FRAILTY: IDENTIFICATION AND MARKERS

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ABSTRACT

Background and aim of the work: Frailty is a state of reduced physiological reserve associated with increased susceptibility to disability. It is associated with a high morbidity and mortality. The aim of this work is to assess the value of some markers in identification and recruitment of frail elderly and to find out the association between these markers and stages of frailty.

Subjects and Methods : A total number of 88 elderly subjects (above 65 years old) were included in this study and they were subjected to thorough history and full clinical examination, anthropometric measures including mid upper arm circumference (MAC), mid calf circumference (MCC), body mass index (BMI)), timed get-up-and-go test (TGUGT), hand grip strength test in addition to laboratory investigations including complete blood picture (CBC), serum albumin, serum alanine aminotransferase (ALT), prothrombin time (PT), partial thromboplastin time(PTT), international normalization ratio (INR), serum Cholesterol, C-reactive protein (CRP) and interleukin-6 (IL-6).

Results : Among the 88 studied elderly subjects and according to Fried criteria of frailty, frailty was found in 36 subjects (40%) while, pre-frailty was found in 22 subjects (26%) and non- frailty was found in 30 subjects (34%). That prevalence of frailty was higher than most epidemiological studies. TGUGT was more prolonged in frail subjects compared to both pre-frail and non-frail. There was a significant decrease in serum cholesterol in frail subjects (125.7$\pm$54.9) compared to both pre-frails (168.1$\pm$17.2) and non-frails (165.3$\pm$29.7). CRP was significantly increased in frails (27.4$\pm$8.1 mg/l) compared to both pre-frails (14.3$\pm$4.5 pg/ml) and non-frails (7.5$\pm$5.5 pg/ml). Also there was a significant increase in IL-6 in frail subjects (30.4 $\pm$ 8.1 pg/ml) compared to both pre-frails (16.3 $\pm$ 4.5 pg/ml) and non-frails (6.5 $\pm$ 5.5 pg/ml).

Conclusion: There is a high prevalence of frailty among elderly population, the causes of this prevalence need further studies. The changes in the markers noticed in the frail elderly may suggest its use in identification and follow up of frailty.

Key words : Frailty, TGUGT, MAC, MCC, CRP and IL-6.

INTRODUCTION

Over the past decade, clinicians and investigators have begun to recognize frailty as a common clinical syndrome associated with a high rate of morbidity and mortality, and therefore deserving rigorous investigations **[1]**.

It has been postulated that there is a continuum of the severity of frailty ranging from non-frailty, pre-frailty and frailty **[2]**.

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There is no single best definition of frailty **[3]**. The vernacular term frailty has been used to describe those who are feeble, weak, the most debilitated and also the oldest old. Synonyms of frailty include defect, deficiency, failing, fallibility, imperfection, infirmity and susceptibility. It describes older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity **[4]**.

Furthermore, no single altered system or etiology defines frailty **[5,6]**. Age is an important feature, but frailty can develop at any age, and chronological age correlates loosely with biologic age **[3]**.

Lang et al. **[7]** reported that clinical markers or indicators are insufficient to differentiate the frailty process from normal aging, and they gave rise to the necessity to detect frailty at a pre-clinical stage with the help of biomarkers.

Evaluation of alterations in human biomarkers and their relationships to differing models of frailty may assist in the determination of the initiation of the processes that eventually led to frailty **[8]**.

IL-6 is a pro-inflammatory cytokine with increased circulating levels in older adults. Age-related increases in IL-6 levels are associated with several pathophysiologic processes, including atherosclerosis, osteoporosis and sarcopenia, and with functional decline, disability and all causes of mortality in older adults **[9]**. In addition, increased IL-6 levels are associated with lower muscle mass and strength even in well-functioning older men and women **[10]**.

SUBJECTS AND METHODS

This work had been carried out in Internal Medicine and Clinical Pathology Departments, Faculty of Medicine, Zagazig University from April 2010 to September 2011.

A total number of 88 elderly subjects (above 65 years) were included in the work. They were recruited from those attending Zagazig University Hospital for management of cataract and from day care center for geriatrics in Zagazig Governorate during the year. Verbal and/or informed consent from the participants or from their relatives to participate in the study was taken.

Criteria used to define physical frailty, Adopted from Fried et al. **[11]**. One must have 3 of the 5 following criteria for frailty, 1-2 for prefrail and zero for non-frail.

Frailty Criteria	**Male**		**Female**	
15 foot walk time-slowness	Height <173 Height >173	>7 seconds >6 seconds	Heigh <159 Height >159	>7 seconds >6 seconds
Hand grip strength weakness	BMI <24 BMI 24.1-26 BMI 26.1-28 BMI >28	<29 <30 <30 <32	BMI <23 BMI 23.1-26 BMI 26.1-29 BMI >29	M17 <17.3 <18 <21
Unintentional weight loss-shrinking	Greater than 5% weight loss in the last year (objective from relatives or subjective from patients and is not due to dieting or exercise)			
Physical Activity Low activity	<383 kilocalories/wk BMR (40 cal/m^2/hour $\pm$ 15%)		<270 kilocalories/wk	
Exhaustion Fatigue	A score of 2 or 3 on either question of the CES-D How often in the last week did you feel this way ? - I felt that everything I did was an effort - I could not get going 0= 1 day, 1= 1-2 days, 2= 2,3,4 days, 3= more than 4 days. BMR: Basal metabolic rate. CES-D: The center for epidemiological studies depression scale.			

All subjects will be subjected to Fried criteria of frailty **[11],** in addition to thorough history taking, complete general examination (with special attention to blood pressure and pulse), arthropometric measurements including MAC (taken midway between the acromioclavicular joint and lateral epicondyl of humerus); MCC measured midway between medial epicondyle of femur and medial malleolus and body mass index (BMI) that measured by dividing weight in kilogram over square of height in meters. Normal BMI values below 25, while values ranging from 25 to 30 are considered over weight and values above 30 are considered obese. TGUG test measures the time needed to complete a series of functionally important tasks. TGUG requires the subject to stand up from a chair, walk a short distance, turn around, return and sit down again. It thus serves as an assessment of dynamic balance. Balance function is observed and scored (normal value 17 seconds) **[14]**. Hand-grip strength test (done by hand-grip dyamometer). The purpose of this test is to measure the maximum isometric strength of the hand and forearm muscles. Hand-grip strength is important for any sport in which the hands are used for catching, throwing or lifting. Also, as a general rule people with strong hands tend to be strong

elsewhere, so this test is often used as a general test of strength **[15, 16].** In addition, we performed laboratory investigations including: CBC, serum albumin, serum ALT, PT, PTT, INR, Total cholesterol, CRP **[12,13]** and IL-6 **[10]**.

High sensitivity CRP (hs-CRP) (Roche/ Hitachi cobas system) :

Done by particle enhanced immuno-turbidimetric assay **[12,13]**. Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies.

IL-6 :

Done by ELISA for the quantitative detection of human IL-6 using Organium Laboratories human IL-6 ELISA kits.

Statistical analysis:

Data were checked, entered and analyzed by using (SPSS version 19).

Data were expressed as mean $\pm$ SD for quantitative variables, number and percentage for categorical variables. ANOVA (F test) and chi-square (X^2), paired t test and validation of the test was done. $P<0.05$ was considered statistically significant.

RESULTS

This work was carried out in Zagazig University hospitals and included 88 subjects. According to Fried criteria, frailty was found in 36 subjects (40%), 23 males and 13 females, their age ranged from 67.9 to 78.3 with mean age of 73.1 $\pm$ 5.2 year while, prefrailty was found in 22 subjects (26%), 9 males and 13 females, their age ranged from 65.0 to 73.0 with mean age of 69.3$\pm$3.8 year and non-frailty was found in 30 subjects (34%), 17 males and 13 females, their age ranged from 66.0 to 72.0 with mean age of 67.6 $\pm$ 3.3 year (Fig. 1).

Table (1) showed a highly significant difference between the studied groups regarding age, while there was no significant difference between them regard their gender.

Table (2) and Fig. (2) show a highly significant difference between the studied groups regarding TGUGT.

Table (3) shows a highly significant difference between the studied groups regarding MAC and MCC (Fig. 3), BMI, Hb, serum cholesterol, serum ALT, WBCs and CRP. Also, there was a significant difference between the studied groups regarding IL-6 (Fig. 4) while, there was no significant difference considering serum albumin and INR.

Table (4) shows that the mean of MAC, MCC and BMI of frail subjects is significantly lower than that of both non frail and pre-frail subjects while, there was no significant difference between non frail and pre-frail subjects. The mean CRP and IL-6 of frail subjects was significantly higher than that of both non frail and pre-frail subjects but there was no significant difference between non frail and pre-frail subjects.

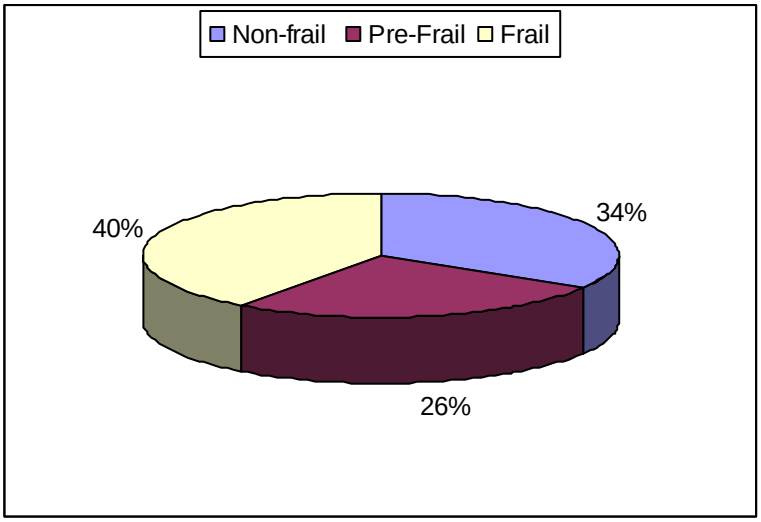

Table (1) : Demographic study (Means ± standard deviation (SD) of age with Chi-square test for prevalence of gender among the studied groups)**.**

Variable	Non-frail	Pre-frail	Frail	F	P
Age (year)	67.6 ± 3.3	69.3 ± 3.8	73.1 ± 5.2	14.2	<0.001 (HS)
Sex				X^2	
F	13	13	13		0.22
M	17	9	23	2.94	(NS)

Table (2) : Chi-square test for prevalence of normal and prolonged timed get-up and go test among the studied subjects.

TGUGT (seconds)	Non-frail		Pre-frail		Frail		X^2	P
	No	%	No	%	No	%		
Normal	24	62.8	11	39.2	3	7	39.47	<0.01 (HS)
Prolonged	6	12.3	11	22.8	33	64.9		

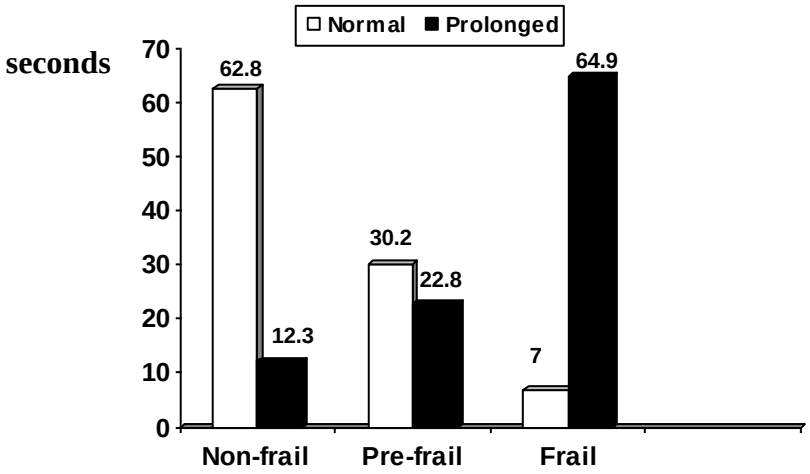

Fig. (2): The ratios between prolonged and normal TGUGT among the studied subjects.

Table (3) : Means ±SD of MAC, MCC, BMI, HB, Serum cholesterol, Serum albumin, ALT, INR, WBCs, CRP and IL-6 among the studied subjects.

Variable	Non-frail	Pre-Frail	Frail	F	P
MAC (cm)	33.2 ±3.6	32.5±4.1	26.1±5.8	22.11	<0.001 HS
MCC (cm)	42.7±4.7	41.0±5.7	34.6±6.1	19.4	<0.001 HS
BMI (kg\m2)	27.7±3.4	27.9±2.3	25.6±3.3	5.23	<0.001 HS
Hb (g/dl)	12.8 + 1.7	13.3 + 1.9	10.4 + 2.6	18.9	<0.001 (HS)
Serum cholesterol (mg/dl)	165.3 + 29.7	168.1 + 17.2	125.7+54.9	12.60	<0.001 (HS)
Serum albumin (g/dl)	4.0 + 0.76	4.13 + 0.82	4.34 + 0.57	1.77	0.1 (NS)
ALT (u/l)	39.05+11.27	37.5 + 17.7	20.6 + 16.5	16.28	<0.01 (HS)
INR	1.4 + 0.90	1.2 + 0.53	1.3 + 0.34	0.82	0.44 (NS)
WBCs $x10^3$ (cmm)	8.7 ±1.6	10.9 ± 2.7	14.22 ± 3.7	32.9	<0.001 (HS)
CRP (mg/l)	7.5 ±5.5	14.3 ± 4.5	27.4 ± 8.1	12.77	<0.001 (HS)
IL-6 (pg/ml)	6.5 ± 5.5	16.3 ± 4.5	30.4 + 8.1	109.2	<0.05 (S)

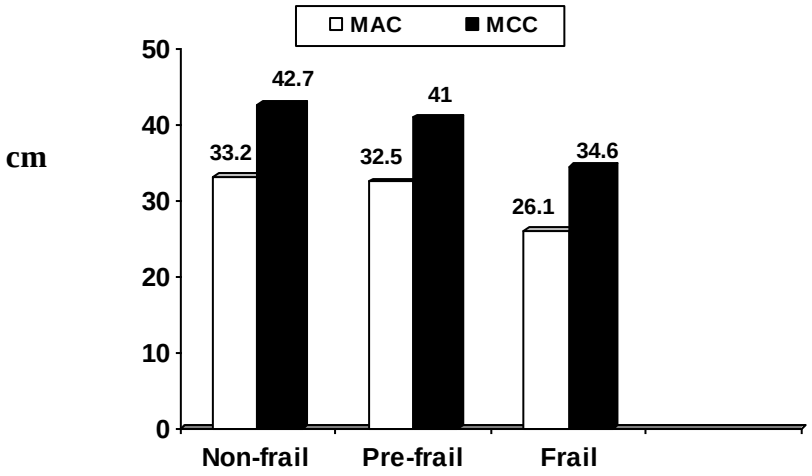

Fig. (3) : Comparison of mean of MAC and MCC among the studied subjects.

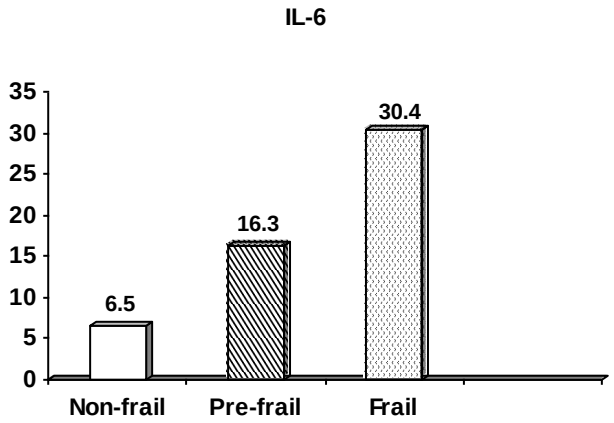

Fig. (4) : Comparison of mean of IL-6 among the studied subjects.

Table (4): Least significant difference for comparison of several means of MAC, MCC, BMI, CRP and IL-6 among the studied subjects.

Item		Non frail	Pre-frail
MAC	Pre-frail	0.58	---
	Frail	0.002	0.001
MCC	Pre-frail	0.23	---
	Frail	0.001	0.003
BMI	Pre-frail	0.81	---
	Frail	0.005	0.004
CRP	Pre-frail	0.13	---
	Frail	0.001	0.003
IL-6	Pre-frail	0.21	---
	Frail	0.001	0.001

DISCUSSION

Frailty has been recognized as a common clinical syndrome associated with a high rate of morbidity and mortality **[1]**.

The current study revealed a significant increase in age of frail subjects (731±5.2 year), compared to both pre-frails (69±3.8 year) and non-frails with no significant difference between pre-frails and non-frails (67.6 ± 3.3 year). These results support the study of Woods et al. who reported a significant association between age and frailty **[17]**.

In addition, the current study showed no significant association between gender and frailty. However, some investigators reported a significant association between female gender and frailty **[18]**, and this may be explained by the included females in their study who might be suffering from other comorbidities.

Also, there was a significant prolongation in TGUGT in frail subjects compared to both pre-frails and non-frails with no significant difference between pre-frails and non-frails. This is in agreement with Mathias et al. who found prolonged TGUGT in geriatric patients and suggested that it can serve as performance test **[14]**.

Considering MAC, there was a significant decrease in MAC (26.1±5.8 cm) in frail subjects compared to both pre-frails (32.5 ± 4.1cm) and non-frails (33.2 ± 3.6 cm) with no significant difference between pre-frails and non-frails. This finding agrees with that obtained by Cesari et al. who found that low MAC was significantly associated with an increased mortality risk in men and women **[19]** and Flegal et al. who found that low MAC was

more strongly associated with mortality than those with low BMI **[20]**. Furthermore, Wijnhoven et al. reported that MAC seemed a more feasible and valid anthropometric measure of thinness than BMI in elderly **[21]**.

The current study showed also a significant decrease in MCC (34.6±6.1 cm) in frail subjects compared to both pre-frail (41.0 ± 5.7 cm) and non-frail (42.7 ± 4.7 cm) with no significant difference between pre-frails and non-frails. This agrees with that obtained by Cesari et al. who found that low MCC was significantly associated with an increased mortality risk in men and women and Wijnhoven et al. who found significant association between MCC and mortality in elderly**[19,21]**.

Measuring BMI, there was a significant decrease in BMI (25.6±3.3 kg/m^2) in frail subjects compared to both pre-frails (27.9±2.3 kg/m^2) and non-frails (27.7 ± 3.4 kg/m^2) with no significant difference between pre-frails and non-frails. This is in agreement with that obtained by Marchesini et al. who found increased mortality risk at low BMI values in old age and agree with Bahat et al. who concluded that better functional status in the elderly was associated with higher BMI even in BMI ≥30 kg/m^2 **[22,23]**.

In this study, we assessed several potential biomarkers of frailty. As regard the Hb concentration, there was a significant decrease in Hb concentration (10.4±2.6 g/dl) in frail subjects compared to both pre-frails (13.3 ± 1.9 g/dl) and non-frails (12.8 ± 1.7 g/dl) with no significant difference between pre-frails and non-frails. This goes in the same way with that obtained by Chaves et al. who demonstrated a direct link in elderly women between the presence of anemia and the occurrence of frailty **[24]**. The association between frailty and anemia may be due to decreased intake of foods, vitamins and iron or due to many causes of chronic blood loss which are common in elder persons.

We found also that serum cholesterol level was significantly decreased in frail subjects (125.7±54.9 mg/dl) compared to both pre-frails (168.1 ±17.2 mg/dl) and non-frails (165.3± 29.7 mg/dl) with no significant difference between pre-frails and non-frails. This is in harmony with that obtained by Reiner et al. who identified low serum cholesterol as a risk factor for frailty **[25]**. These results agree also with that of Schalk et al. who reported that low cholesterol level might be associated with decline in functional status which is one of the components of frailty**[26]**.

Measuring serum albumin level, there was no significant difference between the studied subjects (frails, pre-frails and non-frails) but this differs from other numerous studies that reported higher mortality in community-dwelling older people with a low serum albumin. Reuben et al. stated that the relative risk

for mortality in healthy non-disabled older persons was 2.2 times higher in subjects with an albumin level below 4 g/dl **[27]**. Also Takata et al. found that lower serum albumin concentration was an independent predictor of mortality in 70 years old people in community-dwelling population **[28]**. On the other hand, Schalk et al. found no association between lower serum albumin and functional decline in the elderly **[26].** This controversy may be due to different nutritional states in those studies or due to the presence of diseases that affect serum albumin level.

The current study showed also a significant decrease in ALT levels in frail subjects (20.6±16.5 u/l) compared to both pre-frails (37.5±17.7 u/l) and non-frails (39.0±11.2 u/l) with no significant difference between pre-frails and non-frails. This agrees with the study of David et al. that revealed a substantially lower ALT level in older persons **[29]**. The presence of significant decrease in serum ALT level in frail elderly compared to both pre-frails and non-frails in the absence of significant changes in other liver function tests may point to the value of low serum ALT as a marker of frailty, a result that needs further studies to verify.

Also, there was a significant increase in WBCs count in frail subjects (14.22 ± 3.7 cmm) compared to both pre-frails (10.9 ± 2.7 cmm) and non-frails (8.7 ± 1.6 cmm) with a significant increase in pre-frails compared to non-frails. This goes in the same way with that obtained by Ruggiero et al. who found a direct relationship between frailty and elevated WBCs count (specifically neutrophils and monocytes) and demonstrated a potential synergistic interaction between WBCs and IL-6 in their association with frailty **[30]**. Indeed, frailty was found to be associated with increased WBCs count in addition to CRP (which are recognized as an important markers of systemic inflammation), this suggests a role of inflammation in aging so frailty is named inflammaging **[31]**. So, in the current study, we assumed that WBCs can be considered as a marker not only of frailty but also, for the identification of pre-frailty; an assumption that needs further studies to clarify.

Considering serum CRP levels, there was a significant increase in serum CRP in frail subjects (27.4±8.1 mg/l) compared to both pre-frails (14.3 ± 4.5 mg/l) and non-frails (7.5±5.5 mg/l) with no significant difference between pre-frails and non-frails. This is in agreement with Walston et al. and Puts et al. who showed a significant association between elevated CRP level and frailty **[32,33]**. It also goes in harmony with the results obtained by Yoshida et al. who found elevated CRP levels in elderly with poor physical performance **[34]**. Our results may give support to the theory of inflammaging mentioned before.

As regard IL-6 there was significant increase in IL-6 level in frail subjects (30.4±8.1 pg/ml) compared to both pre-

frails (16.3±4.5 pg/ml) and non-frails (6.5±5.5 pg/ml). This agrees with the CHIANTI study that was carried out on 1020 subjects of 65 years and older to identify the risk factors for late-life disability and demonstrated that high levels of IL-6, CRP and IL-1 were significantly associated with poor physical performance and muscle strength. In addition, high circulating levels of TNF-α and IL-6 have been related to cardiovascular diseases and frailty **[19]**.

In summary, our results suggest that the observed changes with frailty (increasing age, WBCs, CRP, IL-6 and TGUGT and decreasing in ALT, Hb%, serum cholesterol, MAC,MCC and BMI) can suggest their use to identify frailty and to assess the degree of its severity. However, other prospective studies are needed to clarify this role.

Finally, we hope that this study may highlight the problem of frailty which affects a big sector of the population that is progressively growing in our community.

SUMMARY AND RECOMMENDATIONS

1- There is high prevalence of frailty among studied elderly population, the causes of which need further studies to identify.
2- The changes in the markers noticed in frail elderly may suggest their use in the diagnosis and follow up of frailty, a suggestion that still in its infancy and needs further studies.
3- The significant elevation of CRP, IL-6 and WBCs in frail elderly, which are markers of inflammation, may give support to the theory of inflammaging.

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