Concentrations of C-reative protein and leukocytes as predictors of adverse health factors in the period of 30 days post-hospital discharge

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Concentrations of C-reative protein and leukocytes as predictors of adverse health factors in the period of 30 days post-hospital discharge

Abstract: C-reactive protein (CRP) and leukocytes are blood biomarkers involved in "Inflamm-Aging", which is a risk factor for the onset and progression of age-related diseases. Studies show that higher serum concentrations of these biomarkers are associated with functional disability, increased risk of low muscle strength, decreased muscle mass and mortality in the elderly. The objective was to estimate the predictive power and discriminating criteria of C-reactive protein and leukocyte concentrations for the risk of adverse health factors in the elderly within 30 days after hospital discharge (HD). Prospective cohort study using exploratory methods and blood biomarkers with 135 older adults admitted to medical and surgical clinics at a government hospital. The elderly were monitored at home after 30 days of HD for adverse health factors (rehospitalization, falls, amount of medication consumed, disability in basic and instrumental activities of daily living and mortality). CRP> 2.4; ≥ 0.7 and> 24.7 mg / dL and leukocytes ≥ 6.410; ≥ 8.690 and> 8.310 mm³ were discriminant for rehospitalization, falls and mortality within 30 days after HD, respectively. The cut-off points described may be used as a reference in the screening of hospitalized elderly vulnerable to adverse health events after hospital discharge.

Key words: Chronic inflammation; Biomarker panels; Leukocyte count; C-Reactive Protein; Related syndromes and pathologies; Risk assessment; Screening programmes; Ageing; Elderly's health.

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1. Introduction

Biological aging is characterized by a chronic level of inflammation, with the elevation of blood biomarkers in response to physiological and environmental stressors. Such biomarkers keep the immune system at the activation state, but of low level. As opposed to the acute inflammation, activating the immune system causes the inflammatory demand to cease [1].

This phenomenon known as ″Inflamm-Aging" is a risk factor for morbidity and mortality in the elderly, and plays a role in the initiation and progression of age-related diseases such as type II diabetes mellitus, Alzheimer's disease, cardiovascular diseases, osteoporosis and cancer, as well as frailty and sarcopenia [2].

However, the etiology of inflammation in the senescence process and its potential causal role in contributing to adverse health outcomes remain largely unknown. The identification of pathways that control aging-related inflammation is therefore important to understand whether treatments that modulate inflammation may be beneficial in the elderly [3].

Among the blood biomarkers involved in ″Inflamm-Aging" are C-reactive protein (CRP) and leukocytes. Studies have shown that higher serum concentrations of CRP are associated with functional disability, increased risk of low muscle strength, decreased muscle mass [4], and mortality risk with significant associations in the elderly [5].

A population-based survey [6] and clinical investigations [7,8] confirmed that high leukocyte counts, even within the normal range, are associated with late development of cardiovascular diseases, type II diabetes mellitus, metabolic syndrome, depressive behavior, and some other chronic conditions in the elderly, besides increased risk and association with all-cause mortality [5,9].

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Leukocytes are counted at a negligible cost and with high precision in routine medical check-ups. They are is important not only as inflammatory markers and precursors of disease progression and poor prognosis but are also very useful predictors of long-term survival in the elderly [6, 7]. It is, therefore, vital to evaluate leukocytes for clinical diagnosis.

Although white blood cell count is performed in routine clinical care, it is still unclear why a clinically recorded "normal" value is associated with mortality. It is therefore necessary to know the meaning of the prognosis of this test because it may be useful in early detection of morbidities, even in asymptomatic people, allowing potential interventions to avoid future adverse health effects, with possible modifications of an inflammatory state [9].

The identification of patients at increased risk of adverse health events using a comprehensive early assessment by a multidisciplinary geriatric team during the hospitalization period of elderly patients could facilitate discharge planning and clinical management. During the discharge of the patient, a short-term clinical evaluation should be included in the process in order to confirm the safety of the discharge or identify problems, with the benefit of new interventions or investigations in the home environment [10].

Studies based on inflammatory biomarkers can be part of the comprehensive clinical evaluation of the elderly, as well as serve as a reference for health professionals to predict adverse risks, especially in post-discharge care. The recognition of this condition through blood biomarkers can be considered a common, more economic and widely accepted practice in the hospital environment. In addition, it enables objective and adequate outcome measurements and also allows a better understanding of health phenomena related to inflammation. Such post-discharge measurements are able to offer

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subsidies to the planning and implementation of health promotion and protection strategies, prevention of disabilities, falls, re-hospitalization, and early mortality in elderly patients. The objective of this study was to estimate the predictive power and the discriminant criterion of the CRP and leukocyte concentrations for the risk of adverse factors to the health of elderly patients within 30 days after hospital discharge.

2. Materials and Methods

2.1. Design, Data Source and Study Population

We conducted a prospective longitudinal study. Elderly people aged 60 years and over in a university hospital (which has 296 active beds) in the state of Minas Gerais, Brazil, in the first half of 2013 to the second half of 2014 were eligible.

The number of hospitalizations of elderly patients in medical and surgical clinics in 2012 was verified for sample calculation, totaling 1455 elderly people of both sexes. Thus, a prevalence of 33.2% for the hospital setting was considered [11]. An accuracy of 3.55% and 95% confidence interval (CI) were observed for a finite population of 445 eligible admissions, reaching a sample of 266 elderly patients. Considering a loss of 50% sampling, the maximum number of interviews was 530. The recruitment process took place by systematic random sampling with a k = 2 interval. From the total elderly patients, 150 were evaluated for serum CRP levels and number of leukocytes in the hospitalization period.

The inclusion criteria were: age 60 and over; patients of both sexes; residence in the urban area of the city of Uberaba, Minas Gerais; hospitalized in the medical and surgical clinics; absence of cognitive decline evaluated by the Mini Mental State Examination (MMSE) [12]. In the hospital setting, elderly patients with neurological diseases were excluded.

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2.2. Data Collection Instruments and Procedures

The medical records of the elderly were reviewed during the study period for inclusion in the sample. Thus, data collection occurred in two moments (T1 and T2). In T1, the evaluation was performed in the period of hospitalization of the elderly in medical and surgical clinics. In T2, the evaluation occurred at home after 30 days of hospital discharge. The interviews had an average duration of 60 minutes and were carried out by the researchers, who had been duly trained by the coordinator of the project.

In T1, the socioeconomic and demographic profile of the patients was evaluated, including the following variables: sex (male or female); age in years (60 to 69 and ≥ 70 years); marital status (single, married or living with spouse, widowed or divorced); schooling in years of study (illiterate, 1 to 2, ≥ 3 years); monthly individual income in minimum salaries (no income, up to 2, ≥ 3 salaries); and biomarkers.

For measurement of biomarkers, a 5 mL sample of peripheral venous blood was obtained after a 12-hour fast, before the examination. Blood was collected on the second day of hospitalization by the lab technician of the studied hospital. The blood sample was distributed in two tubes for analysis: the first tube was free of anticoagulant for determination of serum CRP concentration, and the second tube had tetracyclic ethylenediamine acid for total count of leukocytes. Serum CRP concentrations were measured by an immunoturbidimetric method in the automated Roche Cobas Integra 400 plus analyzer (Roche Diagnostics, Basel, Switzerland), and the general leukocyte count was performed in the XE2100-D equipment (Roche Diagnostics).

In T2, at the patients' home, 30 days post-discharge, the following adverse health factors were evaluated: **1- Functional incapacity**: we used the Katz Index in its Brazilian validated version to evaluate basic activities of daily living (BADL) [13], consisting of six items that measure the individual's performance in self-care activities, which obey a

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hierarchy of complexity as follows: feeding, sphincter control, transference, personal hygiene, ability go get dressed, and bathing. The classification of this index ranges from zero to six, from independent in all the six functions to dependent in all the six functions; **2 - Re-hospitalization:** this variable was categorized into yes and no; **3 - Occurrence of falls:** this variable was categorized into yes and no; **4 - Consumption of medicines:** number of medicines used with regularity and prescribed by a physician and verification whether the names and dosages were in accordance with the most recent medical prescription; 5- **Mortality:** this variable was categorized into yes and no.

2.3. Statistical Analysis

We used descriptive statistics to identify the sample with frequency distribution and cutoff points of CRP and leukocyte concentrations and the predictive power for adverse health factors were identified through Receiver Operating Characteristic (ROC) curves, as well as their sensitivity and specificity. The larger the area under the ROC curve, the higher is the power of cutoff points to identify the presence of adverse factors. The lower limit of the area under the ROC curve to accept cutoff points as predictive of adverse factors was established at 0.60 [14] with a 95% confidence interval (CI). Cutoff points as predictors of adverse factors were determined after calculating sensitivity and specificity values. The level of significance was set at 5% ($p \leq 0.05$).

The statistical analyses were performed in the Statistical Package for Social Sciences (SPSS) version 20.0 and Medcalc version 11.4.4. The study was approved by the Human Research Ethics Committee of the Federal University of Triangulo Mineiro (Protocol nº 2511/2012), in accordance with Resolution 466/2012.

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3. Results

A total of 150 elderly patients were evaluated in the T1, in the hospital context, 56 (41.4%) from the medical clinic and 94 (69.6%) from the surgical clinic. However, in T2, 30 days post-discharge, 135 elderly were identified; there was, therefore, a loss of 15 elderly patients (addresses not provided). Of these, nine died and 126 were evaluated for adverse events after 30 days of hospital discharge.

Regarding the socioeconomic and demographic profile of the elderly, the majority were male, 60 to 69 years old, married or living with a partner, with more than 3 years of schooling, and with income less than or equal to $ 300.00 (Table 1).

Table 1: Distribution of socioeconomic and demographic variables.

Variables	N	%
Sex		
Male	79	58.5
Female	56	41.5
Age range		
60-69 years	79	58.5
≥ 70 years	56	41.5
Marital status		
Single	6	4.4
Married or living with a partner	76	56.3
Widowed or divorced	53	39.3
Education (years of study)		
0	23	17.1
1-2 years	25	18.5
≥ 3 years	87	64.4
Income		
No income	6	4.4
≤ $300	80	59.3
> $300	49	36.3

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The results of sensitivity and specificity of plasma concentrations of CRP and leukocytes as discriminants of adverse health factors (re-hospitalizations, occurrence of falls, mortality, consumption of medicines, disability in BADL) within 30 days after hospital discharge are presented in areas under the ROC curve. The areas were higher than 0.50, with emphasis on the variables re-hospitalization, occurrence of falls, and mortality (Table 2).

Table 2. Areas under the ROC curve and sensitivity and specificity values among CRP and leukocyte scores as predictors of the presence of adverse health factors.

	CRP			**Leukocyte**		
Adverse health factors	Area under the ROC curve	Sensitivity (%)	Specifity (%)	Area under the ROC curve	Sensitivity (%)	Specifity (%)
Re-hospitalization	0.547	60	59.38	0.558	53.33	69.61
Occurrence of falls	0.592	62.5	69.90	0.584	88.89	35.19
Consumption > 2 medicines	0.534	70.33	46.67	0.512	70.10	43.33
Disability in basic activities of daily living	0.514	41.67	75.26	0.523	80	36.27
Mortality	0.563	27.27	100	0.650	72.73	63.79

ROC, receiver operating characteristic; CRP, C-reactive protein

In the areas under the ROC curve with the cutoff point of the CRP and leukocyte concentrations for adverse health factors (Figure 1 to 2), we highlight that CRP > 2.4; ≥ 0.7 and > 24.7 mg/dL and leukocytes ≥ 6,410; ≥ 8,690 and 8,310 mm3 were discriminant for re-hospitalization (A), occurrence of falls (B), and mortality (C) (Figure 1).

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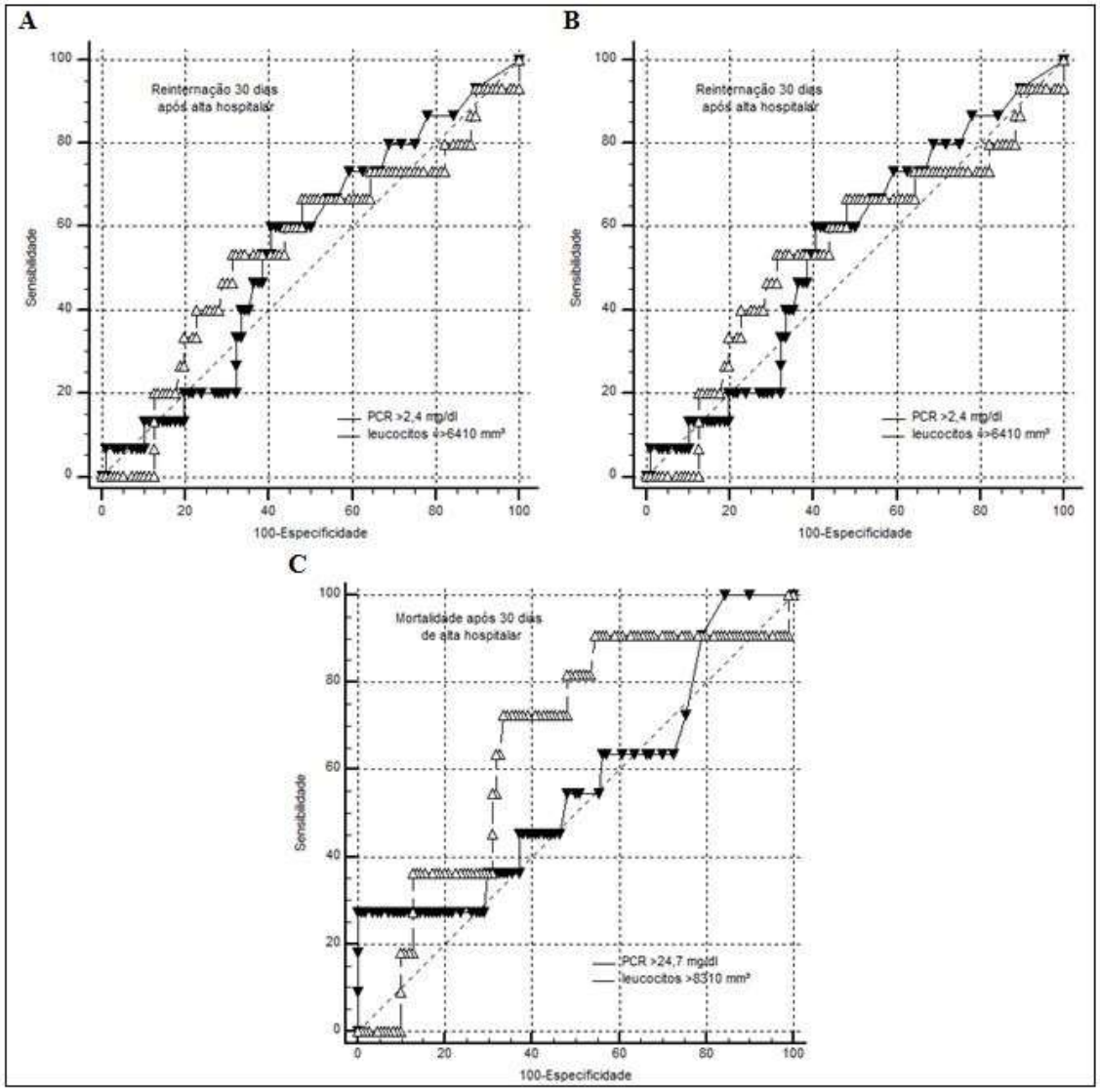

Fig.1. ROC curve showing discrimination between the PCR cutoff point and the leukocyte concentrations for adverse health factors: re-hospitalization (A), occurrence of falls (B) and mortality (C) in elderly.

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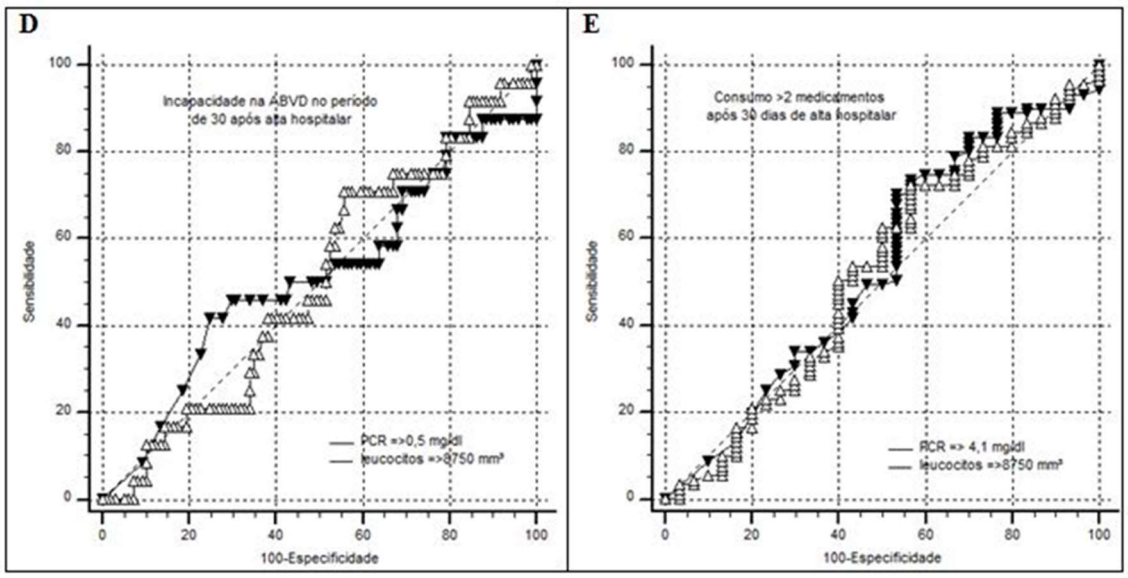

Fig. 2. ROC curve showing discriminations between the PCR cutoff point and the leukocyte concentrations for adverse health factors: consumption of medicines (D) and disability in BADL (E) in elderly.

4. Discussion

CRP and leukocyte concentrations were discriminant for re-hospitalization, occurrence of falls, and mortality. The measurement of these biomarkers in the hospitalization period can guide health professionals in the decision making, envisaging a planned hospital discharge, in order to avoid early re-hospitalization. At this point, care transition programs can contribute to decision making.

Research on care transition programs showed that intensive follow-up post-hospitalization reduces new hospitalizations and financial costs [15]. A systematic review showed that the risk of hospital readmission can be reduced by up to three months in elderly patients with any medical condition if there is a hospital discharge plan appropriate to the patient, as insertion of effective interventions [16].

However, a study examining interventions associated with reduced readmission rates in the short- (≤ 30 days), medium- (31-180 days) and long-term (181-365 days)

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showed that only high-intensity interventions were associated with short-term re-hospitalizations. Moreover, transitional care was more effective among people over 60 years of age and those admitted to general medical facilities [17].

The dosage of biomarkers of the elderly at hospital admission can guide the care to be provided by the multidisciplinary team at the time of discharge, especially in the next 30 first days, in order to avoid adverse outcomes such as re-hospitalizations.

A study in the literature shows that elderly people with increased levels of these biomarkers are more susceptible to falls [18]. The discriminant biomarkers for the occurrence of falls within 30 days after hospitalization may signal the need to emphasize preventive guidelines for patients at greater risk. There is a need for the elderly to be evaluated for risk of falls at hospital discharge and at other health services [19].

Elderly from medical-surgical units reported that they did not initially recall the interventions aimed at fall prevention received at discharge. These results suggest that health professionals need to provide information more clearly to patients and their families so that interventions are effectively implemented by the patients and caregivers without misunderstandings, in a process of collaboration and partnership [20]. Risk behavior is common among older people, because they are often independent but have difficulty recognizing their physical limitations [21].

With the increase of the elderly population attended in hospitals, it is verified that up to 25% of the vulnerable elderly patients experience an adverse event after discharge [22]. Furthermore, the elderly have more than twice the risk of having a hip fracture after hospitalization, especially in the first month post-discharge [23].

The picture of fall exposure can be mitigated. A systematic review on fall prevention showed that patient education either alone or in conjunction with a

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multifactorial intervention demonstrated that these interventions are effective in reducing falls rates during hospitalization and post-hospital discharge [24].

The mortality variable obtained the lowest sensitivity for the adverse factors represented by the CRP levels, being 27.2%, while the specificity for this biomarker was 100%. The area under the ROC curve was the largest of the adverse factors for leukocytes and was represented by high sensitivity and specificity, demonstrating that leukocytes are moderate predictors of the adverse factor mortality at 30 days post-discharge.

Data from the PolSenior project identified that a single measure of CRP concentrations in 3,632 elderly individuals was a good predictor of mortality in the entire elderly population of the research, including elderly patients who were aged without morbidity [25].

The establishment of cutoff points of CRP and leukocyte concentrations may lead to the early diagnosis of the condition of vulnerability to adverse health factors, even during hospitalization, making it possible to choose preventive measures that hinder the advance the adverse factors after hospital discharge.

To date, no single biomarker has proven to be an adequate substitute for predicting the adverse consequences of aging, such as functional decline, morbidity or mortality [26].

As in other studies with inflammatory biomarkers, one of the main limitations is the lack of specificity, because it is not yet known exactly whether the inflammation is causal, compensatory or an epiphenomenon; whether the inflammatory state is due to the aging process or to the underlying disease [27, 28].

The study has two limitations: 1. The biomarkers were measured statically, only once, at the baseline, during the hospital stay. 2. Part of the study population was

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composed of elderly patients from the surgical clinic, in the pre-surgical and post-operative phase, which may cause changes in the levels of the biomarkers involved.

More evidence is needed through experimental studies to confer to these biomarkers a predictive power of the possible adverse health factors after hospital discharge. To do this, it is necessary to identify and monitor the behavior of biomarkers, such as CRP and leukocytes, in the hospitalization process and hospital discharge. These biomarkers may be useful for the development of the therapeutic plan, such as interventions aimed at avoiding re-hospitalizations, directing health promotion actions, and preventing new adverse health outcomes.

5. Conclusion

CRP and leukocyte concentrations were discriminant for re-hospitalization, occurrence of falls, and mortality at 30 days after hospital discharge. The identification of changes in CRP and leukocyte concentrations in hospitalized elderly patients may predict the risk for adverse health conditions post-discharge. Furthermore, it may be an important strategy to be used in public health, especially considering that the hospitalization condition allows tests for measurement of biomarkers.

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