Aging Clinical and Experimental Research (2021) 33:463–467
https://doi.org/10.1007/s40520-020-01526-y

SHORT COMMUNICATION

Inflammation, pressure ulcers and poor functional status predict negative rehabilitation outcomes in postacute geriatric patients

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Received: 24 June 2019 / Accepted: 28 February 2020 / Published online: 11 April 2020

Abstract
The purposes of this retrospective study were to document the prevalence of serum C-reactive protein (CRP), a biomarker of inflammation, and its potential predictive value for Rehabilitation outcomes in post-acute elderly inpatients. The medical records of 304 elderly subjects admitted to our Rehabilitation Institute for any disease following an acute event were examined. High levels of CRP (> 0.5 mg/dl) were present in 100% of the subjects, and the value > 1.5 mg/dl ($n = 86$) predicted unfavourable outcomes ($n = 28$; 32.5% of the patients: death or transfer to other institutions). Among the patients with favourable outcomes (discharge home $n = 255$), 62.7% still exhibited severe disabilities. Pressure ulcers and low functional status also predicted unfavourable outcomes. The study highlights the need for future investigations into the possible reduction of CRP levels, after an intensive nutritional approach and combined physical interventions.

Keywords C-Reactive protein · Rehabilitation · Outcomes · Disability · Elderly

Introduction

Rehabilitation (Rehab) after acute disease, trauma and surgery plays a key role in elderly subjects in preserving or regaining physical independence, limiting the risks of disability, which is a major factor for dependency, institutionalisation, recurrent hospitalisation, falls, and increased demands for health care needs [1, 2].

Although nutrition [3] and physical/cognitive functions [2, 4] have been documented to predict geriatric Rehab outcomes, the role of possible persistent systemic inflammation (SI) after index events as a potential predictor of Rehab outcomes has not been investigated.

In this study, we hypothesised that SI may be prevalent in post-acute geriatric patients and may negatively affect Rehab outcomes, given its potential for deteriorating physical and cognitive functions [5] and inducing insulin resistance [6], which greatly contributes to physical/cognitive decline [7].

Therefore, the first objective of this retrospective study was to document the prevalence of SI in geriatric patients who were admitted to our Rehab Institute and to consider whether it could be used to predict Rehab outcomes.

The second objective was to document the prevalence of patients who were discharged home when they still had SI, hypoalbuminemia (hypoAlb) or anaemia, which are risk factors for reduced life and functional prognoses, and/or an insufficient functional recovery.

Methods

We examined the medical records of 329 elderly subjects who were consecutively admitted to our geriatric Rehab institute (GRI) between January 2015 and January 2017 for any diagnosis following an acute event (or a reacutisation

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of a chronic disease), a surgical intervention or skeletal trauma. Twenty-five cases were excluded because of prefixed exclusion criteria, i.e., death within 2 weeks from admission ($n=3$), delirium ($n=8$), self discharge ($n=14$), cancer, cancer-related surgery, thyroid diseases, renal insufficiency (serum creatininemia ≥ 2 mg/dl), and diabetes on insulin treatment. The following variables were considered in the 304 remaining patients: anthropometrics (Body Mass Index, BMI: kg/m^2), the biohumoural profile including serum C-Reactive protein (CRP) (a biomarker of inflammation), Albumin (Alb), Haemoglobin (Hb), and the Barthel Index (BI) [8], which is used to describe a subject's functional status (the total score is 0–100, where 100 is the maximal functional performance). Moreover, we considered the prevalence of pressure ulcers. Pressure ulcer/injury is localised damage to the skin and underlying soft tissue that occurs as a result of intense and/or prolonged pressure, generally associated with shear [9].

For the primary objectives of the study, we defined the presence of systemic inflammation (SI) as serum CRP > 0.5 mg/dl according to the value that represents the upper limit of normality in our laboratory. Primary objectives were also rehabilitation outcomes intended as (a) unfavourable outcomes (death, transfer to acute hospital or long-term facilities for a need to continue long-term Rehab therapy) and (b) favourable outcomes (discharge home). The secondary objectives were the prevalence of SI, hypoAlb (< 3.5 g/dl), anaemia (Hb < 12 g/dl in females, < 13 g/dl in males), and poor functional status (BI < 68/100) [2] in subjects who were discharged home.

The clinical documentation reported that all the patients had undergone Rehab programmes that were specific to their disease typology (2 sessions a day × 45 min each × 5 days a week).

Statistical analysis

All the analyses were carried out using the SAS/STAT statistical package, release 9.4 (SAS Institute Inc, Cary, NC, USA). The results are expressed as mean ± standard deviation (SD).

Using a threshold of 1.5 mg/dl for CRP (obtained by truncating the upper quartile of CRP to the first decimal), the population was stratified into two groups (CRP ≤ 1.5 mg/dl or > 1.5 mg/dl). Between group comparisons were carried out by the χ^2 test, exact Fisher's test or Mann–Whitney U test, as appropriate.

Logistic regression models were used to identify factors that were predictive of Rehab outcomes. The set of variables considered as potential predictors of outcome were age, albumin, haemoglobin, lymphocyte count, dichotomised CRP, creatinine, BI, presence of pressure ulcers, and etiology (surgery or medical).

Finally, the difference between the discharge and admission values of clinical variables in the two groups of patients were assessed and compared between-groups (CRP ≤ 1.5 mg/dl vs. > 1.5 mg/dl) and within-group (values at T0 vs. T1, Wilcoxon signed-rank test).

All tests were two-tailed and the level of statistical significance was set at $p < 0.05$.

Results

The study found a prevalence of S.I. in the vast majority (70%) of the analysed subjects on admission to GRI. The characteristics of the entire population are reported in Table 1.

Table 2 reports the rehabilitation outcome in patients with CRP ≤ 1.5 mg/dl and CRP > 1.5 mg/dl.

Table 1 Characteristics of the study patients at admission to the geriatric rehabilitation institute

N	304
Age (years)	81 ± 8.4
Sex (% population)	72.4 F + 27.6 M
Weight (kg)	63.7 ± 15.9
BMI (kg/m^2)	25.3 ± 5.5
Days from acute event	20 ± 5
Diseases	
Surgical interventions	
N (%)	199 (65.5%)
Hipfracture/replacement (%)	60.6%
Upper arm fracture (%)	29.4%
Knee replacement (%)	10%
Medical	
N (%)	105 (34.5%)
Stroke, Parkinson, Chronic obstructive pulmonary disease, Pneumonia, Chronic peripheral artery disease, bedridden	
Pressure ulcers	
N (%)	58 (19.1%)
Biohumoural variables	
Glucose (mg/dl) (n.v. 76–100)	105 ± 22.7
Urea (mg/dl) (n.v. 16–43)	46 ± 15.8
Creatinine (mg/dl) (n.v. 0.6–1.2)	0.97 ± 0.09
Erithrocyre sedimentation rate (mm I^{a}h) (n.v. ≤ 12)	32.4 ± 12.9
C-reactive protein (mg/dl) (n.v. < 0.5)	2.03 ± 3.75
Albumin (g/dl) (n.v. 3.5–5)	3.33 ± 0.48
Haemoglobin (g/dl) (n.v. ≥ 12F; ≥ 13 M)	11.7 ± 1.4
Total lymphocyte count (n°/mm^3) (n.v. 1500–2500)	1750 ± 1023
Functional status	
Barthel index (scores 0–100)	29.5 ± 25.6

Data are presented as mean ± standard deviation

Table 2 Association of systemic inflammation (CRP: C-Reactive protein) of admitted patients and subsequent rehabilitation outcomes

	Dichotomised CRP on admission (mg/dl)	
	≤ 1.5 $n = 218$	> 1.5 $n = 86$
Rehabilitation outcome		
Discharge at home	197 (90.4%)	58 (67.5%)
Death	0 (0%)	7 (8.1%)
Acute hospital	0 (0%)	5 (5.8%)
Long-term facilities	21 (9.6%)	16 (18.6%)

The percentages expressed the distribution of patients with favourable/unfavourable outcomes

Statistical analysis: Fisher's exact test $p < 0.0001$

Unfavourable outcomes occurred in 28 out of 86 (32.6%) patients with CRP > 1.5 on admission and in 21 out of 218 (9.6%) patients with CRP ≤ 1.5, while a significantly lower portion of patients with CRP > 1.5 mg/dl were discharged home (67.5% vs. 90.4%).

The prevalence of SI, hypoalb and anaemia were respectively 54.1%, 59.3% and 65.3% of the patients who were discharged home. Among subjects who achieved favourable outcomes ($n = 255$), 62.7% did not achieve a BI > 68/100 score.

When the subjects who were moved to long-term facilities ($n = 37$) and those who were discharged home with BI ≤ 68/100 are pooled together, unsatisfactory retrieval of functional status occurred in 66.3% of the entire population.

Table 3 reports the results of logistic regression analysis for the potential predictors of Rehab outcome. Only dichotomised CRP, the barthel index (negative association) and the presence of pressure ulcers were identified by the logistic regression analysis as significant and independent predictors of outcome. In particular, the odds ratio indicated that (holding all other variables constant) a CRP > 1.5 mg/dl was associated with a 5.0 fold increase in the risk of a negative outcome with respect to CRP ≤ 1.5 mg/dl, a unit increase in the barthel index was associated with a 0.94 fold decrease in the risk of a negative outcome, and the presence of pressure ulcers (19.1%) was associated with a 6.4 fold increase in the risk of a negative outcome with respect to the absence of pressure ulcers.

The value of clinical variables at admission and discharge, stratified for the SI rates are shown in Table 4.

Pressure ulcers were present in 14.1% of the discharged patients. The length of GRI stay was 50.7 ± 18.3 days.

Discussion

In this study we found persistent inflammation in most of the subjects admitted to GRI, and that a level of CRP > 1.5 mg/dl was significantly associated with a negative Rehab outcome. Moreover, there was an insufficient improvement of functional status as well as the permanence of negative biological indicators; the latter are risk factors for reduced survival and physical independence in most of the subjects who were discharged home.

Possible inflammation of premorbid status exacerbated by the acute event may explain the persistence of SI.

Persistent inflammation was likely to have been a sequela of the metabolic response to the acute events that the patients suffered. Inflammation at 2–3 months after the index event may be related to the duration of the metabolic response to stress, which can last for several years after an injury [10]. Prolonged inflammation may also be favoured by age [5] and/or underlying chronic disease/comorbidities. Inflammation undermines life and functional

Table 3 Predictors of rehabilitation outcomes in the admitted elderly patients

Variables	Df	Wald χ^2	p	Odds ratio (95%CI)
CRP (> 1.5 vs. ≤ 1.5 mg/dl)	1	11.1	0.0008	5.00 (1.94–12.84)
Barthel index[a]	1	9.1	0.0026	0.94 (0.91–0.98)
Decubitus	1	14.2	0.0002	6.36 (2.43–16.65)
Age	1	2.8	0.09	1.06 (0.99–1.13)
Gender (F vs. M)	1	0.1	0.79	0.88 (0.34–2.26)
Haemoglobin	1	0.5	0.47	1.14 (0.80–1.64)
Lymphocyte count	1	0.6	0.43	1.00 (1.00–1.01)
Albumin	1	0.2	0.67	1.29 (0.40–4.19)
Creatinine	1	0.4	0.51	0.97 (0.89–1.06)
Etiology (surgical vs. non surgical)	1	0.1	0.74	1.17 (0.45–3.02)

Statistical analysis: logistic regression analysis

[a]The test is composed of 10 items relating to subjects' activities of daily living: feeding, bathing, grooming, dressing, bowel and bladder control, toilet use, transfer from bed to chair and *viceversa*, mobility and climbing stairs

Table 4 Time course of clinical variables relative to the degree of inflammation observed on admission to the geriatric rehabilitation institute

Variables	CRP on admission≤ 1.5 ($n=218$)		CRP on admission> 1.5 ($n=86$)		p value for Δ
	Admission	Discharge	Admission	Discharge	
BMI (kg/m^2)	24.9 ± 5.2	24.4 ± 4.8†	26.1 ± 5.1	25.1 ± 5.2‡	0.09
Haemoglobin (g/dl)	11.8 ± 1.4	11.8 ± 1.4	11.2 ± 1.4	11.4 ± 1.3	0.52
Lymphocyte ($n \times$ mm^3)	1750.5 ± 785.8	1759.0 ± 756.1	1737.8 ± 1544.1	1763.4 ± 1072.6	0.28
Albumin (g/dl)	3.4 ± 0.4	3.7 ± 0.4‡	3.0 ± 0.5	3.5 ± 0.5‡	0.015
CRP (mg/dl)	0.61 ± 0.34	1.18 ± 1.86†	5.6 ± 5.44	2.9 ± 3.7‡	< 0.0001
Creatinine (mg/dl)	9.7 ± 9.4	10.2 ± 9.0‡	9.8 ± 5.8	10.0 ± 4.4^	0.84
Barthel index	34.2 ± 27.0	54.0 ± 30.3‡	21.5 ± 20.3	39.4 ± 30.4‡	0.25

Reported p values are from the Mann–Whitney U test (between-group comparison of Δ = difference between values at T1-values at T0)

^$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; Wilcoxon signed-rank test testing (within-subject) values at discharge vs. values on admission

prognoses by inducing multiorgan failure and altered immune response leading to increased risk of mortality. Moreover, inflammation promotes muscle hypercatabolism and dysfunction, and inhibits muscle repair, which are all factors that cause a subject's functional decline [11]. Finally, inflammation can impair insulin signalling for glucose transport [6] and intracellular glucose metabolism, thus causing body wasting and cognitive alterations, especially in elderly subjects [12]. It would, therefore, not be surprising for CRP, which has a direct pro-inflammatory activity [13], to be found to be significant for Rehab outcomes.

It is important to note that the measure of CRP is easily available and its predictive capacity may be especially useful for clinical settings, in addition to the functional and nutritional assessments.

Systemic inflammation is likely to have contributed to lower circulating Alb and Hb.

Pressure ulcers were also shown to be an independent predictor for unfavourable Rehab outcomes. Pressure ulcers perpetuate/accentuate (vicious circle) inflammation, increase the risk of infection, cause tissue protein breakdown and body wasting, and lengthen hospital stay [14].

On admission to our GRI, patients had severe impairment of functional status that was likely to have been the result of a combination of multiple factors including premorbid functional status, the rates of inflammatory and metabolic responses to the acute event, intercurrent acute clinical events as possible complications, and inadequate attention to nutrition and function in the acute hospital stay. Therefore, it is not surprising that, on admission, low function contributed to poor rehabilitation outcomes of the study patients. The current investigation indirectly suggests a need for supporting patients' physical and cognitive function as early as possible after the resolution of an acute event.

Patients who were discharged home undoubtedly had significant Rehab improvements in functional status, but the changes were unsatisfactory in more than 60% of them. This suggests limited efficacy of the Rehab programmes the patients had been provided with and/or high disease severity.

Anaemia and hypoalb [15–17] are likely to have contributed to low functional status. We postulate that a slight change in patients' body weight during Rehab, albeit not significant, might suggest a negative body protein-energy balance from a nutritional standpoint. This could be additive to anaemia and hypoalb in contributing to low functional status.

The results suggest that reductions in the degree of inflammation, particularly in subjects with higher inflammation rates, may be associated with important gains in both physical independence and in circulating Alb and Hb. Future investigations addressing the problems of how to reduce inflammation and improve dysprotidemia and physical performance are warranted, given that inflammation has clinical, functional and social implications for both the short and long-term follow up [18].

For these aims, nutrition interventions tailored to the metabolic alterations in patients could be helpful given that nutrition down-regulates cytokine production [19], and improves dysprotidemia [16] and functional status.

Importantly, combined nutrition and exercise training has proved to be effective in reducing frailty in elderly subjects [20].

In any case, long term studies are needed to document whether nutrition and physical exercise could change the burden of inflammation and patients prognosis.

A major limitation of the study was the absence of data on patients' nutritional intakes that have a great impact on physical and cognitive functions and mood, especially in a period of patient clinical metabolic recovery. A strength of

this study was to highlight the problem of inflammation as a factor that hinders the functional recovery of postacute geriatric patients.

Funding The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical standards

Conflict of interest The author Roberto Aquilani is a scientific consultant at Professional Dietetics (Milano, Italy). The other authors declare no conflict of interest.

Statement of human and animal rights The protocol was approved by the Ethical-Technical Committee of our GRI (Atti/2018/SM/R002/2018 February 23).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Fried LP, Guralnik JM (1997) Disability in older adults: evidence regarding significance, etiology, and risk. J Am Geriatr Soc 45:92–100
2. Bellelli G, Magnifico F, Trabucchi M (2008) Outcomes at 12 months in a population of elderly patients discharged from a rehabilitation unit. J Am Med Dir Assoc 9:55–64
3. Diekmann R, Wojzischke J (2018) The role of nutrition in geriatric rehabilitation. Curr Opin Clin Nutr Metab Care 21:14–18. https://doi.org/10.1097/MCO.0000000000000433
4. Calle A, Onder G, Morandi A (2018) Frailty related factors as predictors of functional recovery in geriatric rehabilitation: the sarcopenia and function in aging rehabilitation (SAFARI) multicentric study. J Nutr Health Aging 22:1099–1106. https://doi.org/10.1007/s12603-018-1060-2
5. Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol Biol Sci Med Sci 69:S4–9
6. D'Alessandris C, Lauro R, Presta I et al (2007) C-Reactive protein induces phosphorylation of insulin receptor substrate-1 on Ser307 and Ser612 in L6 myocytes, thereby impairing the insulin signalling pathway that promotes glucose transport. Diabetologia 50:840–849
7. Honors MA, Kinzig KP (2012) The role of insulin resistance in the development of muscle wasting during cancer cachexia. J Cachexia Sarcopenia Muscle 3:5–11. https://doi.org/10.1007/s13539-011-0051-5
8. Mahoney Barthel FI (1965) Functional evaluation: the barthel index. Md State Med J 14:61–65
9. Edsberg LE, Black JM, Goldberg M et al (2016) Revised national pressure ulcer advisory panel pressure injury staging system: revised pressure injury staging system. J Wound Ostomy Cont Nurs 43:585–597
10. Lheureux O, Preiser JC (2017) Role of nutrition support in inflammatory conditions. Nutr Clin Pract 32:310–317. https://doi.org/10.1177/0884533617695242
11. Zoico E, Roubenoff R (2002) The role of cytokines in regulating protein metabolism and muscle function. Nutr Rev 60:39–51
12. McNay EC, Recknagel AK (2011) Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. Neurobiol Learn Mem 96:432–442. https://doi.org/10.1016/j.nlm.2011.08.005
13. Verma S, Wang CH, Li SH et al (2002) A self-fulfilling prophecy: C-Reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 106:913–919
14. Thomas DR (2014) Role of nutrition in the treatment and prevention of pressure ulcers. Nutr Clin Pract 29:466–472
15. Greiwe JS, Cheng B, Rubin DC et al (2001) Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. FASEB J 15:475–482
16. Aquilani R, Zuccarelli GC, Condino AM (2017) Despite inflammation, supplemented essential amino acids may improve circulating levels of albumin and hemoglobin in patients after hip fractures. Nutrients 9:E637. https://doi.org/10.3390/nu9060637
17. Beavers KM, Brinkley TE, Nicklas BJ (2010) Effect of exercise training on chronic inflammation. Clin Chim Acta 411:785–793. https://doi.org/10.1016/j.cca.2010.02.069
18. Yoshimura Y, Yamaga M, Koga H (2018) Systemic inflammation and sarcopenia in recovery stage of stroke: the negative impact on functional rehabilitation outcomes. Annals Phys Rehabil Med 330:1769–1775
19. Qin HL, Su ZD, Hu LG (2002) Effect of early intrajejunal nutrition on pancreatic pathological features and gut barrier function in dogs with acute pancreatitis. Clin Nutr 21:469–473
20. Fiatarone MA, O'Neill EF, Ryan ND et al (1994) Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 330:1769–1775