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Letter to the Editor

C-reactive protein, lipoprotein (a) and cystatin C levels increase with multimorbidity in older persons

Dear Editor

Multimorbidity, the co-existence of chronic diseases within the same individual has been associated with a low-grade pro inflammatory status and different epidemiological and clinical studies have found that the "low-grade chronic proinflammatory state" typical of older persons [1,2] is characterized by high levels of serum cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF-alpha), and acute phase proteins, such as C-reactive protein (CRP), that are considered risk factors for several chronic diseases [3] and predict a variety of adverse health outcome [4,5]. Thus, it is reasonable to hypothesize that older persons with chronic inflammation are more likely to be affected by or to develop multimorbidity.

In spite of this potential clinical utility, the above mentioned markers, with the exception of CRP, are not available in the majority of clinical laboratories since they are mainly used for research purpose and few commercial diagnostic kit with standardized protocols, well defined range limits, quality internal and external controls are available on the most used platform. Therefore, even if they provide useful information, their application in the daily clinical practice is difficult and often expensive. For this reason we investigated the relationship between inflammatory biomarkers that can be easily measured and adopted by most clinical laboratories with multimorbidity. In particular we investigate the relationship of CRP, Lp(a), and Cyst-C levels with multimorbidity in a sample of community-dwelling older collected for the study 'ANZIANI IN-RETE', a prospective population-based study already described by Bianchetti et all [6]. In this population of 134 people we evaluate multimorbidity as the number of chronic diseases within each participant. Commercially available assays were used according to manufacturer's instruction to evaluate serum Lp(a) (the latex lipoprotein reagent; Siemens Healthcare Diagnostics), Cyst-C and CRP plasma levels (with immunoassay techniques; Siemens). We used the biomarkers levels both as linear variables and categorized according to the references values suggested by the literature and by manufacturer's instruction and adopted by clinicians (Lp(a) > 0,3 g/L, Cyst-C value >1.11 mg/L and CRP > 5 mg/L).

Table 2
Linear regression model testing the association between laboratory data (categorized) and number of chronic diseases.

Number of Chronic Disease	Coef.	P > z	[95% Conf.Interval]	
Cyst C	0.926	0.044	0.025	1.828
Lp(a)	1.529	0.001	0.625	2.432
CRP	0.961	0.038	0.052	1.870
Sex	−0.726	0.071	−1.514	0.063
Age	−0.002	0.945	−0.062	0.058

Variables were summarized as mean ± standard deviation for continuous variables and frequencies for discrete variables. The Chi-square statistic, Goodman and Kruskal's gamma and Spearman's Rho were used to study bi-variate associations between the socio-demographic variables, the inflammatory markers and the number of chronic diseases. To determine factors independently correlated with the number of chronic pathologies multivariate analysis were carried out by multiple linear regression models. All p-values < 0.05 were considered to be statistically significant.

Population enrolled for the study included 134 participants, the mean age was 77.7 (SD 7.6); 59.3% were women Mean value of Lp(a) was 0,2 g/L (SD 0.32), 4,69 mg/L (SD 0,32) and 1.11 mg/L (SD 0,47) for CRP and Cyst C respectively . Sociodemographic and laboratory data according to being affected by 0/1, 2–3 or >4 chronic diseases are showed in Table 1. Increasing age, female sex and lower education were significantly associated with higher number of diseases.

The majority of persons in the group of those with zero or 1 disease had normal levels of the markers, as the number of chronic diseases increased the percentage of person with normal value of the markers decreased.

We also run two multivariate linear regression models to test the association between the three biomarkers and multimorbidity (number of diseases). The first model include CRP, Lp(a) and Cyst-C categorized according to previously defined cut-off points. Higher levels of all the three markers were associated with higher number

Table 1
Bi-variate analysis between the number of chronic pathologies, the socio-demographic variables and the bio-markers variables. ** indicates a p-value < 0.01, * indicates a p-value < 0.05 and "·" indicates a p-value < 0.1.

Number of Chronic Disease	0/1	2/3	4 or more	Test	*P*-value
Age mean(SD)	73(1.2)	77.3(0.94)	78.9(0.73)	Spearman's Rho = 0.24	0.0005**
Female sex, %	45.8	52.4	66.1	Goodman and Kruskal's gamma = −0.29	0.07·
Education, median(IQR)	13(13–18)	13(8–18)	13(8–13)	Spearman's Rho = −0.20	0.007**
Inflammatory markers					
CRP <5 mg/L, %	92.9	82.2	65.3	Goodman and Kruskal's gamma = 0.49	0.03*
Lp(a) <0.3 g/L,%	85.7	86.4	60.3	Goodman and Kruskal's gamma = 0.56	0.005**
Cyst C < 1.11 mg/L,%	91.7	61.5	43.1	Goodman and Kruskal's gamma = 0.51	0.004**

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Table 3
Linear regression model testing the association between laboratory data (continuous) and number of chronic diseases.

Number of chronic pathologies	Coef.	P > z	[95% Conf. Interval]	
Cyst C	1.467	0.021	0.220	2.714
Lp(a)	1.771	0.005	0.522	3.020
PCR	0.002	0.930	−0.052	0.057
Sex	−0.906	0.033	−1.737	−0.074
Age	0.003	0.927	−0.062	0.068

of diseases after adjusting for age and sex (Table 2). The second model was run including CRP, Lp(a) and Cyst-C as continuous variables. Results from this model showed that Lp(a) and Cyst-C, but not CRP were still significantly associated with increasing number of diseases (Table 3).

Our data showed that higher value of all the three biomarkers correlated with an increase in the number of chronic conditions, both when dichotomized as "high" versus normal and as continuous variables. Among the three of them, CRP present some limitation in evaluating multimorbidity since levels of CRP rise significantly during acute inflammation making evaluation of multimorbidities more difficult, and furthermore positive values of this marker, even if correlate with multimorbidities, do not correlate with the number of chronic disease that affect the individual. Therefore, Lp(a) and Cyst-C could be more intriguing candidates for monitoring multimorbidity.

Elevated plasma Lp(a) levels have been reported to be an independent risk factor for coronary heart disease and stroke, but, to the best of our knowledge, there are very few example that studied a possible role for Lp(a) in the aging process or multimorbidity [7]. While Cyst-C has been studied as a marker of renal function, other studies have highlighted the potential role of Cyst-C as a marker of more general systemic inflammation [8,9].

Very interestingly the above mentioned markers are independently associated suggesting the possibility that they could be used independently to monitor different type of morbidity even if, unfortunately, we were not able to evaluate this issues in the present study since our sample was too small. Furthermore differently from the most studied markers of inflammation, we propose the use of diagnostic assay already available in most of clinical laboratories. Standardized protocols, well defined range limits, quality internal and external controls and low costs compared to research assay make them more interesting for monitoring inflammation and related health conditions in older person.

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Conflict of interest

The authors do not have any conflict of interest to disclose.

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