

## Prevalence of frailty in older people in Veneto (Italy)\*

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### ABSTRACT

**Context:** Both frailty and multimorbidity are strong predictors of clinical endpoints for older people. In Italy, the interventions targeting chronicity are mainly based on the treatment of diseases: sufficient epidemiological literature is available about these strategies. Less is known about the territorial distribution of the frailty status.

**Aims:** To estimate the prevalence of frailty in older people (65+) and to evaluate the relationship between frailty and multimorbidity.

**Methods and material:** A group of general practitioners working in Veneto (Italy) was enrolled on a voluntary basis. Older individuals were both community dwelling and institutionalized patients, that is, the older people normally followed by Italian general practitioners. A centrally randomized sample was extracted from the pool of physician-assisted elderly. Each doctor evaluated the frailty status through the CSHA Clinical Frailty Scale and the multimorbidity status through the Charlson score (Frailty = CSHA Clinical Frailty Scale's score >4; serious multimorbidity = Charlson score ≥4). Prevalence and its confidence interval (CI) 95% were evaluated through the Agresti's method for proportions. The relation between frailty and multimorbidity was studied through a logistic regression model adjusted for age and sex.

**Results:** Fifty-three physicians were enrolled, whose population of elderly individuals ( $N = 82919$ ) was highly representative of the population of Veneto. The prevalence of frailty in the randomized sample of 2407 older people was 23.18% (CI 95%: 21.53%–24.91%). Sex was shown to be a strong predictor of frailty (female status OR = 1.58  $p < .0001$ ) and multimorbidity was shown to be an independent predictor only for individuals <85 years of age.

**Conclusions:** In Veneto, more than 20% of elderly people are frail. Physicians should pay close attention to frailty and multimorbidity because both are important prognostic factors toward clinical endpoints relevant to territorial care. The CSHA Clinical Frailty Scale (easy and quick) should become part of their professional routine.

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### KEYWORDS

Elderly; Rockwood Clinical Frailty Scale; frailty; Charlson score; multimorbidity; cross-sectional design; prevalence

## Introduction



Frailty and multimorbidity represent the more important hallmarks of aging and they are a primary concern about the care of older adults<sup>1</sup>. Today, there is an unanimous agreement that frailty should be considered a condition in its own right. Frailty represents an independent risk factor for numerous endpoints<sup>2,3</sup> and it must be clearly distinguished from the conditions of disability and multimorbidity, equally important and independent but often superimposed on it<sup>4</sup>.

The frequent overlap of the three conditions makes the classification of these patients very complex. For example, in a Canadian study of 740 elderly the frail subjects (7.4%) 29.1% were disabled on the ADL scale and 92.7% on the IADL scale and 81.8% were characterized by significant multimorbidity<sup>4</sup>.

The conceptual and operational definition of frailty and the respective models are very different. Although some authors point out the relative independence between frailty and multimorbidity<sup>4</sup>, the issue is complex. For example, many definitions of frailty also take into account the presence of multimorbidity or disability. These conditions can be independent endpoints but at the same time can themselves predispose to a greater risk of frailty<sup>3</sup>. So, the debate on whether incorporating multimorbidities or disabilities in the scales is still open.

In fact, the multimorbidity as a frailty item generally represents a share of irreversible frailty (eg: stroke, osteoporosis): that does not conform to the concept of a reversible and dynamic condition, accepted by other authors<sup>5</sup>.

Furthermore, the frailty models adopted by researches are extremely heterogeneous, while in some researches disability

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is considered as an outcome and in others as a determinant of the frailty status.

The prevalence of frailty shows to be so very heterogeneous, depending on the definition adopted and the tools used for measuring it<sup>6–9</sup>. Few data are available about the Italian territorial setting<sup>10–17</sup>. Liotta<sup>10</sup> evaluated a random sample of 1331 community-dwelling older adults resident in the Lazio-Region of Italy. In this study, a validated questionnaire (the Functional Geriatric Evaluation questionnaire) was administered by trained public health nurses. Prevalence of frail ( $FS \geq 10$ ,  $\leq 50$ ) and very frail ( $FS < 10$ ) individuals was 13.9% and 7.6%, respectively.

Roppolo<sup>11</sup> examined 267 community-dwelling older adults through Cardiovascular Health Study (CHS) index and the Tilburg Frailty Indicator (TFI), showing that frailty prevalence rate was strictly dependent on the index used (CHS = 12.7%; TFI = 44.6%). Other Italian experiences investigated the prevalence in the general population of particular forms of frailty (Cognitive Frailty<sup>12,13</sup>; Osteoporotic Criteria for frailty<sup>14,15</sup>) or investigated the prevalence of frailty in particular clinical conditions (dementia<sup>16</sup>) or in hospital settings<sup>17</sup>.

The study of the territorial distribution of frailty and multimorbidity is essential for important welfare implications. In Italy, the interventions targeting chronicity are mainly based on the treatment of diseases: sufficient epidemiological literature is available about these strategies.

For example, for the Veneto-Region, prevalence data on the entire population are available for 50 types of cancer, for chronic renal failure, diabetes, Chronic Obstructive Pulmonary Disease (COPD), rare diseases, celiac disease<sup>18</sup>.

Much less is known about the territorial distribution of social factors that are important determinants of frailty and that are not necessarily associated with diseases. To our knowledge, prevalence studies on frailty based on representative samples of the territorial setting in Italy are very few<sup>10,11</sup>.

The primary objective of our research was to estimate the prevalence of frailty in the older population (i.e. 65+ years) normally assisted by 53 general practitioners in Veneto (Italy). Our study evaluated both community-dwelling and institutionalized people, since Italian general practitioners follow both these kinds of patients.

Secondary objectives were to estimate that prevalence in subgroups categorized by age and sex. Third objective was to explore the relationship between frailty and multimorbidity in order to test the extent to which multimorbidity can in itself be a prognostic factor of frailty.

## Subjects and methods

Our research is an observational cross-sectional study.

Some general practitioners who work in Veneto have been enrolled on a voluntary basis. Everyone had to use the same professional software (Millewin<sup>R</sup>)<sup>19</sup>.

The 53 doctors involved in the initiative were members of the Scientific Society “Società Italiana di Medicina Generale e delle Cure primarie” (SIMG) or sympathizers.

Data of recruited patients were anonymously collected (only the physicians knew the identity of the patients – see below) and were treated in compliance with the laws that regulate privacy and execution of observational research in Italy.

In Veneto, the general practitioners assist this type of older adults: 1. patients who are able to autonomously reach the doctor's office 2. home-dwelling patients who are unable to walk (followed up with home visits) 3. institutionalized patients in nursing homes. All these seniors (i.e. aged 65 and over) constituted the research population of our study.

Each researcher received and decrypted a list of centrally randomized patients. If codes were of deceased patients or for other reasons no longer assisted by the doctor, the researcher had to replace them in casual mode in the manner described in [Appendix C](#).

Frailty was measured through the CSHA Clinical Frailty Scale<sup>20</sup>, particularly suitable for the professional routine in a general practice. The CSHA Clinical Frailty Scale<sup>20</sup> scale allows to calculate a score ranging from one to seven (one: best state, seven: worst state), being the frailty status defined by a score  $>4$ . This instrument was well validated both in reliability and in predictive value<sup>6</sup>.

The multimorbidity was evaluated through the Charlson Index (CCI)<sup>21</sup>, defined by the presence/absence of 23 conditions characterized by different prognostic weights; a CCI  $\geq 4$  characterizes a condition of multimorbidity with clinical significance<sup>22</sup>.

The research took place in two phases.

In the first phase, a unique dataset was constructed, represented by the whole population in charge of the recruited physicians.

Anonymized data were extracted from records of individual physicians through a custom SQL query (details on request). This was built to obtain, in addition to the personal data of all assisted patients (sex, date of birth), also the data relevant to the 23 conditions necessary to calculate the Charlson Index<sup>21</sup>. Each condition was defined through ICD-9 codes<sup>23,24</sup> (see also [Appendix B](#)). The individual patient data were rigorously anonymous in compliance with the current Italian legislation. To judge whether the population assisted by the physicians involved was representative of the general population of Veneto, we compared the composition in sex and age-decades with the official data provided by the region<sup>25</sup>. The comparison was made using both graphic methods and formal statistical tests.

In the second phase, we extracted a random sample of 65+ people from the dataset that we constructed as described for the first phase using a randomization stratified by sex and three classes of age (65–74; 75–84;  $\geq 85$ ). Then, we assigned to physicians their randomized patients identified by an anonymous code. Each doctor decrypted the codes using a utility that we provided and assessed each patient's frailty status using the CSHA Clinical Frailty Scale<sup>20</sup> (details on request). We evaluated the quality of the randomization process comparing the distribution of three classes of age (65–74; 75–84;  $\geq 85$ ) between the entire 65+ aged population and the randomized sample of patients evaluated

**Table 1.** Characteristics of the analyzed sample.

	All	Females	Males
N	2407 (100.00%)	1393 (57.87%)	1014 (42.13%)
Age (sd)	75.97 (7.65)	76.7 (8.00)	74.94 (7.02)
Frailty (Rockwood score > 4) (%)	23.18%	28.06%	16.46%
Multimorbidity (Chalson Score $\geq$ 4) (%)	21.10%	21.80%	20.11%
Myocardial infarct	2.72%	1.21%	4.78%
Congestive heart failure	4.87%	4.17%	5.82%
Peripheral vascular disease	5.09%	2.28%	8.94%
Cerebrovascular disease	21.93%	21.02%	23.18%
Dementia	2.06%	2.66%	1.25%
Chronic pulmonary disease	21.32%	20.26%	22.77%
Connective tissue disease	4.82%	5.92%	3.33%
Ulcer disease	5.53%	4.48%	6.96%
Mild liver disease	0.88%	0.61%	1.25%
Diabetes	18.90%	15.55%	23.49%
Diabetes with end organ damage	0.13%	0.08%	0.21%
Hemiplegia	0.44%	0.38%	0.52%
Moderate or severe renal disease	7.98%	6.75%	9.67%
Any tumor	7.85%	12.22%	1.87%
Lymphoma	1.05%	1.06%	1.04%
Leukemia	0.44%	0.68%	0.10%
Moderate or severe liver disease	0.09%	nd	0.21%
Metastatic solid tumor	0.31%	0.30%	0.31%
AIDS	0.04%	0.08%	nd
Hypertension	70.31%	70.11%	70.58%
Depression	18.29%	21.78%	13.51%
Cellulitis – skin ulcers	5.04%	5.54%	4.37%
Dicumarol use	4.74%	3.79%	6.03%

(\*see main text, see [Appendix D](#)).

Table 1 illustrates the characteristics of the analyzed sample. The chronic conditions (Diagnoses) represent the index diseases for the calculation of the Charlson Index; the percentages identify the prevalence of the diseases into the single strata (All, Females, Males); obviously a patient can have more than one disease.

through the CSHA Clinical Frailty Scale<sup>20</sup>. The comparison was made both graphically and through statistical approach.

Researchers agreed to participate to our research on voluntary basis; therefore, we did not know the quality of their medical records. This problem does not concern the information of frailty status (because all of them received the same instructions) but rather the coding of the necessary 23 conditions for the calculation of the Charlson score<sup>21</sup>, that we had to use for evaluating the relationship between frailty and multimorbidity. For this reason, we evaluated the quality of medical input using an indirect way ([Appendix D](#)).

### Statistical analysis

We calculated the sample size accepting a usual level of confidence (95%) and programming a relative precision of  $\pm 30\%$ . The expected prevalence of frailty that we used in the calculations referred to the proportions of frail individuals detected in three age strata by a cross-sectional study cited by Rockwood<sup>26,27</sup>. After correction for finite population<sup>28</sup> the theoretical sample size corresponded so to 1808 65+ aged individuals. We took into account a drop-out of 20% of physicians, increasing so the sample size to 2260 individuals. The prevalence of 65+ age-stratum in an epidemiological dataset of primary-care medical records in Veneto region is 25.47% (MilleinRete<sup>29</sup>) so the general population capable of generating 2260 elderly was 8873 units. Assuming that a doctor could not examine more than a tenth of his elderly pool, the population necessary to research amounted to 88732 individuals. That is, admitting that an Italian general

practitioner assists 1500 patients on average, 59 general practitioners seemed to be necessary for our research.

We compared the distribution of age-strata between different populations using both graphic methods and formal (Kolmogorov and Smirnov) statistical tests<sup>30,31</sup>.

We evaluated the prevalence of the frailty and its CI 95% in our randomized sample through the Agresti's method for proportions<sup>32</sup>.

We standardized the frailty prevalence by sex and five classes of age ( $\geq 65 < 70$ ,  $\geq 70 < 75$ ,  $\geq 75 < 80$ ,  $\geq 80 < 85$ ,  $\geq 85$ ) using the official data provided by the Veneto region<sup>25</sup>.

We studied the relation between frailty and multimorbidity through a logistic regression model considering as covariates age, sex and comorbidity.

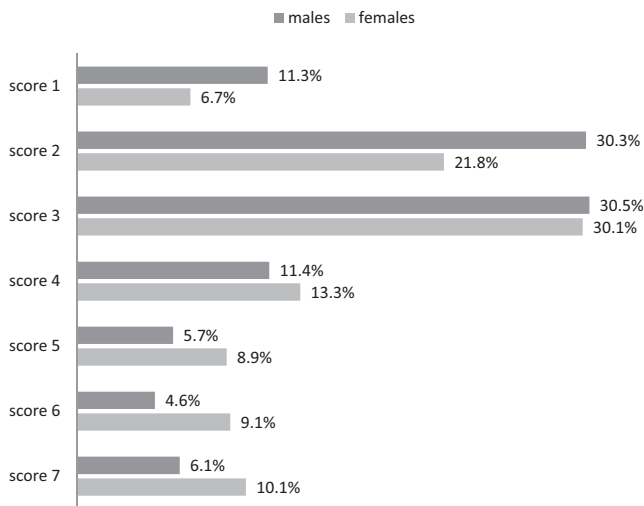
All analyses were done using STATA14 SE software.

### Results

The first phase of the research took place in 18 days; the second in 13 days (for details see [Appendix E](#)).

Fifty-eight general practitioners agreed to be recruited; 53 doctors completed the research, so the general drop-out rate corresponded to 8.6% (i.e. less than half as expected).

The whole population assisted corresponded to 82919 individuals, with a prevalence of 26.32% of subjects aged 65+ ( $N=21825$ ). The distribution of five age classes of this population was almost perfectly comparable to that of the Veneto population illustrated by the official ISTAT data<sup>25</sup> (Kolmogorov–Smirnov test  $p = .979$  – details on request).



**Figure 1.** Distribution of the Rockwoods scores in the 2407 65+ evaluated. For each category, the sum of the percentages gives 100.00%. The distribution of the values of the Rockwood's frailty score shows to be approximately bimodal.

The researchers evaluated the frailty status in 2407 individuals (Table 1).

In detail, 2191 elderly patients were randomized; however, were finally evaluated through CSHA Fraity Scale 2407 subjects. Of these, 2072 had been selected through central randomization; other 335 were not randomized but were evaluated anyway: 119 replaced patients initially randomized but unavailable since dead or no longer assisted (they were chosen by the doctors as described above); the other 216 represented extra selections made in the presence of some ambiguous identification codes (they were selected in the same way).

Forty-nine of the 53 physicians were characterized by good quality of data-input (Appendix D); 2280 of the 2407 evaluated were patients of those (Appendix A). The sex and age-distributions in the whole sample of 65+ aged and in the evaluated and randomized subgroups were well balanced (Appendix A).

Of the 2407 individuals included in our research, 1393 (57.87%) were females; the proportions of women in the three classes of ages were: 54.76% ( $n=621$ ) for the stratum  $\geq 65 < 75$ ; 56.20% ( $n=503$ ) for the stratum  $\geq 75 < 85$ ; 71.16% ( $n=269$ ) for the stratum  $\geq 85$ .

The distribution of CSHA Clinical Frailty Scale's<sup>20</sup> scores in that sample is illustrated in Figure 1; the distribution of these values shows to be roughly bimodal.

The crude prevalence of Frailty (CSHA Clinical Frailty Scale<sup>20</sup> score  $>4$ ) stratified by sex and three age-strata is illustrated in Table 2; for the full sample corresponds to 23.18% (21.53%–24.91%): this estimation can be considered as primary result of our study.

Frailty shows to be more frequent in women respect to men both in the whole sample and in the age-strata. The crude prevalence in the whole sample ( $n=2407$ ) is 28.06% for women and 16.46% for men, while the values for age-strata are: F = 4.21% M = 2.88% for the age-stratum  $\geq 65 < 70$  ( $n=587$ ), F = 10.26% M = 8.94% for the age-stratum  $\geq 70 < 75$  ( $n=547$ ), F = 17.79% M = 14.29% for the  $\geq 75 < 80$  stratum ( $n=536$ ), F = 45.85% M = 28.57% for the  $\geq 80 < 85$

stratum ( $n=359$ ), F = 73.98% M = 55.05% for the  $\geq 85$  stratum.

The standardized prevalence of frailty using as standard population the official data of Veneto region (ISTAT 2017<sup>25</sup>) and sex and five age-classes as covariates corresponds to 22.63% (21.24%–24.02%); see also Appendix F.

The prevalence of frailty status in some frequent clinical conditions are illustrated by Table 4.

We examined the relationship between frailty and multimorbidity after exclusion of four physicians, so the relationship was examined in a subsample of 2280 evaluated patients characterized by optimal data input in their medical records. This subsample was also used to estimate the prevalence of the clinical conditions illustrated in Table 1 and to estimate the prevalence of the frailty in these conditions (Table 4).

The prevalence of significant multimorbidity (i.e. of a Charlson Score  $\geq 4$ ) regards 21.62% of these 2280 elderly patients. The values of the Charlson Index measured in this subgroup ranged from 0 to 12. The proportions of the individual scores were as follows: score 0: 13.99%; score 1: 24.56%; score 2: 23.46%; score 3: 16.36%; score 4: 10.44%; score 5: 5.79%; score 6: 2.5%; score 7: 1.18%; score 8: 0.83%; score 9: 0.61%; score 10: 0.04%; score 11: 0.13%; score 12: 0.09% .

Figure 2 illustrates the prevalence of five mutually exclusives categories. As can be seen, the prevalence of frailty shows to increase with age, while the prevalence of significant multimorbidity tends to decrease.

In detail, the proportions of patients without frailty and without significant multimorbidity (that is with Charlson score  $< 4$  and Frailty score  $\leq 4$ ) showed a strong and progressive decrease with the advance in age. At the same time, the proportions of frail/not multimorbid patients (that is, with Charlson score  $< 4$  and Frailty score  $> 4$ ) and frail/multimorbid patients (Charlson Score  $\geq 4$  and Frailty score  $> 4$ ) shows to increase with the advance in age. On the other hand, the proportions of multimorbid/not frail patients (Charlson Score  $\geq 4$  and Frailty score  $\leq 4$ ) show to increase with age up to the age group  $\geq 75 < 80$  and then to decrease (Figure 2).

Of the 1787 patients characterized by a not significant multimorbidity (Charlson score  $< 4$ ) 311 (17.40%) were frail; conversely, of the 493 patients characterized by significant multimorbidity (Charlson Score  $\geq 4$ ) 279 (56.59%) were not.

We explored the details of the relationship between frailty and multimorbidity through three models of logistic regression (Table 3) in which the condition of frailty was the outcome and age, sex and multimorbidity were the predictors. The model with interaction shows the best goodness of fit and the best response to model-diagnostics (Table 3). To be a female shows to be strongly associated to the frailty status (OR = 1.58  $p < .0001$ ). Also, multimorbidity status (i.e. a Charlson score  $\geq 4$ ) shows to be an independent frailty-predictor but not in the most advanced ages: the variable "age" acts in fact as an important confounder toward multimorbidity. The statistical study of the interaction age/multimorbidity demonstrates for the multi-morbid subjects (i.e. with

**Table 2.** Age and sex distribution of the prevalence of Frailty Status (so defined by a Rockwoods score  $>4$ ) in the sample of 2407 elderly individuals evaluated with the Rockwoods Clinical Frailty Scale (% value and 95% confidence intervals).

Age stratum		Female	Male	tot
$>=65 < 75$	n	621	513	1134
	Prevalence % (CI 95%)	7.24 (5.44–9.57)	5.65 (3.93–8.02)	6.52 (5.22–8.12)
$>=75 < 85$	n	503	392	895
	Prevalence % (CI 95%)	29.22 (25.41–33.34)	19.89 (16.23–24.14)	25.13 (22.40–28.08)
$>=85$	n	269	109	378
	Prevalence % (CI 95%)	73.97 (68.41–78.86)	55.04 (45.69–64.05)	68.51 (63.66–72.99)
tot	n	1393	1014	2407
	Prevalence % (CI 95%)	28.06 (25.77–30.48)	16.46 (14.31–18.88)	23.18 (21.53–24.91)

The prevalence of frailty shows to be higher in the female gender in all age-strata; in the whole sample it corresponds to 28.06% (25.77%–30.48%) for females and 16.46% (14.31%–18.88%) for males respectively (ratio F/M = 1.7).

**Table 3.** Univariate and multivariate logistic regression models exploring the relationship between frailty (i.e.: Rockwood score  $>4$ ) and comorbidity (i.e.: Charlson Score  $\geq 4$ ).

Logistic regression models – Outcome : to be frail (ie having CSHA Clinical Frailty Scale score  $>4$ ) We analyzed 2280 elderly people assisted by doctors with good quality of data-input (see main text, see Appendix D)

	I. Monovariate logistic models OR (CI 95%) Z test P	II. Multivariate logistic model without interactions OR (CI 95%) Z test P	III. Multivariate logistic model with interactions OR (CI 95%) Z test P
To be female	OR = 1.83 (1.49–2.25) $p < .0001$	OR = 0.46 (0.22–0.69) $p < .0001$	OR = 1.58 (1.25–2.01) $p < .0001$
Having a Charlson Score $\geq 4$	OR = 3.64 (2.93–4.51) $p < .0001$	OR = 1.18 (0.94–1.43) $p < .0001$	OR = 4.21 (3.20–5.53) $p < .0001$
To be aged $\geq 85$	OR = 12.64 (9.77–16.34) $p < .0001$	OR = 2.42 (2.16–2.69) $p < .0001$	OR = 15.78 (11.44–21.76) $p < .0001$
Age $\geq 85$ X Charlson $\geq 4$	–	–	ROR** = 0.33 (0.19–0.58) $p < .0001$
<i>Model diagnostics</i>			
Pregibon test	–	Z -3.07 $p = .002$	Z = 0.32 $p = .748$
Hosmer-Lemeshow test	–	Chi2 = 18.18 df = 4 $p = .0011$	Chi2 = 3.05 df = 4 $p = .54$
AIC statistic	–	1952.257	1939.972

\*Note: the exponentialized coefficient of the interaction variable is a ratio of odds ratios ROR.

We explored the details of the relationship between frailty and comorbidity through three models of logistic regression in which the condition of frailty was the outcome and age, sex and comorbidity were the predictors.

The multivariate model without interactions (II) does not fit well: this can be seen from the outputs of the Pregibon test ( $p = .002$ ) and the Hosmer-Lemeshow test ( $p = .0011$ ); the AIC statistic (1952.27 versus 1939.972) shows also that the informative contribute is worst respect that of model III (i.e. that with the interaction).

The multivariate model with interactions (III) shows the better goodness of fit (Hosmer-Lemeshow test  $p = .54$ ) and the better pattern of covariates (Pregibons test  $p = .748$ ). To be female shows to be a significant predictor of frailty status and Age shows to be a significant confounder in the relations between comorbidity and frailty.

In detail, multimorbidity has been shown to be an independent predictor of frailty only for patients under the age of 85. The linear combination of the non-exponentialized coefficients of the variables involved in the interaction (third model of Table 4) allowed in fact to calculate for patients with multimorbidity (i.e. with Charlson score  $\geq 4$ ) compared to those without multimorbidity (i.e. with Charlson score  $< 4$ ) an Odds Ratio of frailty correspondent to OR = 4.21 (3.20–5.53)  $p < .0001$  in subjects under 85 years and to OR = 1.42 (0.88–2.29)  $p = .149$  in subjects 85+ years old, respectively. So, a serious comorbidity shows to be a prognostic factor for frailty only under 85 years of age.

Charlson score  $\geq 4$ ) OR of frailty = 4.21 ( $p < .0001$ ) for  $< 85$  people and OR = 1.42 ( $p = 0.149$ ) for  $\geq 85$  people (see footnote of Table 3 for details).

Table 4 illustrates the prevalence of the state of fragility in some common chronic diseases.

## Discussion

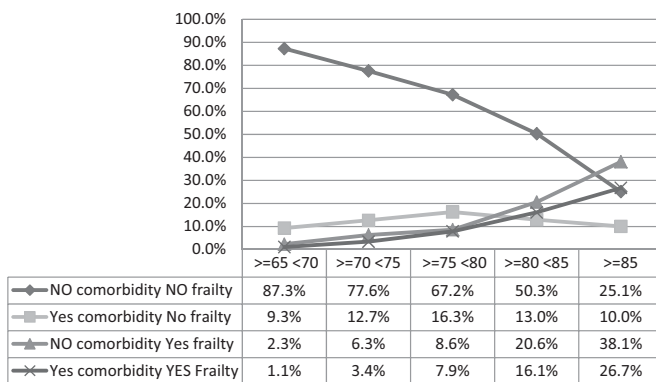
By our knowledge, this research represents the first Italian experience in which the prevalence of the frailty was examined through the CSHA Clinical Frailty Scale<sup>20</sup> in a random sample of older people representative of the general population.

These seniors are geriatric patients normally followed by the general practitioners in office, at home or in nursing home.

Few Italian studies evaluated the territorial distribution of the frail elderly patients<sup>10–14,17</sup>. Instead there is a wide variety of literature about the prevalence of chronic diseases; for the Veneto region, for example, very solid data are available<sup>18</sup>. Nevertheless, the identification of frail patients appears essential, insofar as the determinants of frailty can be also very different from those of the multimorbidity<sup>3,5</sup>. So, the activation of territorial assistance networks based only on the management of the chronic diseases may be insufficient, being the frailty a risk factor of death and institutionalization<sup>3,5</sup>.

**Table 4.** The table illustrates the prevalence of frailty in some clinical condition in 2280 elderly people evaluated for frailty status and with optimal data input (see main text, see Appendix D).

Conditions	All	Females	Males
Myocardial infarct	32.26%	37.50%	30.43%
Congestive heart failure	54.95%	70.91%	39.29%
Peripheral vascular disease	25.00%	30.00%	23.26%
Cerebrovascular disease	32.00%	37.55%	25.11%
Dementia	87.23%	94.29%	66.67%
Chronic pulmonary disease	24.49%	28.46%	19.63%
Connective tissue disease	44.55%	50.00%	31.25%
Ulcer disease	28.57%	37.29%	20.90%
Mild liver disease	40.00%	25.00%	50.00%
Diabetes	29.00%	36.10%	22.57%
Diabetes with end organ damage	33.33%		50.00%
Hemiplegia	60.00%	40.00%	80.00%
Moderate or severe renal disease	48.35%	52.81%	44.09%
Any tumor	26.82%	26.09%	33.33%
Lymphoma	45.83%	42.86%	50.00%
Leukemia	50.00%	55.56%	
Moderate or severe liver disease	50.00%	50.00%	50.00%
Metastatic solid tumor	42.86%	50.00%	33.33%
AIDS			
Hypertension	24.64%	29.98%	17.38%
Depression	32.37%	33.80%	29.23%
Cellulitis – skin ulcers	52.17%	53.42%	50.00%
Dicumarol use	54.63%	72.00%	39.66%



**Figure 2.** Prevalences of mutually exclusive combinations of frailty and serious comorbidity. Standardization for sex of five classes of age (standard population: Veneto's official data<sup>25</sup>) – the combinations of frailty and multimorbidity illustrated by the graph are mutually exclusive: so, for each stratum of age the sum of the percentages gives 100.00%.

Our research has attempted to contribute to the dissemination of knowledge in this field using a tool<sup>20</sup> validated in terms of predictability and reproducibility but at the same time very simple, usable without excessive loss of time during the daily care practice.

We did not find Italian experiences in the territorial setting that have used the CSHA Clinical Frailty Scale<sup>20</sup>, but we found two international studies conducted through that tool on similar classes of ages,<sup>33,34</sup>

In our experience, more than a fifth of the older people (23.18%) shows to be frail.

Nongeriatric physicians are more familiar with the problems related to multimorbidity compared to the problems related to the frailty, because the frailty is often associated with psycho-social determinants<sup>5</sup>: these determinants do not belong to the physical domain, which is the main object of the medical profession. For this reason, territorial

epidemiological researches have more focused on the prevalence of diseases compared to the prevalence of frailty.

In our opinion, the choice to generate a random sample from the pool of people assisted by physicians recruited in our research is a good compromise between the need to work with a representative sample and to avoid the problems of compliance that inevitably arise with other better methods of investigation for a prevalence study, such as evaluations of people sampled from electoral lists: the big sample that constitutes the population assisted by the doctors is very similar to that of Veneto in terms of distribution of the two sexes and of the five age classes taken into consideration.

In fact, one of the more important problems linked to a low compliance to medical or telephone interviews is a type of selection bias known as healthy user bias<sup>35</sup>. Data from sicker or more depressed patients can be missing due to unavailability (such as for institutionalized patients) or due to their refusal of the interview. This bias in our case could severely underestimate the prevalence of frailty.

This consideration could explain the difference in the results between our research and other studies conducted with the CSHA Clinical Frailty Scale<sup>20</sup> Ge and coll<sup>33</sup> assessed the prevalence of frailty in a random sample of families in the Central region of Singapore: trained interviewers evaluated 520 older people (mean age: 70.46) through the CSHA Clinical Frailty Scale<sup>20</sup>. The prevalence of frailty was 13.07% (10.43%–16.26%), but 46.7% of eligible patients dropped-out. Chang<sup>34</sup> assessed the frailty status via telephonic interview in a random sample of 845 older people (mean age 70.9 years). The estimated prevalence of frailty was 11.0% (95%CI 9.06, 13.3) but compliance reached only 29.1% (drop out: 70.9%).

We instead obtained a compliance of 100% of the sample because the frailty of each patient was evaluated by her own physician, well informed about the physical and psycho-social problems of his patients, all important determinants of frailty status.

The level of compliance reached in our study could reasonably rule out the presence of healthy user bias.

It is noteworthy that our sample shows a higher prevalence of depressive status (17.82% vs 9.26%<sup>33</sup>: it is possible that depressed patients, characterized by a prevalence of frailty of 32.4% (Table 4) refused interview more often than nondepressed subjects. Moreover, we noted a bimodal distribution trend of the Frailty Score of the CSHA Clinical Frailty Scale<sup>20</sup> (Figure 1), like other Authors<sup>20</sup>. This distribution could suggest the presence of two distinct groups in the population: a group of community-dwelling older adults and a group of institutionalized older people<sup>20</sup>. The risk of being frail and dropping out the interviews is differential in the two groups, being higher in institutionalized than in community-dwelling patients. This could have biased the estimate of frailty in studies based on interviews.

In our study, frailty status shows to be more frequent in female (28.06% vs. 16.46%, prevalence ratio = 1.67 - Table 2). This is coherent with the results of other studies (despite heterogeneous prevalence estimates): Fried<sup>36</sup> and Syddal<sup>37</sup>

report for example a Female/Male prevalence ratio of 1.48 and 2.07, respectively.

Frailty status shows to be more frequent in older elderly persons, especially after 75y.

We noted a prevalence of 6.52%, 25.13% and 68.51%, respectively, in the  $\geq 65$ -<75,  $\geq 75$ -<85 and  $\geq 85$  age-stratum. In the  $\geq 85$  stratum 55.04% of males and 73.97% of females showed to be frail (Table 2).

Our observation is coherent with results of other studies. Fried reports prevalences of 3.2% in 65–70 years old patients, 9.5% in 75–79 years old patients, and 25.7% in 85–89 years old patients<sup>36</sup>. Ge<sup>33</sup> reports prevalences of frailty (=CSHA Clinical Frailty Scale<sup>20</sup> score  $>4$ ) of 5.9% in 65–74 years old and 23.14% in over 75 years old patients in a subsample of 520 65+ older people. Chang<sup>34</sup> reports a prevalence of 4.59%, 11.60% and 18.42%, respectively, in 65–68 years old, in 69–73 years old and in 74–79 years old patients.

Our data (Figure 2) seem to suggest both a progressive increase of the prevalence of frailty and a trend to decrease of the prevalence of multimorbidity with advancing age; however, these results must be interpreted with caution.

Frailty and multimorbidity are in fact related in a complex way. Frailty develops with multisystem physiological decline, but it is possible that an individual is phenotypically frail without comorbidities. However, the effects of a single severe disease, either manifest or undiagnosed, could add further complexity<sup>38</sup>. In our study, a significant multimorbidity status (Charlson score  $\geq 4$ ) shows to be an independent predictor of frailty only in people aged  $\leq 85$  years.

The cross-sectional design of our study limits after all the conceivable consideration about the true relationship between frailty and comorbidity. Anyway, if both frailty and co-morbidity are important and independent prognostic factors for death, a severe co-morbidity could play a role, because sicker patients in the oldest strata could already be dead.

The condition of multimorbidity can moreover to be associated with a prognosis *quoad vitam* more serious than the condition of frailty.

In our experience (Table 4), frailty status shows to be particularly frequent in some common chronic clinical conditions. About a quarter of hypertensive patients are frail, as well as about one-third of diabetics and of patients affected by cerebrovascular/coronary disease or depression. Moreover, about half of patients affected by chronic heart failure and about 90% of patients with dementia shows to be frail.

For this reason, it is important that care networks are developed to address both clinical determinants of disease and psycho-social determinants of frailty.

### Strength of our research

We analyzed a stratified random sample that is highly representative of a population that was representative in turn of the general population of Veneto, so we are reasonably confident about our inferences.

The tool we used for estimating frailty (CSHA Clinical Frailty Scale<sup>20</sup>) is very simple to apply (only few seconds for

every known patient), it provides reproducible results and it is well predictive of important geriatric outcomes. Our not sponsored study was simply to implement, so it was executed quickly and with motivation by all recruited Physicians, with very low rates of medical drop-out.

### Limitations of our research

The best approach for a cross-sectional study of prevalence should consider a random sample directly extracted from the general population (i.e. by means of electoral or telephone directories), but this can be very expensive and exposes to problems like poor compliance and healthy user bias.

We used a tool that was rarely applied in prevalence studies of frailty status. For this reason, our results could be compared only with those of two other experiences. However, we believe that our contribution could be extended to other settings, since the CSHA Clinical Frailty Scale<sup>20</sup> tool is easy to use in the real world of the primary care.

The historical data that we used to calculate the Charlson Score can be biased by heterogeneity in the quality of the input of the physicians that we enrolled. Nevertheless, we tried to select the best data comparing the prevalence of the diseases with those of a validated benchmarking.

We are planning a second phase of the research aimed at evaluating the individual frailty determinants in the sample we have recruited; in this occasion we will take into account also other important covariates (i.e. admission to a nursing home).

### Conclusions

Our research shows that one in five elderly people in Veneto is affected by frailty. Often physicians focus more on morbidity than on psychosocial factors of older people. Nevertheless, the individuation of frail individuals is important because frailty is a predictor of death and other geriatric endpoints but often it is a reversible condition.

Physicians should pay close attention both to frailty and comorbidity. Frailty is easy to measure with the scale we used. The use of the CSHA Clinical Frailty Scale<sup>20</sup> should become part of the routine of the general practitioners.

### Transparency

#### Declaration of funding

There is no funding to declare for this study.

#### Declaration of financial/other relationships

The authors have no financial or other relationships to disclose. JDA peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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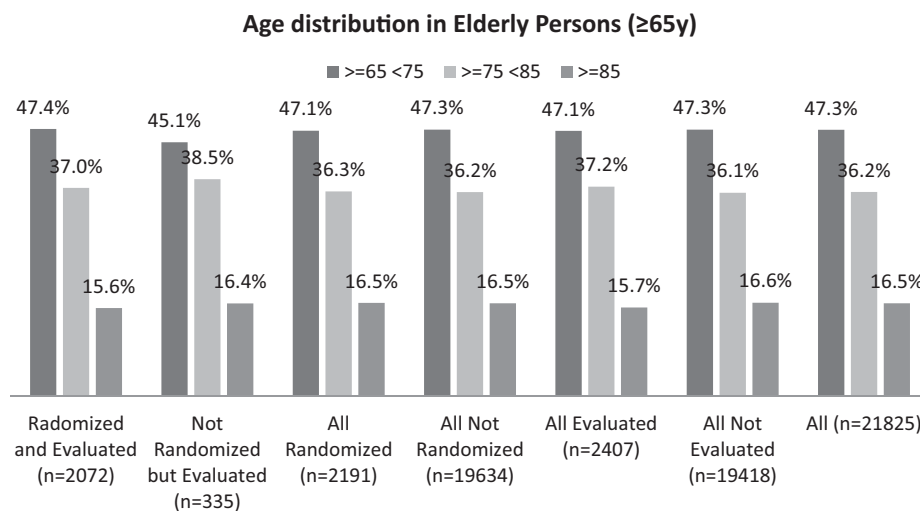
## Appendices

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Note: Bibliographical references refer to those mentioned in the main text unless otherwise specified

## Appendix A



### Appendix A– Age-distribution in the sample that was evaluated with CSHA Clinical Frailty Scale: comparison between the age classes of some groups of 65+ aged people

All age-distributions are similar: Kolmogorov-Smirnov test: Randomized and Evaluated vs Non randomized and Evaluated  $p = 0.997$ ; Randomized vs Not randomized  $p = 1.00$ ; Evaluated vs Not Evaluated  $p = 0.998$ . So, we can reasonably infer that the sample of evaluated patients is representative

## Appendix B – ICD9-CODES or charlson comorbidity index

Twenty three codified conditions are necessary for the calculation of the Charlson Comorbidity Index in the version validated for primary care medicine<sup>21</sup>. Each condition was defined for the 19 items pertinent to old version of the Charlson Index<sup>23</sup> through the ICD-9 codes defined by Dejo<sup>24</sup>.

We report below the codes that we used for identify the other 4 conditions necessary for the calculation of Charlson Comorbidity Index in the version validated for primary care medicine<sup>21</sup> that were not cited by the original article of Charlson<sup>23</sup>

Depression: ICD-9: 311% 296.2% 296.3% 296.5% 300.4%  
 Use of warfarin ATC: B01AA03  
 Hypertension: ICD-9: 401-405.X  
 Skin ulcers/cellulitis ICD-9 707% 707.% 440.24 682.9 785.4

## Appendix C – RANDOMIZATION and selection of patients to evaluate

The second phase of the research concerned the randomization of a sample of 65+ elderly people and the evaluation of their frailty status through the Rockwood scale. We extracted the random sample from the dataset that we constructed as described for the first phase (see text). Then, we assigned to physicians their randomized patients identified by the anonymous code. For this procedure, each doctor has initially extracted in an Excel sheet his entire population of 65+ aged through a second SQL query provided by us. Then, each doctor decrypted the codes of the patients assigned by the randomization using a utility that we also provided (as Excel worksheet) and assessed each patient's frailty status using the Rockwood scale. After the evaluation, he returned the list of his randomized patients, deleting the sensitive data and using the same anonymous code we used when sending. If some of the codes concerned deceased patients or for other reasons no longer assisted by the doctor, the researcher had to replace them with the adjacent 65-year-old patients in the list provided by us, first in the lower row and then in the upper row if the patient in the lower row was not analysable for any reason, and so on.

SQL syntax used for the selection of 65+ individuals

```
[SQL]
select distinct
p.codice codice,
n.pa_medi id_medico,
p.nascita data_nascita,
p.cognome cognome,
p.nome nome
from
  pazienti p,
  nos_002 n,
  cart_pazpbl c
where p.nascita < '1952-06-30' and
  p.codice = n.codice and
  p.codice = c.codice and
  p.pa_convenzione not like '%I%' and
  (
  p.decesso is null or p.decesso > '2017-12-31'
  ) and
  (
  n.pa_drevoca is null or n.pa_drevoca > '2017-12-31'
  ) and
  n.pa_medi='DEMO_3Q'
order by codice;
```

## Appendix D – EVALUATION of the quality of the historical data registered by researchers in their medical records

Researchers agreed to participate to our research on voluntary basis; so we did not know the quality of their medical records. This problem does not concern the relevant information of frailty status, (because all of them received the same instructions) but rather the coding of the necessary 23 conditions for the calculation of the Charlson comorbidity score, that we had to use for evaluating the relationship between frailty and comorbidity (see text). For this reason, we evaluated the quality of medical input using an indirect way. Firstly, we calculated for every physician the prevalence of each of the 23 conditions in his dataset. Secondly, for each physician we calculated the decile position for each of these prevalences among the entire pool of prevalences of all recruited physicians. Thirdly, for each physician we calculated the median of his 23 decile positions, assuming that physicians with lower <median score> were also characterized by the worst input. Fourthly, we ranked in deciles these <median scores> into the pool of all recruited physicians. Finally, for each class (=decile) of <median score> we compared the prevalence of significant comorbidity status (ie of a Charlson Score  $\geq 4$ ) in five age-classes with the same prevalences found in a benchmarking-dataset of ~140000 medical records (MilleinRete 2014<sup>29</sup>) characterized by known high quality of input (i.e. of a median ITOT<sup>D1</sup> score =0.74). Then we excluded the physicians belonging to the categories of <deciles of median score> where the difference in the distribution of the prevalence of a Charlson Score  $\geq 4$  was significant to the distribution statistics (see below). A total of 2,280 patients were assisted by the other (nonexcluded) 49 physicians characterized by good quality of data-input

## Appendix D references not reported by main document

D1 Health Search

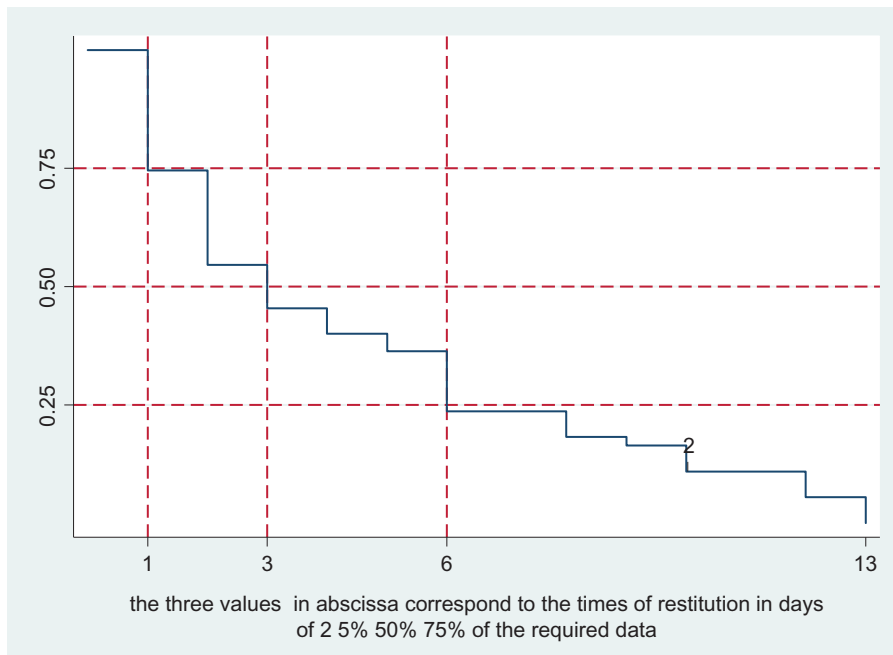
Istituto di ricerca della SIMG: Società Italiana di Medicina Generale e delle Cure Primarie

VIII Rapporto Health Search anno 2013/2014

(access: 15 June 2018)

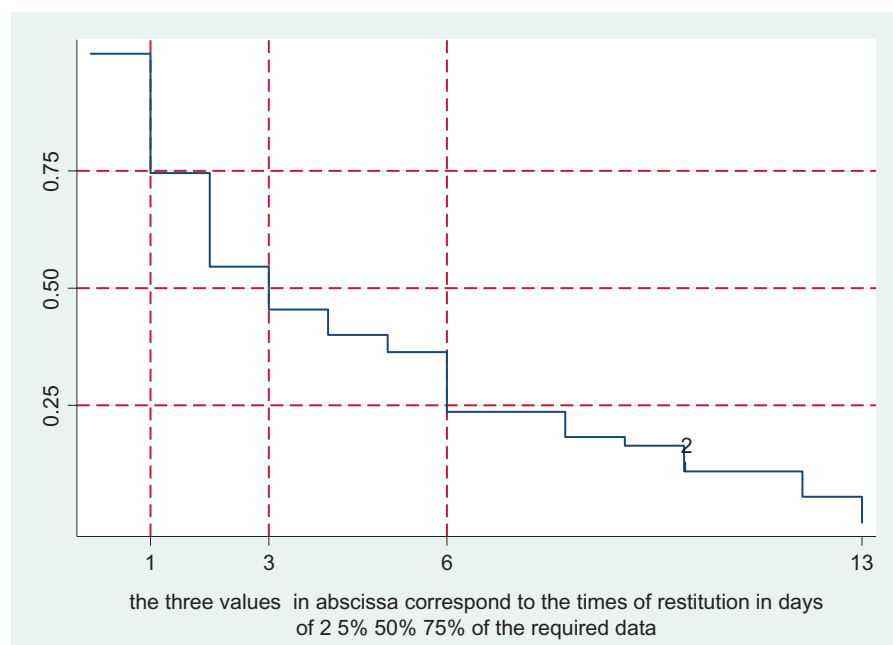
[https://healthsearch.it/documenti/Archivio/Report/VIIIReport\\_2013-2014/VIII%20Report%20HS.pdf](https://healthsearch.it/documenti/Archivio/Report/VIIIReport_2013-2014/VIII%20Report%20HS.pdf)

## Appendix E - TIMING of the research analysed through kaplan-MEIER estimator

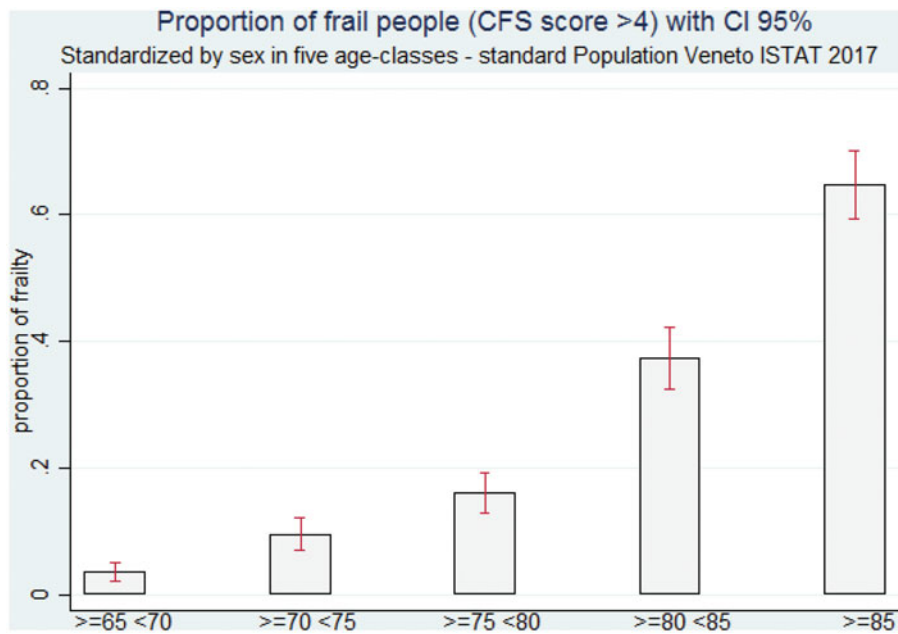


**Appendix E Figure 1** - The first phase of the research took place in 18 days.

58 general practitioners agreed to be recruited; on the fourth day we received soon 50% of the individual datasets. Three doctors did not respond even after being solicited. So, 55 physicians began the second phase. Of them, 2 did not respond.



**Appendix E Figure 2** – The second phase took place in 13 days; on the third day we received soon 50% of the individual frailty-evaluations. So, 53 physicians completed our research.

**Appendix F – STANDARDIZED prevalence of frailty status**

Frailty Prevalence (CSHA Clinical Frailty Scale)	≥65 < 70	≥70 < 75	≥75 < 80	≥80 < 85	≥85
CI 95% lower limit	2.06%	7.13%	12.97%	32.49%	59.45%
<b>Punctual estimation</b>	<b>3.56%</b>	<b>9.61%</b>	<b>16.08%</b>	<b>37.42%</b>	<b>64.74%</b>
CI 95% upper limit	5.05%	12.09%	19.18%	42.35%	70.03%

**Appendix F** (Table And Figure) prevalence of frailty (ie of Rockwood Score >4) standardised by sex in five strata of age (Standard population: official data of Veneto Region 2017(Veneto ISTAT 2017))<sup>25</sup>