Gruppo di ricerca geriatrica

Journal club del Venerdì

9 Marzo 2007

FRAGILITA' E RIABILITAZIONE

Uno sguardo generale

Fabio Guerini

UO Recupero e Rieducazione Funzionale - Clinica "Ancelle della Carità", Cremona
Gruppo di Ricerca Geriatrica, Brescia

The Foolishness of Eos

- Despite thousands of pages in the geriatric literature dedicated to the concept of frailty, its definition remains elusive.
- Understanding the pathways to and consequences of frailty continues to be a fundamental aspiration of many geriatricians and researchers in the aging field.

- What is it about frailty that so profoundly tears at the core of our geriatric soul?

Ferrucci et al. J Gerontol 2006

Difficoltà di una definizione

Stedman's Medical Dictionary fails to list the concept of frailty

Cohen, J Gerontol 2000

"liability to be crushed or to decay, either in material or immaterial sense . . . moral weakness, instability of mind, liability to err or yield to temptation"

The Oxford Dictionary, 2006

Difficoltà di una definizione

Le definizioni di Frailty “abbondano”, definendola come sinonimo di disabilità, comorbidità, età avanzata.

Un ostacolo maggiore a qualsiasi intervento sulla frailty è l’assenza di uno strumento di screening valido e standardizzato

Un numero crescente di geriatri ha operato uno sforzo nella definizione di frailty come sindrome biologica.

Fried, J Gerontol 2001

Aspetti Biologici

- Frailty come sindrome biologica:
  - ridotta riserva e resistenza agli eventi stressanti, risultante dal declino cumulativo di diversi apparati, che rende l'organismo più vulnerabile ad eventi avversi
- Alterazione di una omeostasi:
  - markers biologici di fragilità.

Hemmermann, Ann Intern Med 1999

Ipoalbuminemia

- L’albumina sierica è un fattore di rischio indipendente di mortalità in soggetti anziani
- L’albumina sierica rappresenta un predittore di mortalità a lungo termine tra soggetti non-istituzionalizzati e di mortalità a breve termine in quelli istituzionalizzati

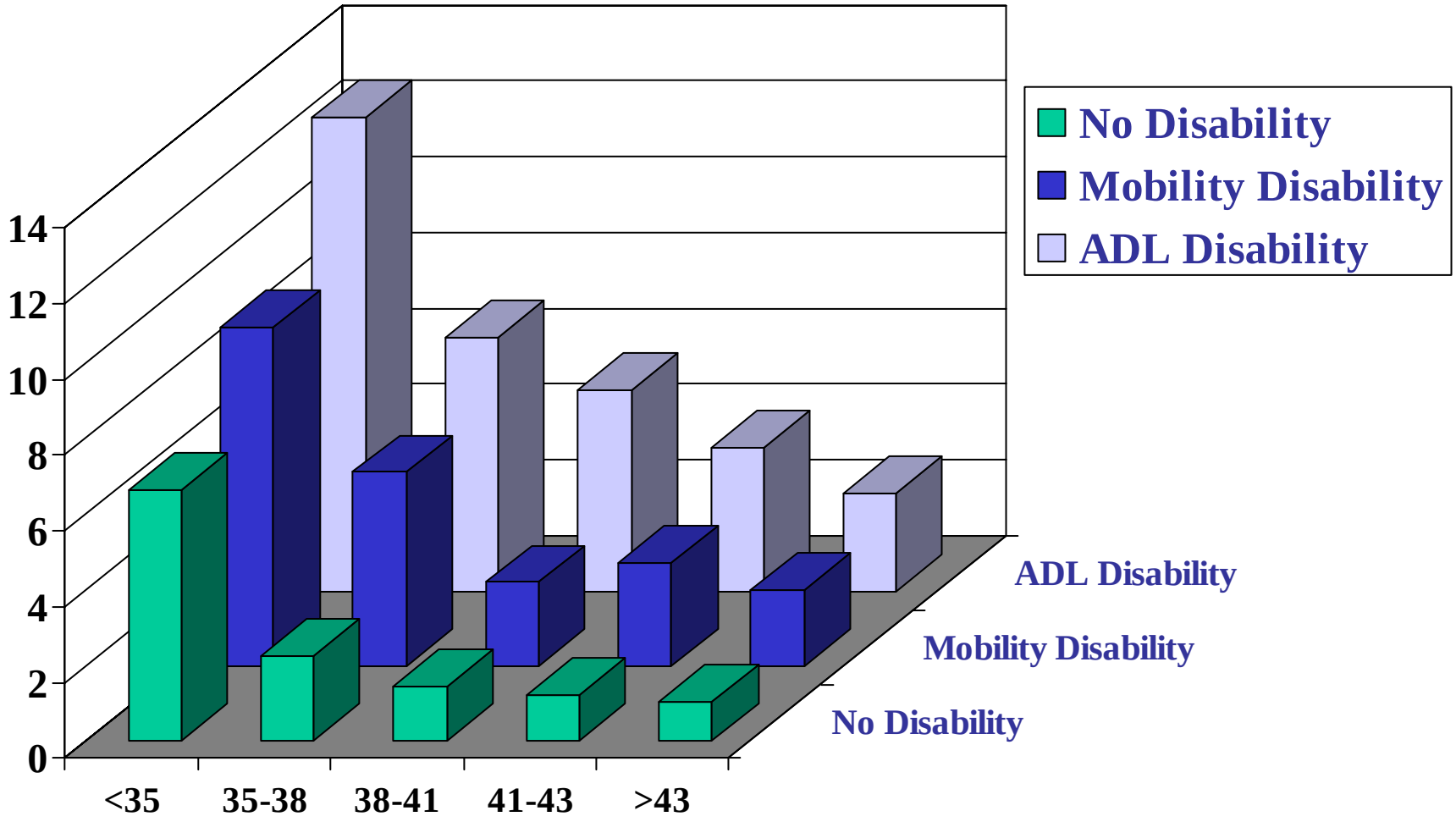
Sahyoun et al, J Clin Epidemiol 1996

Ipoalbuminemia

- Una misura combinata di albumina e disabilità rivela un forte gradiente di rischio di mortalità e può servire da semplice ed utile indice di fragilità

Reuben DB et al, 2000

Rischio Relativo di Mortalità



Mod. da Corti et al,
JAMA 1994

Ipoalbuminemia

L'associazione tra ipoalbuminemia e mortalità a breve termine non è legata esclusivamente alla malnutrizione o alle patologie croniche concomitanti

Albumin g/dl	n/deaths	A		B	
		RR[a]	95% CI	RR[b]	95% CI
>3.4	343/31	1.0		1.0	
3.3-3.4	46/6	1.5	0.7-3.6	1.4	0.6-3.4
3.1-3.3	64/13	2.5	1.3-4.7	1.6	0.8-3.2
<3.1	58/16	3.4	1.9-6.3	2.5	1.2-5.1

Rozzini et al, J Clin Epidemiol 1997

Ipoalbuminemia

- L’ipoalbuminemia può essere vista come un marker non-nutrizionale di fragilità
- Spia di una serie di condizioni biologiche associate che portano ad outcome negativi

Rozzini et al, J Clin Epidemiol 1997

Ipocolesterolemia

Bassi livelli di colesterolo sierico possono essere considerati un marker ematologico indipendente di fragilità nel paziente anziano ospedalizzato

Rappresenta un predittore di mortalità in RSA, Ospedale e in comunità

Ranieri P, Rozzini R, Franzoni S, Barbisoni P, Trabucchi M.
Exp Aging Res. 1998 Apr;24(2):169-79

Variabili Biologiche

- **Ipocolesterolemia**
  - Bassi livelli di colesterolo sono associati a compromissione delle funzioni cognitive, all'età, alla disabilità, all'alta comorbilità, alla politerapia ed alla malnutrizione

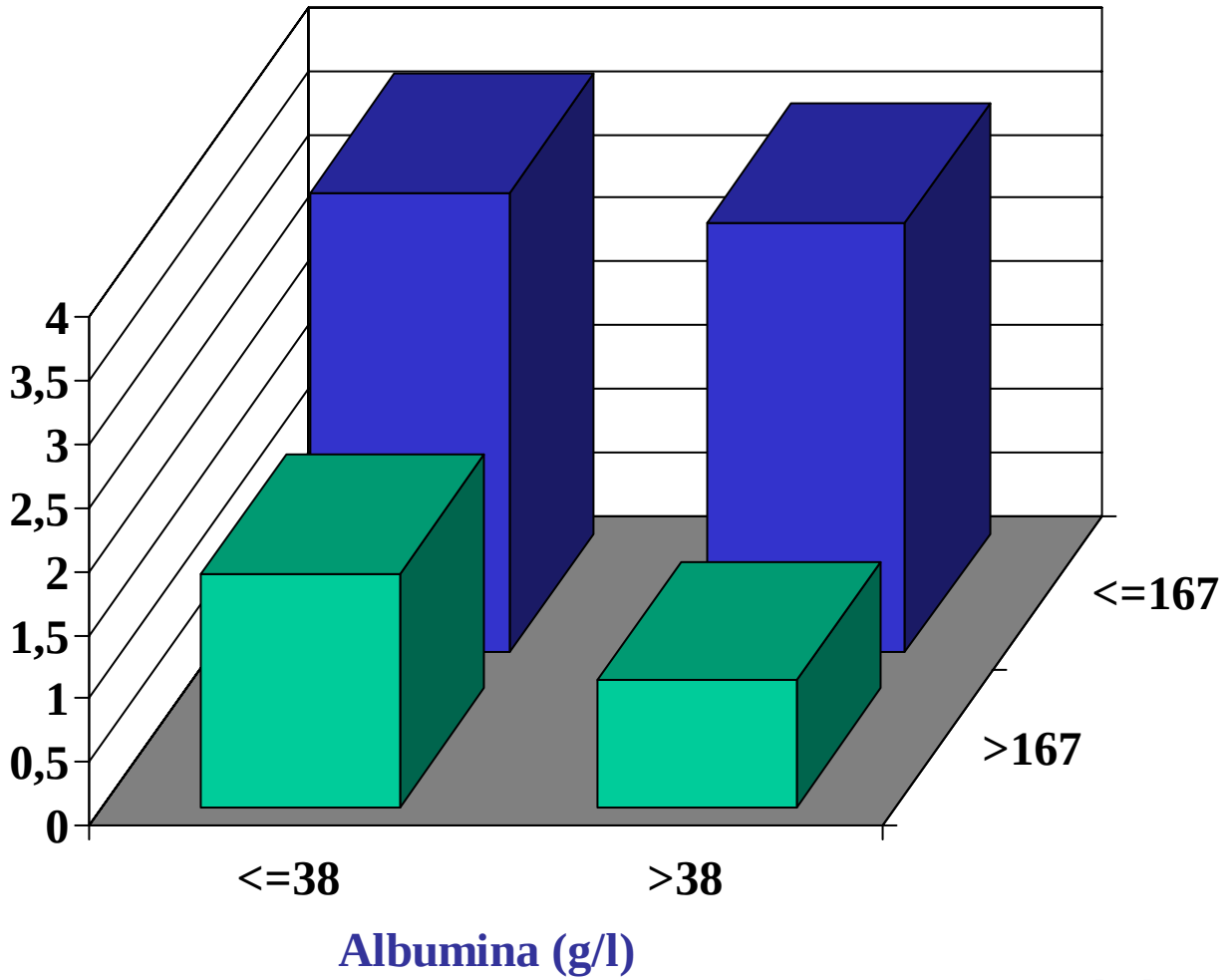
Ranieri et al, 1998

Variabili Biologiche

- **La concomitanza di bassi livelli sierici di albumina e di colesterolo può identificare anziani con buono stato funzionale ma che sono ad elevato rischio di mortalità e declino funzionale**

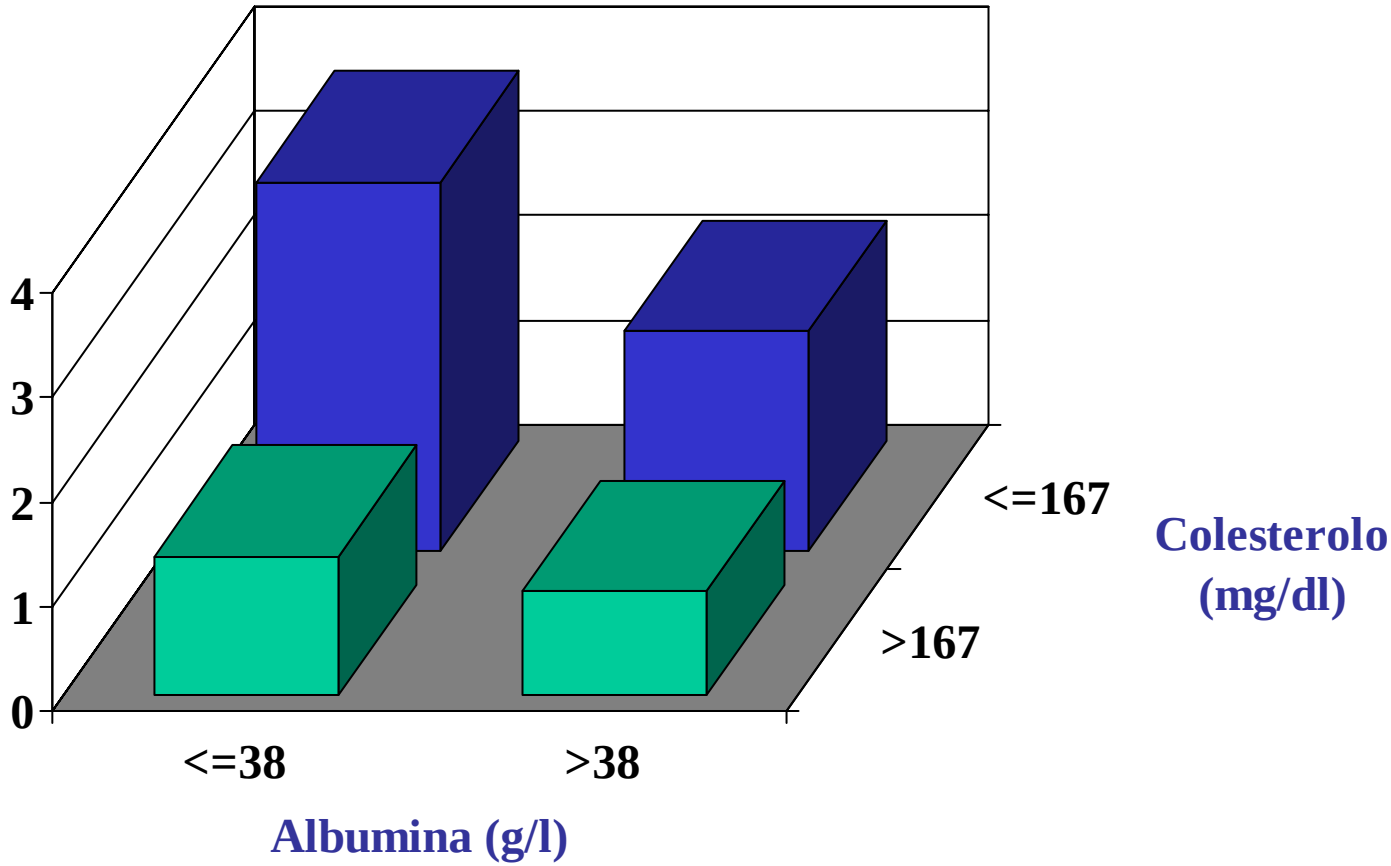
Reuben DB et al, 1999

Rischio Relativo di Mortalità a 3 anni



Mod. da Reuben et al, 1999

Rischio Relativo di Mortalità a 7 anni



Mod. da Reuben et al, 1999

Markers Proinfiammatori

•L’alterazione del’omeostasi metabolica è stata sempre più spesso associata ad una over-espressione di marcatori dell’infiammazione.

Bortz, J Gerontal 2002

Markers Proinfiammatori

- Elevati livelli di IL-6 si associano all'insorgenza di disabilità fisica in soggetti sani al domicilio

Ferrucci et al., JAGS 1999

- Elevati livelli di markers infiammatori (IL-6, PCR) sono associati a elevata morbidità e mortalità in soggetti anziani

Harris et al., Am J Med 1999

Markers Proinfiammatori

•Elevati livelli di IL-6 e TNF-alfa si associano a scarsa massa e forza muscolare in persone funzionalmente autonome

•Massa muscolare: appendicular skeletal muscle mass (dual-energy x-ray absorptiometry, DXA), midthigh cross-sectional muscle area (CT)

•Forza muscolare: isometric grip strength, isokinetc knee extensor strength

Visser et al., J Gerontol 2002

Markers Proinfiammatori

Parameter	White Men	Black Men	White Women	Black Women
Appendicular Muscle Mass (kg)				
Low**	24.3 (0.2)	26.8 (0.3)	16.2 (0.1)	19.7 (0.2)
Intermediate	24.9 (0.1)	27.0 (0.2)	16.2 (0.1)	19.1 (0.1)‡
High	24.4 (0.2)†	26.0 (0.3)†,‡	15.9 (0.1)†	18.9 (0.2)‡
	.6§	.05	.1	.003
Thigh Muscle Area (cm^2)				
Low	251.9 (2.3)	282.6 (3.9)	172.2 (1.5)	206.4 (2.1)
Intermediate	258.2 (1.9)	285.0 (3.2)	171.5 (1.4)	203.6 (1.9)
High	254.5 (2.2)	264.2 (4.1)†,‡	166.6 (1.8)†,‡	197.5 (2.6)‡
	.5	.002	.03	.01
Grip Strength (kg)				
Low	75.0 (1.0)	83.1 (1.5)	46.8 (0.6)	52.1 (0.8)
Intermediate	75.7 (0.8)	82.5 (1.3)	44.4 (0.5)‡	50.0 (0.7)‡
High	73.7 (0.9)	74.1 (1.6)†,‡	43.3 (0.7)‡	47.1 (1.0)†,‡
	.3	.0001	.0002	.0002
Knee Extensor Strength (Nm)				
Low	130.7 (2.3)	139.0 (3.5)	79.8 (1.2)	89.3 (1.8)
Intermediate	134.3 (1.9)	138.5 (3.1)	80.0 (1.1)	86.7 (1.6)
High	126.9 (2.2)†	128.8 (3.8)†	75.1 (1.5)†,‡	81.4 (2.3)‡
	.2	.07	.03	.01

Visser et al., J Gerontol 2002

Markers Proinfiammatori

IL-6 potrebbe avere un effetto diretto sull'atrofia muscolare o svolgere un ruolo patofisiologico centrale in specifiche malattie che ne spiegherebbe l'associazione con il deficit funzionale e con la mortalità

Ferrucci et al, J Am Geriatr Soc. 1999

Frailty e Biologia

- Elevati livelli di IL-6 e PCR predicono l'insorgenza di disabilità e sono associate a maggiore mortalità
- Questi markers di infiammazione hanno però una limitata associazione la performances fisica in soggetti sani

Taaffe et al., J Gerontol 2000

Frailty e Biologia

•Non è ancora chiaro se i livelli elevati di citochine proinfiammatorie siano la “causal pathway” per lo sviluppo di disabilità o un marker di malattia associato alla disabilità

Visser et al., J Gerontol 2002

Dalla biologia alla ricerca di un fenotipo

Frailty in older adults: evidence for a phenotype

Fried L, J Gerontol 2001

Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care

Fried L, J Gerontol 2004

Frailty

- State of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality.
- Frailty can be defined as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation, of multiple physiologic systems.

Fried et al, *Journal of Gerontology, 2004*

Frailty

- This decreased reserve results in difficulty maintaining homeostasis in the face of perturbations, whether they are extremes of environmental temperature, exacerbations of a chronic disease, an acute illness, or an injury.

Fried et al, *Journal of Gerontology, 2004*

Frailty

- Frailty is an **aggregate expression of risk** resulting from age- or disease-associated physiologic accumulation of subthreshold decrements affecting multiple physiologic systems.

Fried et al, *Journal of Gerontology, 2004*

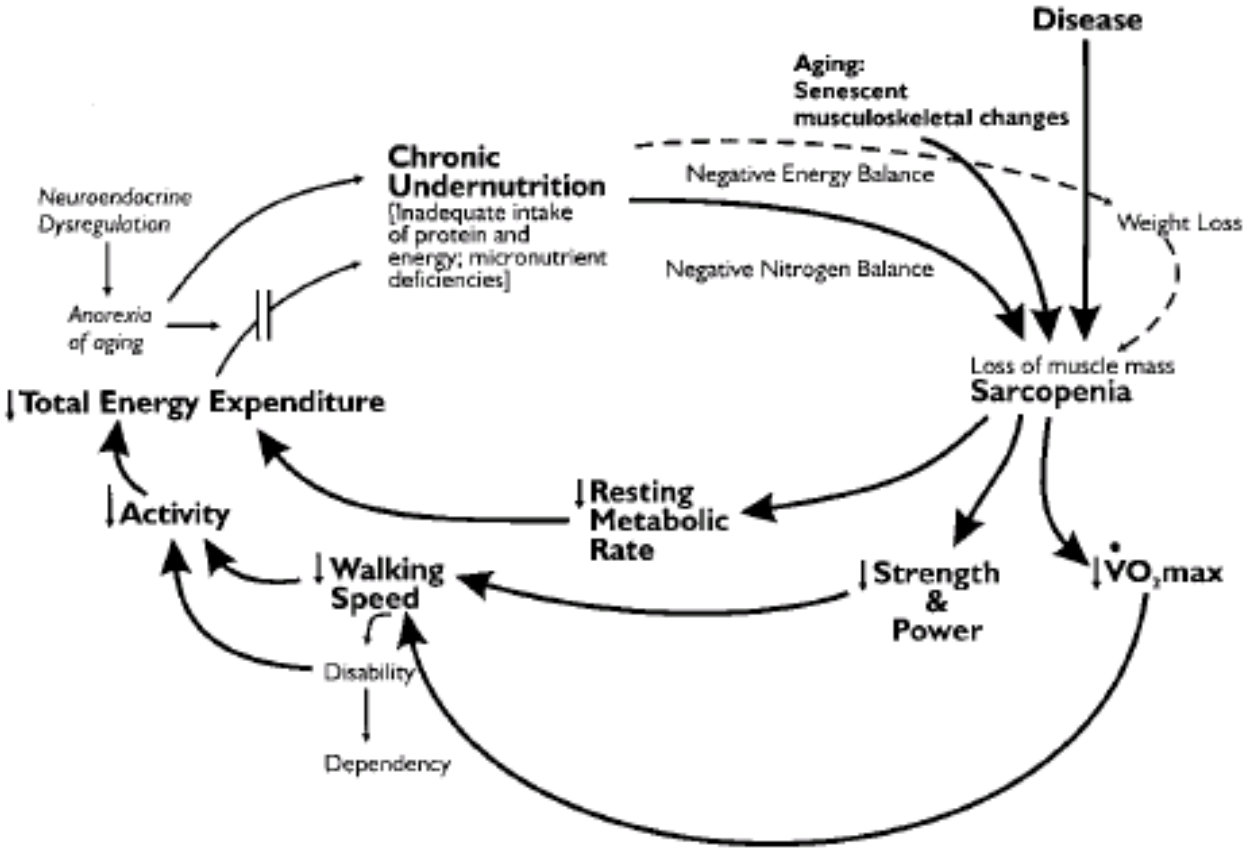
Frailty

Systems in which such physiologic decrements in mass or function have been demonstrated with age:

- neuromuscular, such as sarcopenia and decrease in muscle fiber function;
- osteopenia;
- dysregulation of the hypothalamic axis, of inflammation and of immune function;
- heart rate variability.

Fried et al, *Journal of Gerontology, 2004*

Cycle of Frailty



Fried et al, *Journal of Gerontology, 2001*

Frailty

- When the losses of reserve reach an aggregate threshold that leads to serious vulnerability, the syndrome may become detectable by looking at clinical, functional, behavioral, and biological markers…
- …either when unmasked by stressors
- …in a clinical phenotype of a final common pathway

Fried et al, *Journal of Gerontology, 2004*

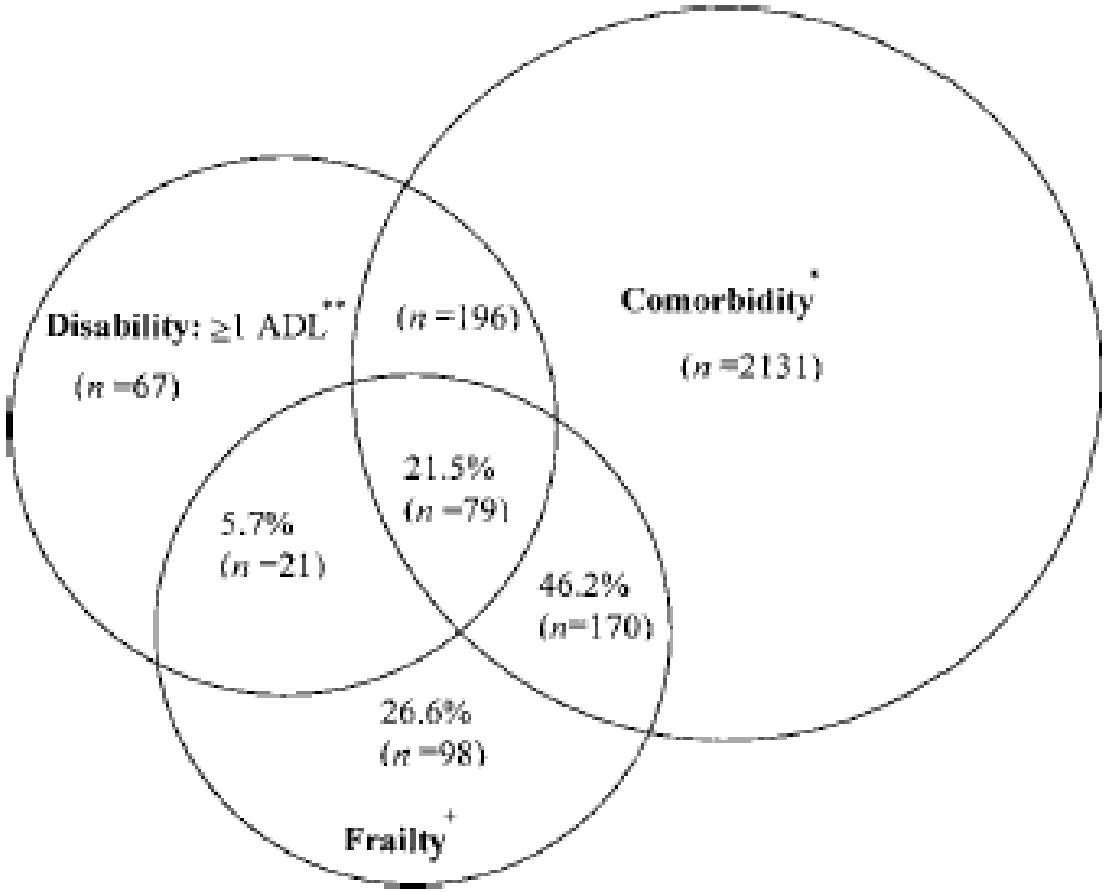
Frailty

Table 1. Frailty-Defining Criteria: WHAS and CHS

Characteristics	WHAS		CHS	
	Definition	%*	Definition	%*
Weight loss	Either of: i) Weight at age 60 – weight at exam ≥10% of age 60 weight or ii) BMI at exam < 18.5 kg/m^2	12.7	Lost >10 pounds unintentionally in last year	7.3
Exhaustion	Self-report of any of: i) low usual energy level (≤3, range 0–10)†, ii) felt unusually tired in last month‡, or iii) felt unusually weak in the past month‡	14.1	Self-report of either of: i) felt that everything I did was an effort in the last week, or ii) could not get going in the last week	21.3
Low energy expenditure§	90 on activity scale (6 items)	19.8	270 on activity scale (18 items)	24.1
Slowness§	Walking 4 m: Speed ≤ 4.57/7 for height ≤159 cm or Speed ≤ 4.57/6 for height >159 cm	31.3	Walking 15 feet (4.57 m): Time ≥ 7 for height ≤ 159 cm or Time ≥ 6 for height >159 cm	38.0
Weakness§	Grip strength: As for CHS	20.8	Grip strength ≤17 for BMI ≤23, ≤17.3 for BMI 23.1–26, ≤18 for BMI 26.1–29, or ≤21 for BMI >29 kg/m^2	26.2
Overall frailty status	Robust	44.9	Robust	33.2
	Intermediate	43.8	Intermediate	55.2
	Frail	11.3	Frail	11.6

Bandeen-Roche et al, *Journal of Gerontology, 2006*

Frailty



Fried et al, *Journal of Gerontology, 2004*

Frailty e Riabilitazione

As a consequence of illness, injuries, or major surgery, many older adults experience a loss of muscle mass and strength, leading to the development of profound deconditioning.

Sullivan et al, *Journal of Gerontology, 2007*

Frailty e Riabilitazione

- There is an accumulating body of evidence in support of progressive resistance exercise training (PRT) as an intervention to delay or reverse sarcopenia.

Binder et al, *Journal of Gerontology, 2005*

Frailty e Riabilitazione

- Numerous studies performed in healthy older adults have consistently shown that high intensity PRT induces significant increases in fat-free mass, muscle fiber area, and muscle crosssectional area

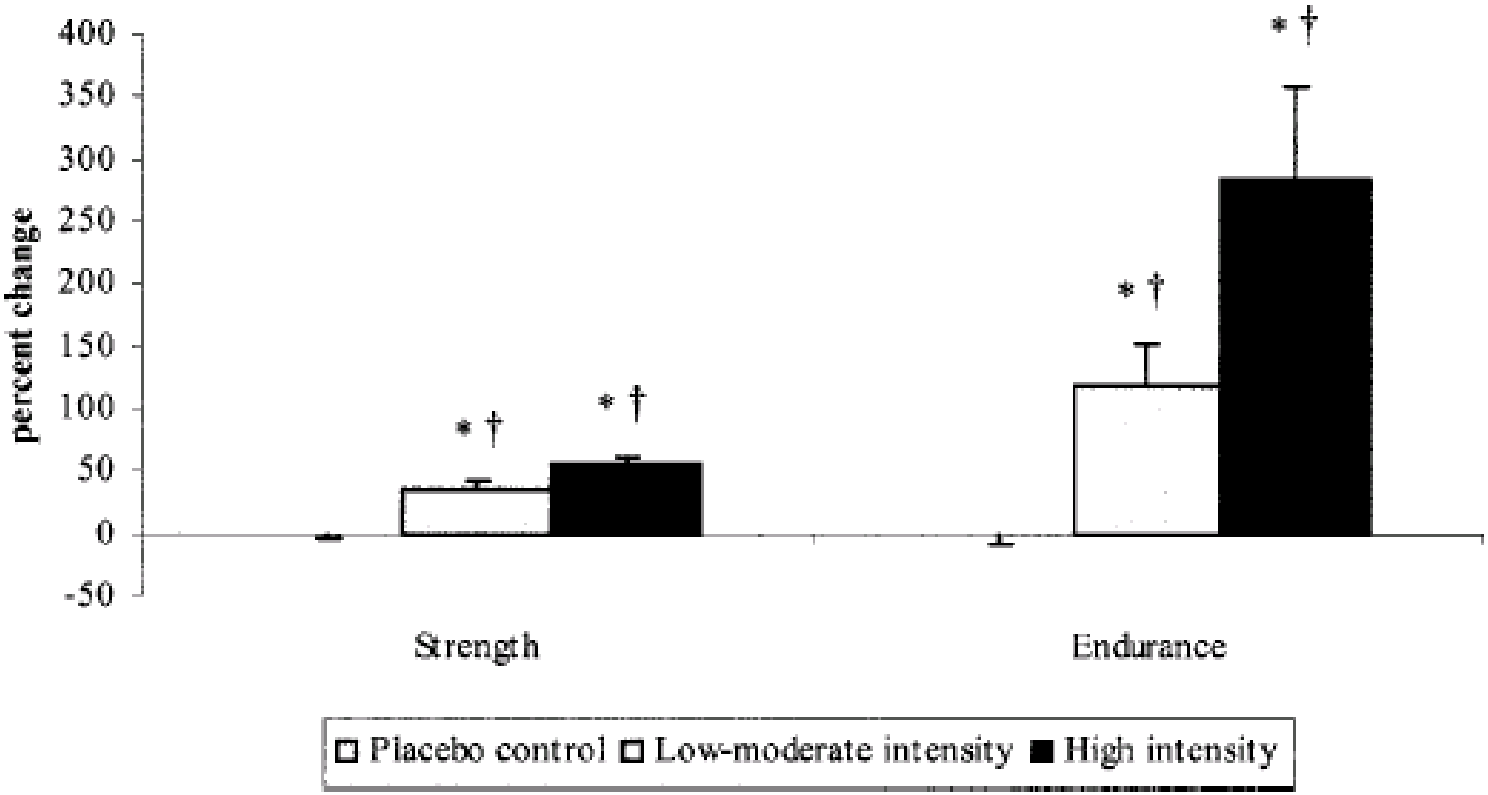
Binder et al, *Journal of Gerontology, 2005*

Frailty e Riabilitazione

- Strong dose–response relationships between resistance training intensity and strength gains, and between strength gains and functional improvements after resistance training.

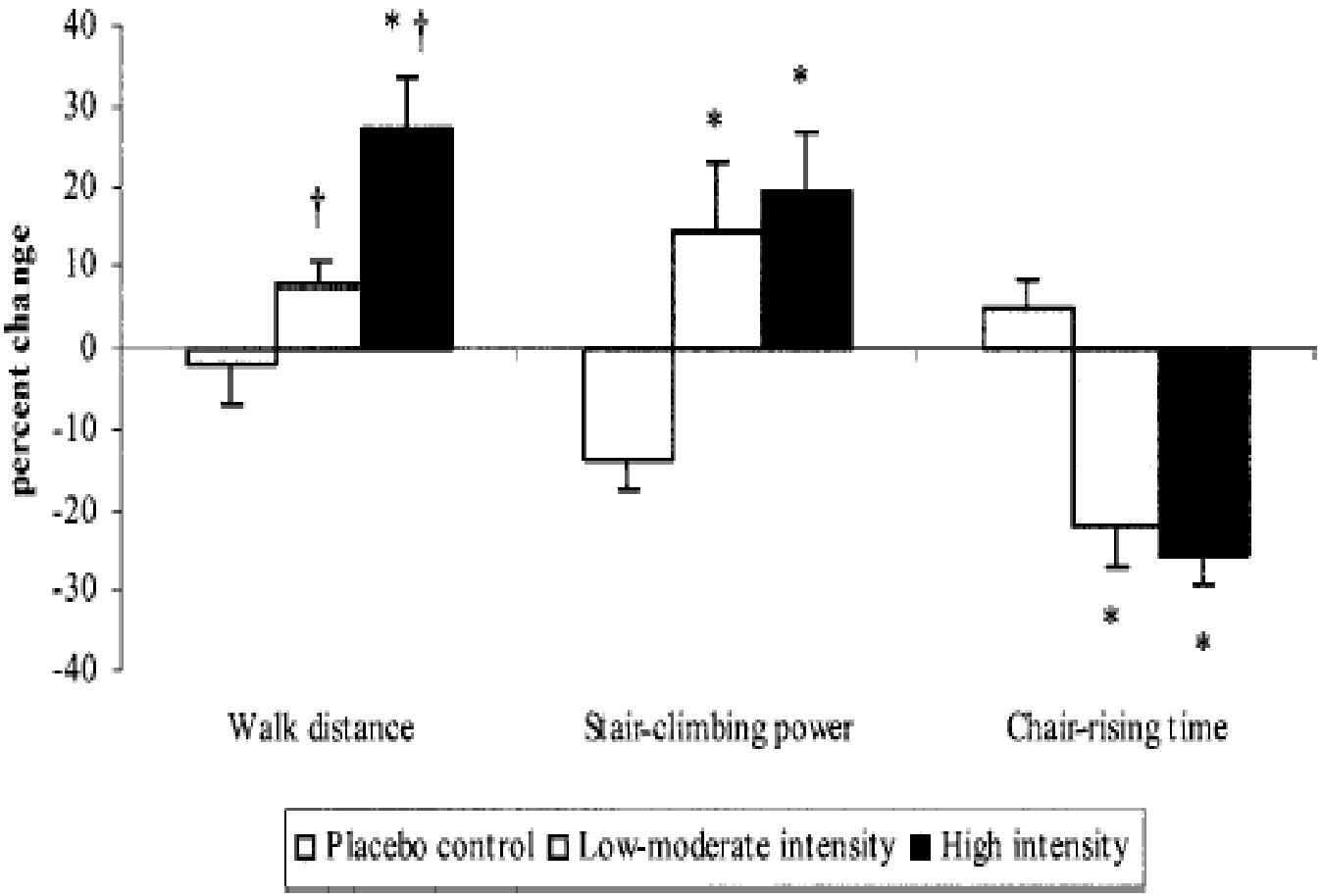
Fiatarone Singh et al, *Journal of Gerontology, 2004*

Frailty e Riabilitazione



Fiatarone Singh et al, *Journal of Gerontology, 2004*

Frailty e Riabilitazione



Fiatarone Singh et al, *Journal of Gerontology, 2004*

Frailty e Riabilitazione: limiti del modello

- 1) active serious illness within the past 6 months or conditions that would contraindicate weight training;
- 2) cognitive impairment judged to interfere with informed consent or completion of assessments or ET;
- 3) neuromuscular disorders more difficult to ameliorate with exercise (severe Parkinson's disease, stroke with hemiparesis,
- myasthenia gravis);
- 4) sensory impairments judged to interfere with following instructions for testing or exercise;
- 5) chronic use of steroids or immunosuppressive drugs;
- 6) use of estrogen, androgen, or progesterone-containing compound
- within 12 months;
- 7) cigarette use within 12 months;
- 8) diagnosis of cancer within 5 years (except for superficial skin cancer).

Binder et al, *Journal of Gerontology, 2004*

Frailty e Riabilitazione: limiti del modello

- (a) cognitive impairment precluding understanding of the written informed consent;
- (b) practice of regular exercise outside of the research activities;
- (c) unstable cardiovascular disease, hypertension, diabetes, or any other unstable medical condition;
- (d) amputations;
- (e) hernias;
- (f) symptomatic known unrepaired aortic aneurysm;
- (g) recent (within 6 months) hospitalization for myocardial infarction, stroke, fracture, eye surgery, or laser treatment;
- (h) skin disease precluding placement of ankle weights;
- (i) musculoskeletal deformity;
- (j) neuromuscular disease;
- (k) symptomatic rheumatoid or osteoarthritis precluding planned exercises.

Fiatarone Singh et al, *Journal of Gerontology, 2004*

Instabilità clinica ed outcome avversi in riabilitazione

- Many older people who no longer need hospital care are unable to return home because of persistent cognitive and physical dysfunction.
- These individuals, who may need rehabilitation and continued medical management, are frequently discharged to post-acute care facilities (rehabilitation hospitals and skilled nursing facilities).

Levenson, Subacute and Transitional Care Handbook, 1996

Instabilità clinica ed outcome avversi in riabilitazione

- Clinical instability is a major problem in elderly patients with chronic illnesses.

- Previous studies have shown that the prevalence of adverse clinical events at discharge from acute care-hospital ranged from 16.8% in hip fractured patients to 19% in patients with pneumonia.

Halm et al, Arch Intern Med 2003

Halm et al, Arch Intern Med 2002

Instabilità clinica ed outcome avversi in riabilitazione

- Marcantonio et al, have shown that 14% of patients yearly admitted to post-acute care (PAC) rehabilitative setting were classified as delirious.
- Of the 551 patients aged 65 and older newly admitted to participating facilities from acute care hospitals, 126 had delirium symptoms on post-acute admission, for an overall prevalence of 23%.

Marcantonio et al, J Gerontol 2006
Marcantonio et al, JAGS 2003

Instabilità clinica ed outcome avversi in riabilitazione

- Several significant changes occurred after the implementation of the inpatient rehabilitation prospective payement sistem.
- Between 1994 and 2001, Inpatient Rehabilitation Facilities
  - increased efficiency as measured by patient functional gain per day
  - decreased the median LOS by 8 days while maintaining a relatively stable gain in functional improvement as measured by FIM

(Ottembacher et al , JAMA, 2004)

Instabilità clinica ed outcome avversi in riabilitazione

- The rate of discharge to home remained stable over time, but mortality after discharge increased after adjusting for age, comorbidities, and admission FIM scores.

(Ottembacher et al , JAMA, 2004)

Instabilità clinica ed outcome avversi in riabilitazione

- The medical stability of the patients admitted over this time may have changed due to the pressure to decrease the acute care LOS and to move patients to inpatient rehabilitation earlier in their recovery.
- The reason for increased mortality over time remains obscure but may reflect changes in admission criteria and medical stability of patients admitted to IRFs

(Esselman, JAMA, 2004).

Considerazioni

- Impatto dell'evento disabilitante sulle variabili di stato nella popolazione riabilitativa post-acuta:
  - Difficoltà ad utilizzare una definizione "statica" di Fragilità (ossia che utilizza dei parametri considerati in condizioni di stato)
  - Complessità dell'utilizzo di parametri di stato complessi (sarcopenia, handgrip) in pz clinicamente instabili

Considerazioni

	GERU Gussago ‘96 (n=511) Mean±SD or n(%) [a]	RACU Cremona ‘06 (n=1225) Mean±SD or n(%) [b]
Age	78.6±7.5	76.6±10.4
Mini Mental State	23.5±4.7	22.8±6.1
IDS-Charlson	5.0±1.7	3.0±2.3
BADL-Barthel Index	2.2±1.8	54.9±27.2
Serum albumin	3.6±0.4	3.1±0.4
Serum cholesterol	194.1±41.1	177.2±42.9
LOS	29.6±13.0	23.8±10.0

Considerazioni

Necessità di ricodificare il concetto di frailty nella popolazione anziana post-acuta:

- fattori predittivi di eventi avversi “dinamici”
- parametri di stato stabili nonostante l’evento acuto

Instabilità clinica ed outcome avversi in riabilitazione

Metodi

- Valutazione all'ingresso e poi quotidianamente in relazione a 7 parametri di instabilità:

Criteri di instabilità clinica.

- *Temperatura >37.8°C*
- *FC> 100/min*
- *FR>24/min*
- *Pressione arteriosa sistolica ≤90 mmHg*
- *SO2 <90% (o PaO2<60 mmHg)*
- *Inabilità a mantenere introito alimentare*
- *Stato mentale alterato**

(Halm et al. JAMA-1998, Arch Intern Med 02)

Instabilità clinica ed outcome avversi in riabilitazione

Metodi

- Ogni variabile clinica è definita stabile dopo che le rilevazioni effettuate sono tutte risultate nella norma nelle 24 ore precedenti.
- Il paziente è definito clinicamente stabile quando i 5 segni vitali, lo stato mentale e la capacità di autoalimentarsi sono conservati da almeno 24 ore.

(Halm et al. JAMA-1998, Arch Intern Med 02)

TABLE 1.a– Demographic and clinical characteristics of 496 patients consecutively admitted to our Rehabilitation and Aged Care Unit, stratified by clinical instability.

	Stable (n=381, 76.8%)	Vital Sign or Delirium (n=63, 12.7%)	Vital Sign and Delirium (n=52, 10.5%)	*p**
	Mean±SD or n(%) [a]	Mean±SD or n(%) [c]	Mean±SD or n(%) [d]	
Age	76.5±9.9 [b,c]	80.7±6.8 [a]	84.3±6.8 [a]	.000
Gender female, n°, (%)	259 (68.0%)	46 (73.0%)	41 (78.8%)	.090
Mini Mental State Examination	23.5±5.3 [b,c]	18.5±6.9 [a]	16.5±7.5 [a]	.000
Geriatric Depression Scale	5.6±3.3	6.4±23.6	6.6±4.1	.315
CIRS	1.7±0.3 [c]	1.8±0.3	1.9±0.3 [a]	.000
Drugs admission	5.1±3.6 [c]	5.8±1.8	6.5±3.2 [a]	.011
Body Mass Index	25.6±6.1 [b,c]	23.7±4.9 [a]	23.2±5.5 [a]	.002
Serum albumin	3.2±0.4 [b,c]	2.9±0.4 [a]	2.9±0.6 [a]	.000
Serum cholesterol	177.1±45.2 [c]	167.3±52.5	156.3±34.3 [a]	.001
MNA **Absent**	224 (69.8%) [b,c]	21 (43.8%) [a,c]	7 (20.0%) [a,b]	
Risk of malnutrition	79 (24.6%)	18 (37.5%)	13 (37.1%)	.000
Malnutrition	18 (5.6%)	9 (18.8%)	15 (42.9%)	

p: significance on anova or Welch test. Differences between groups were checked with a post hoc test.

TABLE 1.b– Clinical and Functional characteristics of 496 patients consecutively admitted to our Rehabilitation and Aged Care Unit, stratified by clinical instability.

	Stable (n=381, 76.8%) Mean±SD or n(%) [a]	Vital Sign or Delirium (n=63, 12.7%) Mean±SD or n(%) [c]	Vital Sign and Delirium (n=52, 10.5%) Mean±SD or n(%) [d]	*p**
IADL	2.0±1.8 [b,c]	3.0±1.9 [a,c]	3.9±1.4 [a,b]	.000
Barthel Index Pre-Admission	86.4±18.6 [b]	79.0±23.0 [a]	81.5±16.0	.007
Barthel Index Admission	63.8±24.1 [b,c]	31.8±22.1 [a]	28.5±20.3 [a]	.000
Barthel Index Discharge	83.4±21.1 [b,c]	62.9±23.2 [a,c]	39.5±32.5 [a,b]	.000
Tinetti Admission	14.1±7.8 [b,c]	6.9±7.9 [a]	4.4±6.5 [a]	.000
Tinetti Discharge	20.7±6.2 [b,c]	15.9±7.9 [a,c]	11.8±7.8 [a,b]	.000
LOS	26.0±10.9 [b]	31.4±27.6 [a]	27.6±17.3	.003
Days of instability	0.0±0.0 [b,c]	10.0±9.3 [a,c]	15.6±13.6 [a,b]	.000

p: significance on anova or Welch test. Differences between groups were checked with a post hoc test.

TABLE 1.c – Clinical characteristics and outcomes of 496 patients consecutively admitted to our Rehabilitation and Aged Care Unit, stratified by clinical instability.

	Stable (n=381, 76.8%) Mean±SD or n(%) [a]	Vital Sign or Delirium (n=63, 12.7%) Mean±SD or n(%) [c]	Vital Sign and Delirium (n=52, 10.5%) Mean±SD or n(%) [c]	*p**
Tipology				.013
Orthopedic	117 (31.0%)	33 (54.1%)	12 (23.1%)	
Neurological syndromes	128 (33.9%)	8 (13.1%)	11 (21.2%)	
Arthritis	46 (12.2%)	-	1 (1.9%)	
Cardio-Pneumo-Surgery	86 (22.8%)	20 (32.8%)	28 (53.8%)	
Rehabilitative Setting				.000
Specialistic	230 (60.5%)	57 (93.4%)	45 (86.5%)	
General Geriatric	150 (39.5%)	4 (6.6%)	6 (11.5%)	
Nutritional support	7 (1.8%)	6 (9.5%)	17 (32.7%)	.000
Contention	9 (2.4%)	18 (28.5%)	20 (38.5%)	.000
Urinary catheter discharge	6 (1.6%)	8 (12.7%)	25(49.0%)	.000
Skin lesions discharge	3 (0.8%)	2 (3.2%)	12 (23.5%)	.000

p: significance on anova or Welch test. Differences between groups were checked with a post hoc test.

Figure 1– Adverse outcome at discharge in a population of 496 patients consecutively admitted to our Rehabilitation Unit, stratified by clinical instability.

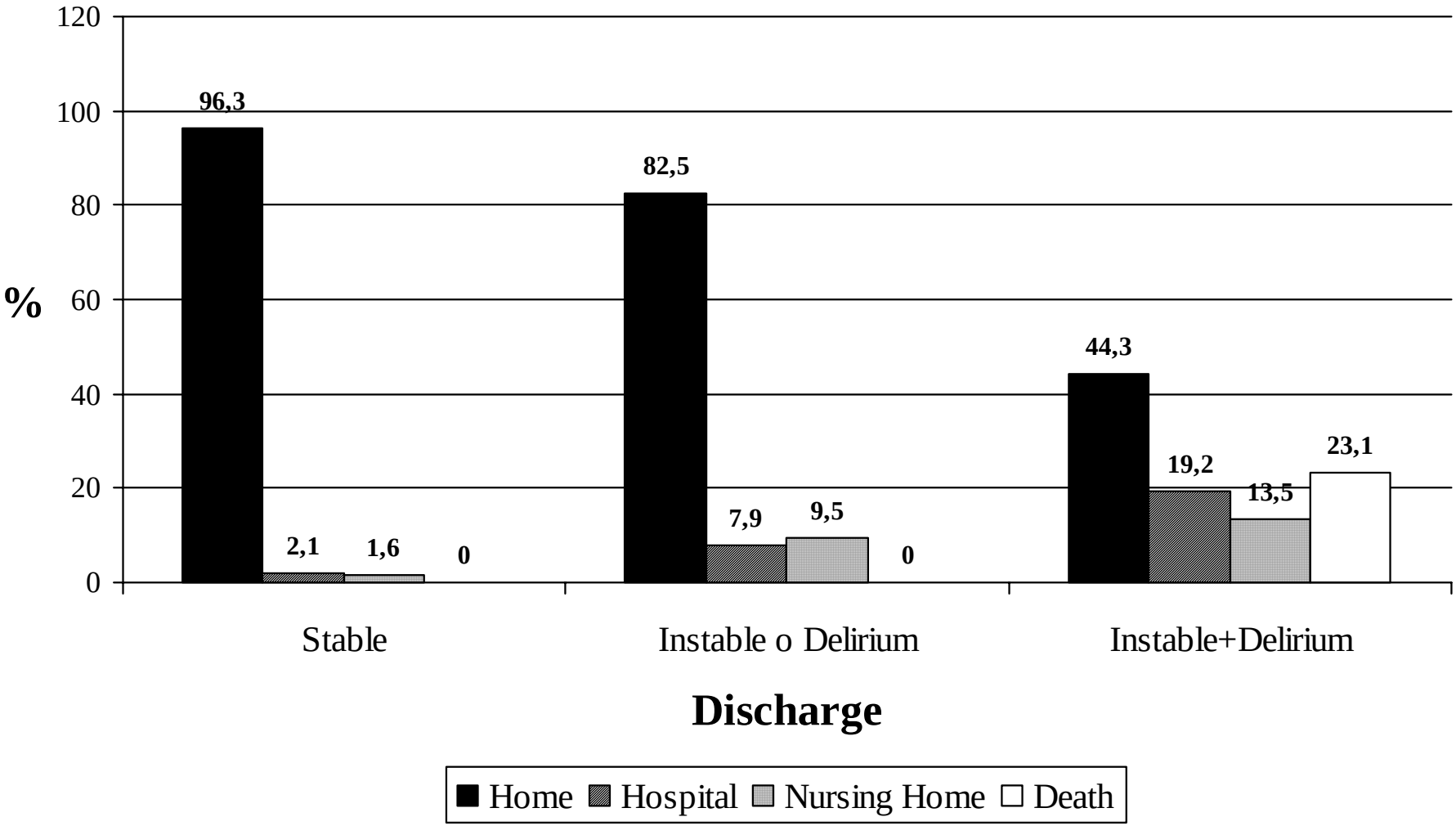


TABLE 2 – Predictors of "Instability+Delirium" in 496 Patients Consecutively Admitted to the Rehabilitation and Aged Care Unit

	OR (Confidence intervals, 95%)	*P*
Age	1.046 (1.0 to 1.2)	.023
Gender	0.983 (0.9 to 1.0)	.962
IADL	1.341 (1.1 to 1.6)	.004
Malnutrition	2.677 (1.2 to 5.9)	.000

Coefficients were computed in a multiple logistic regression model with enter selection of variables (age, gender, BI pre-admission, cholesterol, albumin, IADL, malnutrition).

Conclusioni

- **L'instabilità clinica, misurata secondo criteri validati da Halm in setting per pazienti acuti, predice outcome avversi a breve termine (morte, istituzionalizzazione e trasferimento a ICU) in una popolazione di pazienti anziani consecutivamente ricoverati in una UO Riabilitazione post-acuta**

- **Fattore predittivo "dinamico"**

Conclusioni

- **La malnutrizione e le attività strumentali di vita quotidiana sono gli unici due predittori “di stato” (premorbosi) significativamente associati all’instabilità clinica e quindi all’insorgenza di outcome avversi a breve termine.**

- **Markers di fragilità “stabili”**

So, why are our gerontological souls still bleeding?

Frailty and the Foolishness of Eos

Ferrucci et al, J Gerontol 2006