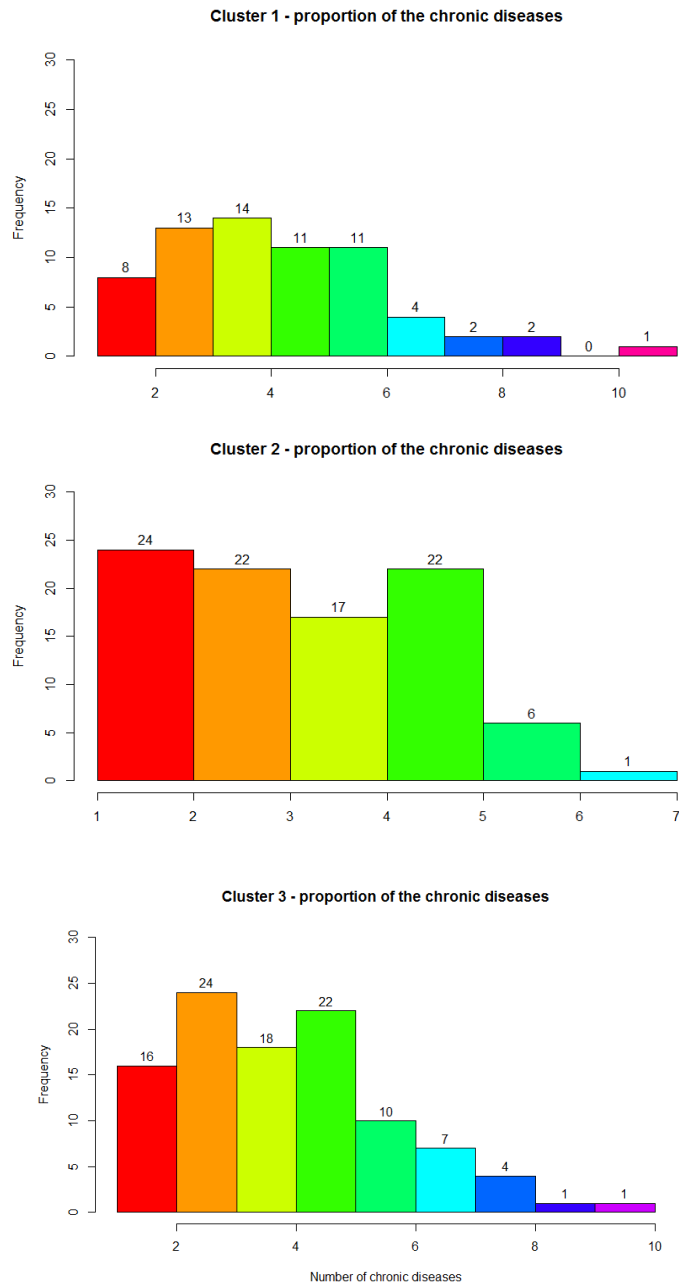


Fig. 4. The number of diagnoses of chronic diseases among clusters.

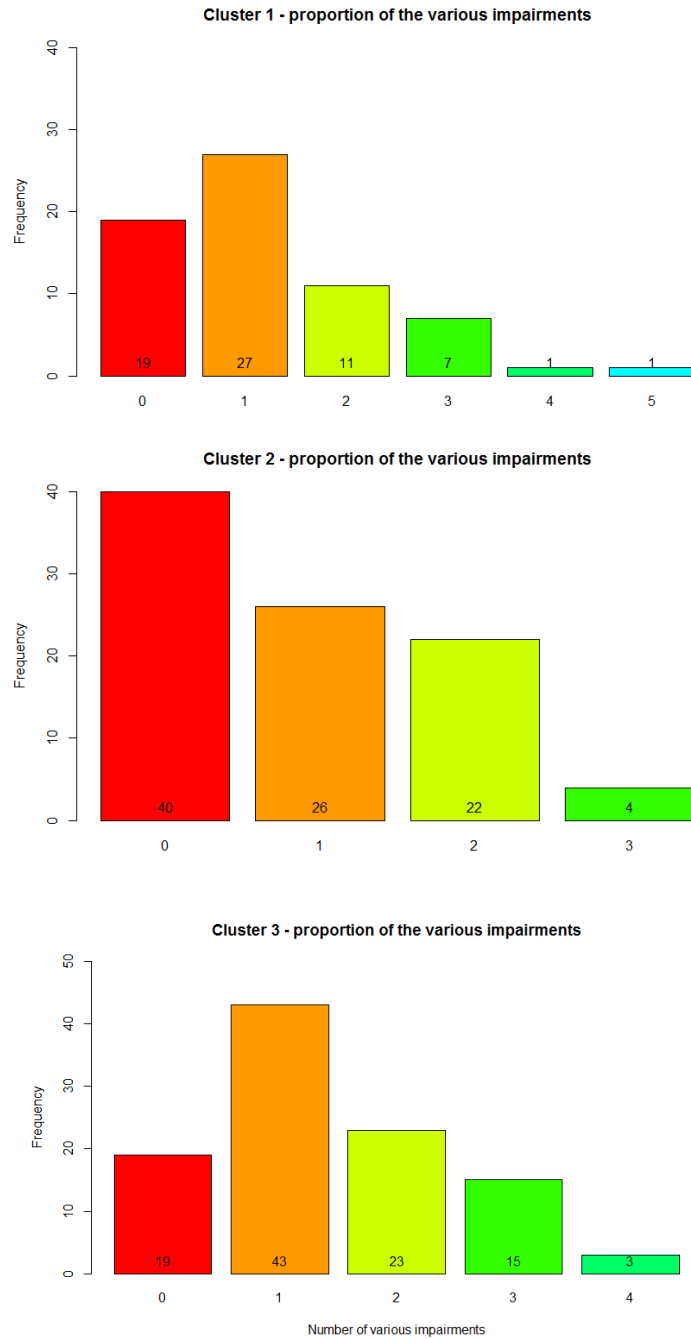


Fig. 5. The number of various impairments like urogenital or incontinence, falls, hear, walk and chronic pain among clusters.

We used the Kruskal-Wallis test also for an evaluation of the difference between three target categories of the patients: prefrail, frail and non-frail (Table 4)

Table 4. The difference between prefrail, frail, and non-frail patients.

Variable (prefrail/frail vs non-frail)	Kruskal-Wallis rank sum test
som com	<i>0.0003</i>
dm	0.954
copd_asthma	0.315
chd_coron_cv_pad	0.065
malig	0.527
osteop	<i>0.005</i>
lumb	0.127
oa	<i>0.006</i>
urogent_incont	0.202
visus	0.891
hear	<i>0.012</i>
fall	<i>0.002</i>
walk	<i>0.0000000006</i>

4 Discussion

We used a small set of laboratory and anthropometric measures, to describe the participants' health status, and the clustering procedure, to identify major clinical phenotypes within the group of older PC patients from the local community (Tables 1 and 2). Surprisingly, the values of the collected parameters have shown a large degree of diversity (Table 1). On the other hand, this characteristic is in line with non-linear age-related dysregulation of multiple body systems, which stays in the background of the clinical expression of multimorbidity [3, 5].

The three clusters have been identified, each containing 66, 92 and 103 patients (Table 2). They overlap to some degree with each other, which is usual in people with multiple comorbidities and accounts for their exceptional heterogeneity (Figure 2) [2],[3].

These characteristics of people in the sample, heterogeneity, and overlapping, are also emphasized by the distribution patterns of prefrail and frail patients in the clusters. Namely, in all three clusters, there are also non-frail, prefrail, and frail patients, but presented with different proportions, their patterns depending on characteristics of patients in the clusters.

Analysis of the clusters has shown that patients in the clusters No. 1 and No. 2 are of a lower age than those in the cluster No. 3 (67.5, 71.1 and 74.2 years, respectively),

and characterized with high values of bmi and wc measures (30.95 vs 34.64 and 100.15 vs 112.96), which according to the knowledge indicate obesity, in the case of the cluster No. 2, even extreme obesity (Table 2) [21].

These two clusters have similar proportions of prefrail and frail vs. non-frail patients; this ratio being somewhat higher in cluster No. 1. Despite these similarities, patients in these two clusters also show some important differences, such as significantly higher proportions of patients diagnosed with diabetes and CVD, in the cluster No. 1, which according to the evidence are two conditions strongly associated with both, obesity and frailty (Table 3) (Figure 3) [22, 23]. This fact can explain a higher proportion of patients in the cluster No. 1 who have reported subjective difficulties in walk, indicating a higher level of physical disability of patients in this cluster, compared to the cluster No. 2 (Table 3) (Figure 3). Some recently published papers highlight the role of measuring gait speed in the screening of patients with CVD who are in particular vulnerability for negative outcomes of hospitalization and surgery [24].

These differences between the clusters No. 1 and 2 may also be associated with differences in participation of males vs. females in these two clusters, as the participation of the males in the cluster No. 1 is relatively higher, than in the cluster No. 2, and compared to the whole sample. Related to these results, it is known that women, in general, gain obesity, and subsequently diabetes and CVD, later than men in the life course, yet in the age after menopause [25]. This fact may explain our results that women, who make a prevalent part of patients in the cluster No. 2, are characterized with an extreme obesity (Table 2), but are still not dominated with diabetes, as it is the case with obese patients in the cluster No. 1 (Figure 3). Extreme obesity has been recognized as a possible cause of prefrailty and frailty, although this fact is in contradiction to what is, in general, considered under the term of frailty, including weakness, muscle loss and unintended weight loss [4, 26].

The cluster No. 3 contains the oldest patients (the prevalent age 74.2 years), who, distinctly from patients in the other two clusters, have reduced renal function (as indicated with the parameter $\text{gfr}=69.02$ vs. 96.27 and 105.75) (Table 2). According to the evidence, frailty is strongly associated with progressive renal impairment, which in this study is highlighted with the highest proportion of prefrail and frail vs non-frail patients, found in cluster No. 3 (a ratio of about 2.6 vs 1.4 and 1.3), compared to the other two clusters [27].

Other characteristics of patients in this cluster, which are markedly different from those in other two clusters, include the lack of obesity (indicated with values of the parameters $\text{bmi} = 27.03$ and $\text{wc} = 92.13$) and reduced muscle mass (indicated with the parameter $\text{mac} = 28.87$ vs. 32.46 and 34.14) [28].

A clinical phenotype that relies on the description with these parameters can be characterized as muscle wasting and frailty, reflecting the both, highly developed levels of frailty and significantly reduced renal function [4, 29]. Other characteristics of patients in this cluster, including lower (than in other two clusters) values of the parameter hb , indicating anemia, and the parameter htc , indicating decreased blood viscosity, as well as moderate (not elevated) values of the parameters fglu and chol , indicating the metabolic status, fasting glucose and total serum cholesterol, are in line with this proposed clinical phenotype [29, 30].

When comorbidities associated with particular clusters were analyzed, a tendency for disorders accumulation has been recognized in cluster No. 3, compared to the other two clusters. This is indicated with the highest proportions, in this cluster, of patients having 3 or more diagnoses of chronic diseases (frequencies 45:46:63) (Figure 4). This tendency is even more emphasized when integrated geriatric conditions are considered, including walking difficulties, falls, hearing loss, urinary incontinence and chronic pain (frequencies 47:52:84) (Figure 5). Of particular disorders, the most prevalent ones, in the cluster No. 3, compared to other two clusters, were: osteoporosis, falls and hearing loss (significant differences) and osteo-arthritis and urinary incontinence (non-significant) (Table 3) (Figure 3). These results, indicating functional disorders accumulation in people of older age, with high levels of frailty expression, can find their support in the growing body of evidence [31]. What is emphasized in this study is the key role of renal function impairment in the development of higher levels of frailty expression. This message is in line with the concept of unsuccessful aging, the course of aging that has been turned towards the development of renal function decline, multimorbidity, functional deficits and frailty [29].

The non-linearity in frailty development, on distribution patterns of chronic medical conditions in the clusters, is visible in Tables 3 and 4. Significant differences among clusters were found in diagnoses of diabetes and CVD (Table 3). When prefrail and frail vs non-frail patients were considered, significant differences were found in diagnoses of osteoporosis and osteo-arthritis, both conditions known to be directly associated with frailty and difficulties in walk (Table 4). The patient group consisted of only prefrail and frail patients, in a great part resembles characteristics of the cluster No. 3, where osteoporosis, osteo-arthritis and other physical dysfunctions have shown a tendency to accumulate (Figures 3 and 5).

5 Conclusions and Future Outlook

For medical research, we usually select a standard, already proved a machine learning method, to ensure the reproducibility of the results. What is innovative in this paper is a research approach, that is, a use of a combination of ML and statistical and graphical methods, for solving a complex medical problem. This research approach requires a significant input of a medical researcher in designing research. The clusters can be considered as a first level analytical method, the results of which can inform more consistent future models.

There is a problem in medical research of small dataset conditions, such as the need for research within one health institution or when the size of dataset is constrained by the complexity and a high cost of large-scale experiments. To meet these constraints, many theoreticians in ML methods, try to adapt these methods to be accurate and appropriate for use in small datasets [32].

By using a set of simple parameters from the general practitioners both electronic health records and patient self-reports, together with the clustering method, it was possible for them to discover new insights into the main clinical phenotypes of the group of older patients from the local community and their associated rates of prefrail

and frail patients. This is an important problem-solving task, characterized by non-linearity and high complexity, which requires a data-driven analytical approach. The setting of a general practitioner is an ideal place for conducting such research, because it provides access to a very large amount and a huge variety of medical data combined with the broad implicit knowledge of the GP. Moreover, this study showed again that the *data-quality* matters most.

There is an urgent need for a closer collaboration between medical experts, particularly general practitioners and machine learning experts. If the GP's want to use the full capability of what can be done by machine learning, there is a need in the near future to include it to the daily routine workflows of the GP's. This calls for simple to use Human-AI Interaction, fostering to understand the data within the context of a medical problem and to support decision making under the constraint of increasing workload and time pressure. Consequently, such methods must be trustworthy, and this requires explainability on demand. To reach such a level of explainable medicine it needs much future research in explainability [33] and causability [34].

Ethics Statement. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, JJ Strossmayer University, Osijek (Ethics approval number 641-01/18-01/01).

Acknowledgements. This work was partially supported by the Slovak Grant Agency of the Ministry of Education and Academy of Science of the Slovak Republic under grant no. 1/0493/16 and The Slovak Research and Development Agency under grants no. APVV-16-0213 and APVV-17-0550.

References

1. Kleinberger, T., Becker, M., Ras, E., Holzinger, A., Müller, P.: Ambient Intelligence in Assisted Living: Enable Elderly People to Handle Future Interfaces. In: Stephanidis, C. (ed.), Springer, Heidelberg, Berlin, New York, 103-112 (2007).
2. Barnett, K., Mercer, S.W., Norbury, M., et al.: Epidemiology of multimorbidity and implications for health care, research and medical education: a cross-sectional study. *Lancet* 38, 37-43 (2012)
3. Onder, G., Palmer, K., Navickas, R., et al.: Time to face the challenge of multimorbidity. A European perspective from the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). *European Journal of Internal Medicine* 26, 157-159 (2015).
4. Fried, L.P., Ferrucci, L., Darer, J., et al.: Untagling the concepts of disability, frailty and comorbidity: implications for improved targeting and care. *Journal of Gerontology* 59, 255-263 (2004).
5. Fried, L.P., Qian-Li, X., Cappola, A.R., et al.: Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences* 64(10), 1049-1057 (2009).
6. Rockwood, K., Andrew, M., Mitniski, A.: A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences* 62, 738-743 (2007).

7. Lang, P.O., Michel, J.P., Zekry, D.: Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 55, 539-549 (2009).
8. Hanlon, P., Nicholl, B.I., Dinesh, J.B., et al.: Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analyses of 493 737 UK biobank participants. *Lancet Public Health* 3, e323-e32 (2018).
9. Nixon, A.C., Bampouras, T.M., Pendleton, N., et al.: Frailty and chronic kidney disease: current evidence and continuing uncertainties. *Clin Kidney J* 11(2), 236-245 (2018).
10. Wallace, E., Salisbury, C., Guthrie, B., Lewis, C., Fahey, T., Smith, S.M.: Managing patients with multimorbidity in primary care. *BMJ* 350, h176 (2015).
11. Hassler, A.P., Menasalvas, E., García-García, F.J., Rodríguez-Manas, L., Holzinger, A.: Importance of medical data preprocessing in predictive modeling and risk factor discovery for the frailty syndrome. *Springer/Nature BMC Medical Informatics and Decision Making* 19(1), 33 (2019)
12. Bandelow, S., Xu, X., Xiao, S., Hogervorst, E.: Cluster analysis of physical and cognitive ageing patterns in older people from Shanghai. *Diagnostics* 6(11), 2-13 (2016).
13. Bertini, F., Bergami, G., Montesi, D. et al.: Predicting Frailty Condition in Elderly Using Multidimensional Socioclinical Databases. In *Proceedings of the IEEE* 106(4), 723-737 (2018)
14. Clegg, A., Bates, C., Young, J., et al.: Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age and Ageing* 45(3), 353-360 (2016)
15. Ketchen, D.J., Shook, C.L.: The application of cluster analysis in Strategic Management Research: An analysis and critique. *Strategic Management Journal* 17(6), 441-458 (1996).
16. Kodinariya, T.M., Makwana, P. R.: Review on determining number of Cluster in K-Means Clustering. *International Journal of Advance Research in Computer Science and Management Studies* 1(6), 90-95 (2013).
17. Kaufman, L., Rousseeuw, P.J.: *Finding Groups in Data: An Introduction to Cluster Analysis*. John Wiley & Sons, Inc. (1990).
18. MacQueen, J. B.: Some methods for classification and analysis of multivariate observations. In: *Proceedings 5th Berkeley Symposium on Mathematical Statistics and Probability*, 281-297 (1967).
19. Kruskal, W.: Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association* 47(260), 583-621 (1952).
20. Corder, G.W., Foreman, D.I.: *Nonparametric Statistics for Non-Statisticians*. Hoboken: John Wiley & Sons, 99-105 (2009).
21. Rydén, L., Grant, P.J., Anker, S.D., et al.: ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *European Heart Journal* 34, 3035-3087 (2013).
22. Sinclair, A.J., Rodríguez-Mañas, L.: Diabetes and Frailty: Two Converging Conditions? *Canadian Journal of Diabetes* 40(1), 77-83 (2016)
23. Afilalo, J., Karunanathan, S., Eisenberg, M.J., Alexander, K.P., Bergman, H.: Role of frailty in patients with cardiovascular disease. *Am J Cardiol* 103(11), 1616-1621 (2009).
24. Chen, M.A.: Frailty and cardiovascular disease: potential role of gait speed in surgical risk stratification in older adults. *J Geriatr Cardiol* 12(1), 44-56 (2015).
25. Chae, C.U., Derby, C.A.: The menopausal transition and cardiovascular risk. *Obstet Gynecol Clin N Am* 38, 477-488 (2011)

26. Porter Starr, K.N., McDonald, S.R., Bales, C.W.: Obesity and physical frailty in older adults: a scoping review of intervention trial. *Journal of the American Medical Directors Association* 15, 240-250 (2014)
27. Cook, W.L.: The intersection of geriatrics and chronic kidney disease: frailty and disability among older adults with kidney disease. *Advances in Chronic Kidney Disease* 16(6), 420-29 (2009).
28. Karniya, K., Masuda, T., Matsue, Y., et al.: Complementary role of arm circumference to body mass index in risk stratification in heart failure. *JACC Heart Failure* 4, 265-273 (2016).
29. Walker, S.R., Wagner, M., Tangri, N.: Chronic kidney disease, frailty and successful aging: a review. *Journal of Renal Nutrition* 24, 364-370 (2014).
30. Fried, L.P., Tangen, C.M., Walston, J., et al.: Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 56, 146-156 (2001).
31. Davidson, J.G.S., Guthrie, D.M.: Older adults with a combination of vision and hearing impairment experience higher rates of cognitive impairment, functional dependence and worse outcomes, across a set of quality indicators. *J Aging Health*, 1-24 (2017).
32. Shaikhina, T., Khovanova, N.: Handling limited datasets with neural networks in medical applications: a small-data approach. *Artef Intell Med* 75, 51-63 (2017)
33. Holzinger, A.: From Machine Learning to Explainable AI. In: 2018 World Symposium on Digital Intelligence for Systems and Machines (DISA), pp. 55-66. (2018)
34. Holzinger, A., Langs, G., Denk, H., Zatloukal, K., Mueller, H.: Causability and Explainability of AI in Medicine. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery* (2019)