Aging and multimorbidity: associations with inflammatory biomarkers

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Background. Even if is well-established that multimorbidity, the co-existence of two or more chronic diseases within the same individual, increases with age and, independently of age, it is strongly associated with frailty, disability, hospitalization, and mortality, little is known about factors associated with multimorbidity beyond age. Epidemiological and clinical studies have found that the "low-grade chronic proinflammatory state" tipical of older persons is characterized by high levels of serum cytokines and acute phase proteins that are considered risk factors for several chronic diseases and predict a variety of adverse health outcomes, including frailty, disability, and mortality. Thus, it is reasonable to hypothesize that older persons with chronic inflammation are more likely to be affected by or to develop multimorbidity. Therefore parsimonious and reliable measures of inflammation may be useful in clinical practice as risk assessment tools, as potential therapeutic targets, and to monitor clinical progression and effectiveness of interventions. 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 the role of C Reactive Protein (CRP), Cystatin C (Cyst-C) and Lipoprotein (a) (Lp(a)) were investigated in the partecipants of the Anziani In Rete (AIR) study.

Methods. In the AIR study a sample was randomly selected by age cohorts (from 65 to 74, from 75 to 84, and ≥ 85 years) and by gender among all the older subjects living in three districts (Brescia Antica, Centro Storico Nord and Centro Storico Sud) located in the city center of Brescia, Italy. Each participant was evaluated with a comprehensive geriatric assessment and multimorbidity was evaluated as the number of chronic diseases within each participant. Information on diseases was derived by a physician using different sources of information; self-reported medical history, medication use, clinical reports and a medical examination. Population enrolled for the study included 134 participants; the mean age was 77.7 (SD 7.6); 59.3% were women.

Demographic and laboratory data of the study population are reported in Table 1.

	mean	median	STD deviation
Age, y	77.7	77	7.65
Chronic diseases, number	4.12	4	2.3
Lp(a)	0.26	0.11	0.32
CRP	4.69	3	7.21
Cyst-C	1.18	1.07	0.47

Table 1. Demographic and laboratory data of the study population

Venous blood samples were obtained and commercially available assays were used according to manufacturer's instruction: serum Lp(a) was measured with the latex lipoprotein reagent, and Cyst-C and CRP plasma levels were measured using immunoassay techniques (reagents from Siemens Healthcare Diagnostics, Den Hague, The Netherlands), all determinations were carried out in Dimension® Vista™ 1500 analyzer (Siemens Diagnostics). For the purpose of the present study, 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; in particular we considered as high values levels of Lp(a) > 0,3 g/L, Cyst-C value > 1.11 mg/L and CRP > 5 mg/L.

Sociodemographic and laboratory data according to being affected by 0/1, 2-3 or 4+ chronic diseases are showed in Table 2.

Disease (number)	**0/1**	**2/3**	**more than 4**	**P-value**
Age, mean(SD)	73(1.2)	77.3(0.94)	78.9(0.73)	0.0005
female sex, %	45.8	52.4	66.1	0.023
education, median(IQR)	13(13-18)	13(8-18)	13(8-13)	0.007
CRP <5mg/L, %	92.9	82.2	65.3	0.03
Lp(a) <0.3g/l,%	85.7	86.4	60.3	0.005
Cyst C < 1.11 mg/L,%	91.7	61.5	43.1	0.004

Table 2: Sociodemographic and laboratory according to number of pathologies.

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 but as the number of chronic diseases increased the percentage of person with normal value of the markers decreased.

Two multivariate linear regression models were run to test the association between the three biomarkers and multimorbidity (number of diseases). The first model was run including 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 of diseases after adjusting for age and sex (Table 3).

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

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

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 4).

Number of chronic disease	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
CRP	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

Table 4. Linear regression model testing the association between laboratory data (continuous) and number of chronic diseases

Conclusion. The main findings of this study show that CRP, Lp(a) and Cyst-C levels increase with increasing number of chronic diseases in older persons. Similarly, the percentage of older persons with normal values of the three markers decrease with multimorbidity. Our findings extend the results of previous studies on the associations between inflammation and multimorbidity in older people by demonstrating a clear association with CRP, Lp(a) and Cyst-C. 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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