White blood cell counts in a geriatric hospitalized population: A poor diagnostic marker of infection

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White blood cell counts in the older population: a poor marker of infection

Short title: Significance of leukocytes in the geriatric unit

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Highlights :

We certify that this work is novel clinical research. A normal absolute WBCC does not rule out infection in geriatric patients. This study suggests that white blood cell count is not a reliable marker in geriatric patients. Consequently, it would also be important to assess the normal value of total and differential WBCC in geriatric patients. However, combined with CRP, WBCC represents a marker of cardiovascular disorders.

There are no conflicts of interests

Abstract:

Introduction: Older people suffer more often and from more severe infections than do younger people. Several studies have shown a correlation between higher white blood cell count (WBCC) and the presence of infection. The usefulness of increased WBCC to assess the presence of infection in geriatric patients is debated. To answer this question, we investigated the correlation between the total and differential WBCC and documented infection in hospitalized geriatric individuals.

Population and Methods: Clinical data (medical history, comorbidities, treatments, geriatric syndromes) and biological parameters were collected from 166 hospitalized geriatric patients (67-106 yrs) presenting with acute inflammation (CRP>10 mg/L) and were compared according to the presence/absence of infection.

Results: The mean WBCC was not significantly different (P=0.71) according to the presence of infection or not, although the mean CRP level was higher in the infected group compared to the noninfected group (P=0.0019). In regression analyses, the presence of infection was not associated with an increase in total and differential WBCC. Additionally, we found a positive correlation between cardiovascular risk factor (CVRF) and WBCC.

Conclusion: In geriatric patients, WBCC is not a reliable biomarker for infection; however, combined with CRP, it represents a marker of cardiovascular disorders.

Keywords: Infection, geriatric patient, aging, leucocytes, C-reactive protein

1. Introduction:

Older people are more frequently affected by severe community-acquired and nosocomial infections than younger people. Older individuals show reduced responses following vaccination and an impaired recovery following infection, which is probably related to a deregulated inflammatory response[1,2].

Total and differential WBCC are traditional markers for infections. Neutrophils are most commonly increased during acute bacterial infection; primarily, there is an increase of immature neutrophils (band neutrophils). Monocytes are associated with the late phase of acute infection and chronic infection. Lymphocytosis commonly identifies acute and chronic viral infections, and eosinophilia identifies parasitic infection[3]. Several studies demonstrated a correlation between white blood cell, lymphocyte, monocyte and/or neutrophil counts and the presence of infection[4,5]. Increased eosinophil count has been associated with the resolution of the infection. In contrast, a decreased eosinophil count and an increase in the neutrophil/lymphocyte ratio are predictive factors of mortality from bacteremia in the general population[5,6]. An elevated total WBCC > 11000 cells/µl is also associated with mortality. Whereas all infections are associated with inflammation, the inflammatory state does not necessarily accompany infection. Total and differential WBCC are also associated with medullar, immune and inflammatory disorders. For example, a high neutrophil count is associated with tissue breakdown, liver disease and stress. Monocytosis and lymphocytosis can reflect hematological diseases. High eosinophil and basophil counts are also observed with allergic reactions[3].

With aging, the correlation between WBCC and infection seems to be less efficient. In the presence of infection, 32% of geriatric patients had neither fever nor increased WBCC, which has been correlated with increased mortality. At the emergency department, 21% of patients with acute

infection do not have an increased WBCC. The majority of these patients presented a chronic inflammatory disease or immunosuppression (diabetes, neoplastic diseases and HIV) such as in geriatric patients[7,8]. In octogenarians, approximately 1/3 of patients with acute surgical abdomen presented no pyrexia or increased leukocyte count[9].

Aging, CV diseases and geriatric syndrome are associated with immune dysfunction related to immunosenescence. Aging is associated with a decrease in naive B and T cells, increases in memory B and T cells and an exhaustion of memory T and B cells, commonly named senescence of T cells. Cell senescence is a reduced capacity for cell proliferation. This phenomenon begins in young individuals but is increased particularly with aging and in patients with chronic infection such as CMV or HIV[10,11]. This decreased immune response in older individuals can explain the reduced responses following vaccination and the susceptibility to infection by new and previously encountered pathogens[12–16]. Innate immunity is also altered with aging and geriatric syndrome. The response of the innate immune system after Toll-like receptor stimulation is impaired with aging and geriatric syndrome [17,18]. Neutrophils present decreased phagocytosis and chemotaxis with aging[19,20]. Geriatric syndromes and cardiovascular (CV) diseases have also been linked with immune dysfunction such as inflammaging and increased WBCC[21–26].

Consequently, altered immune function could blunt the immune stress response of acute infection, making diagnosis more difficult. The significance of increased WBCC or differential for the diagnosis of infection is unknown in geriatric patients with an inflammatory state. Inflammatory states are characterized by an acute-phase response, such as a high level of C-reactive protein (CRP). This acute-phase response appears in both acute and chronic inflammatory states (such as autoimmune diseases, infection and CV diseases) and not only with infection [27,28]. To assess the relationship between WBCC and infection during an inflammatory state in a geriatric population, we have

retrospectively analyzed the presence or not of an increased WBCC or differential in geriatric patients admitted with inflammatory syndrome, with or without a bacterial infection.

~~2.~~ Methods and Population

Between July 2013 and February 2014, data from 166 patients (107 women and 59 men) aged between 67 and 106 years were retrospectively collected. The eligibility criterion was the presence of an inflammatory state, defined as CRP > 10 mg/L. Exclusion criteria were as follows: presence of active cancer, hematologic disease, immunosuppressive treatment (such as corticoids, NSAIDs, chemotherapy and immunotherapy) and antibiotherapy. The patients were recruited from the geriatric unit of Erasme Hospital in Brussels. The study received approval from the Erasme Hospital Ethical Review Board (Brussels, Belgium, Approval n° OM021).

2.1. *Clinical characteristics*

All subjects were analyzed for underlying illnesses by direct questioning, medical records and blood sampling. Social evaluation included determination of age, sex, home (private versus institution) and marital status. Clinical data collected included smoking and alcohol habits, pneumococcal and influenza vaccine status, allergy, body mass index (BMI), medical history, current treatment and reasons for hospitalization. Cardiovascular risk factors (CVRF) were defined as history of stroke, myocardial infarct, cardiac insufficiency, cerebral vascular disease or atheromatosis assessed by carotid or leg Doppler echography or ischemic symptoms, hypertension, type 2 diabetes, hypercholesterolemia or statin treatment, orthostatic hypotension, valvular diseases, atrial fibrillation, sick-sinus syndrome or smoking. Inflammation was defined as CRP > 10 mg/L. Bacterial infection was defined as positive blood culture, positive articular puncture or positive expectorations, pneumonia on

chest radiograph or infection documented with abdominal imagery (echography or CT scan). A positive urinary culture alone was not considered as an infection because of the important prevalence of asymptomatic bacteriuria.

We performed a Comprehensive Geriatric Assessment (CGA) to identify comorbidities and common geriatric conditions. The comorbidities and the severity of the medical problems were scored using the “Cumulative Illness Rating Scale-Geriatric” (CIRS-G), which is an instrument to quantify disease burden. It differentiates older adults with the highest risk and severity of infection with a markedly impaired vaccine response [29]. It comprises a comprehensive review of medical problems of 14 organ systems. It is based on a 0 to 4 rating of each organ system [30]. The “Geriatric Depression Scale” was used to assess the risk of depression (GDS-15) in 15 questions[31]. The assessment of “Activities of Daily Living” (ADL) was made using Katz’s scale. It includes the following items: bathing, dressing, transfer, toilet, continence and eating. Each task is graded on a 4-level scale (1 to 4 for Katz’s scale), where lower levels represent the absence of dependence and upper levels the maximal dependence for the task[32]. Cognitive functions were assessed using the “Mini Mental State Examination” (MMSE). Possible scores range from 0 to 30 points, with scores <24/30 indicating impaired cognitive function[33]. Nutritional status was assessed using the “Malnutrition Universal Screening Tool” (MUST)[34]. Social complexity was defined by the need for an intervention with a social worker (need for home care, rehabilitation nursing home or financial help). The sum of geriatric syndrome includes the following: fall, social complexity, delirium, undernutrition, dependence, depression, dysphagia, incontinence, orthostatic hypotension, inappropriate prescription, and cognitive dysfunction.

Routine biochemical assessment performed in the first 24 hours of admission to a geriatric unit comprised total and differential white blood cell counts, hemoglobin and hematocrit, renal function and ionogram, CRP, albumin, prealbumin, vitamin B12, and folic acid levels.

2.2. *Statistical analyses*

The Stata® software package version 10.2 (Lakeway Drive, Texas, USA) and IBM SPSS version 25 were used for statistical analyses. The Kolmogorov-Smirnov test was used to determine the normality of the data. The Student T test (parametric data) and the Mann-Whitney rank sum test (nonparametric data) were used to compare the mean or median between groups.

As the number of patients was not equivalent between groups presenting with an increase or not of total and differential WBCC, and as the reference value of total and differential WBCC could change with aging, we performed linear regression in place of logistic regression. The dependent variables were total and differential WBCC. The independent variables were the presence of infection, CV RF, geriatric syndrome, CRP, age and sex.

3. Results

3.1. Total/differential WBCC do not differ significantly between patients with documented infections and patients without a documented infection.

The study included 166 patients. Of these, 52% of patients (n=88) presented with an inflammatory state without a documented infection and 48% (n=78) with a documented infection. The characteristics of both groups are summarized in **Table 1**.

Table 1: Characteristics of patients presenting with an inflammatory syndrome, according to the presence of infection or not.

Parameter	Without infection	With infection	
	n=88	n=78	
Gender	24 men /64 women	35 men /43 women	0.43
	Mean (DS) or %	Mean (DS) or %	p
Age	89 (4)	80 (3)	**<0.0001**
Hospital stay (days)	21 (14)	21 (13)	0.9409
Death	7%	4%	0.379
Smoking habits	15%	14%	0.854
Alcohol consumption	12%	15%	0.481
CV RF	1,4 (1,2)	1,2 (1,2)	0.1993
At least one CV disease	72%	62%	0.151
>1 CV disease	40%	36%	0.631
Diabetes mellitus	14%	15%	0.796
Infectious comorbidities			
Sepsis		26%	
High urinary tract infection		37%	

Pulmonary infection		51%	
Hepatobiliary infection		1%	
Peritonitis		0%	
Diverticulitis		1%	
Endocarditis		3%	
Erysipelas		6%	
Arthritis		6%	
Geriatric conditions			
Cognitive impairment	50%	55%	0.511
Falls	50%	38%	0.138
Social complexity	15%	12%	0.502
Delirium	14%	9%	0.320
Malnutrition	53%	53%	0.906
Functional dependency	45%	59%	0.081
Depression risk	36%	19%	**0.017**
Dysphagia	16%	26%	0.140
Incontinence	27%	27%	0.979
Orthostatic conditions	6%	8%	0.631
Inappropriate prescriptions	6%	10%	0.293
Geriatric syndromes	3,2 (2,5)	3,2 (2,2)	0.9301

Patients presenting with a documented infection were significantly younger than patients without a documented infection. The prevalence of geriatric conditions and comorbidities did not differ between groups except for the risk of depression. The total and differential WBCC did not significantly differ between groups **(see Table 2).**

Table 2: Biological values of patients presenting with an inflammatory syndrome

Parameter	Without infection	With infection	
	Inflammatory syndrome without infection n=88	Inflammatory syndrome with infection n=78	
	Mean (DS) or %	Mean (DS) or %	P
WBC ($10^3/mm^3$)	8426 (2583)	8589 (3057)	0.7100
Neutrophils	6109 (2389)	6487 (2994)	0.3720
Lymphocytes	1331 (642)	1161 (651)	0.0954
Monocytes	751 (327)	725 (329)	0.6198
Eosinophils	179 (242)	151 (143)	0.3666
Basophils	52 (98)	31 (46)	0.0783
CRP (mg/L)	55 (53)	87 (76)	**0.0019**
Neutrophils/Lymphocytes	5,76 (4,15)	8,44 (9,38)	**0.0173**

3.2. CRP and neutrophils/lymphocytes ratio are significantly correlated with infection in older patients

Patients presenting with an inflammatory syndrome with a documented infection had a significantly higher CRP level than did patients who had an inflammatory syndrome without documented infections. The neutrophil/lymphocyte ratio was significantly higher in patients with a documented infection **(see Table 2).**

3.3. Total/differential WBCC is correlated with CVRF and CRP

We assessed whether age, sex, CVRF, geriatric syndrome, infection and CRP were associated with increases in total and differential WBCC.

First, we performed Mann-Whitney analyses between patients presenting with an increase or no increase of total and differential WBCC **(see table 3-7)**. No differences between groups were found for infection, the presence of CVRF, age and the presence of geriatric syndrome. CRP was significantly increased in patients with documented infection except for the presence of eosinophils and basophils.

Table 3: Comparison of demographic and potential influenced factors in the study population with regards to WBCC

Median (range)	Normal WBCC (30 patients)	Increased WBCC (136 patients)	p
Age	85 (68-106)	85,5 (67-96)	0.418
CV RF	1 (0-4)	1 (0-5)	0.099
Sex	49 men/87 women	10 men/20 women	0.78
Sum of geriatric syndrome	3 (0-8)	3 (0-8)	0.369
CRP	44 (11-310)	63.5 (11-320)	**0.013**
Infection	63	15	0.84

Table 4: Comparison of demographic and potential influenced factors in the study population with regards to neutrophils count

	Normal neutrophil count (107 patients)	Increased neutrophil count (59 patients)	p
Age	85 (68-106)	85 (67-98)	0.421
CV RF	1 (0-4)	1 (0-5)	0.432
Sex	40 men/67 women	19 men/40 women	0.5
Sum of geriatric syndrome	4 (0-8)	3 (0-8)	0.871
CRP	35 (11-310)	60 (11-320)	**0.003**
Infection	48	30	0.198

Table 5: Comparison of demographic and potential influenced factors in the study population with regards to monocytes count

	Normal monocytes count (113 patients)	Increased monocytes count (53 patients)	p
Age	85 (68-99)	86 (67-106)	0.967
CV RF	1 (0-4)	1 (0-5)	0.472
Sex	39 men/74 women	20 men/33 women	0.68
Sum of geriatric syndrome	3 (0-8)	4 (0-8)	0.48
CRP	44 (11-310)	59 (11-320)	**0.004**
Infection	54	24	0.868

Table 6: Comparison of demographic and potential influenced factors in the study population with regards to eosinophils count

	Normal eosinophils count (163 patients)	Increased eosinophils count (3 patients)	p
Age	85 (67-106)	81 (79-81)	0.063
CV RF	1 (0-5)	1 (0-3)	0.499
Sex	58 men/105 women	1 men/1 women	0.936
Sum of geriatric syndrome	3 (0-8)	4 (0-6)	0.727
CRP	47 (11-320)	32 (27-33)	0.071
Infection	77	1	0.545

Table 7: Comparison of demographic and potential influenced factors in the study population with regards to basophils count

	Normal basophils count (105 patients)	Increased basophils count (61 patients)	p
Age	85 (68-98)	86 (67-106)	0.225
CV RF	1 (0-4)	1 (0-5)	0.328
Sex	44 men/61 women	15 men/46 women	0.025
Sum of geriatric syndrome	3 (0-8)	3 (0-7)	0.662
CRP	56 (11-320)	36 (11-220)	**0.033**
Infection	54	24	0.089

Next, we assessed the association between the dependent factors (total and differential WBCC) and the independent factors (age, CVRF, sum of geriatric syndrome, sex and infection) **(See Table 8)**. We found no relevant association except for lymphocyte count (see below).

Table 8: Associated factors with an increase of total and differential WBCC (without CRP)

Conditions	Significant factors	p Values	Standard coefficient	Adjusted r^2	F values
WBC	None	NS			
Neutrophils	None	NS			
Lymphocytes	Age Gender	0.059 0.0002	-0.008 -0.106	0.063	3.221
Monocytes	None	NS			
Eosinophils	None	NS			
Basophils	None	NS			

Associated factors: age, CVRF, sum of geriatric syndrome, sex and infection

As CRP was significantly associated with infection, we performed the same analyses adding CRP as an independent variable **(see Table 9)**. CVRF and CRP were significantly associated with an increase of neutrophils and WBCC.

Table 9: Associated factors with an increase of total and differential WBCC (with CRP)

Conditions	Significant factors	p Values	Standard coefficient	Adjusted r^2	F values
WBC	CV RF CRP	0.03 0.001	0.171 0.274	0.054	2.558
Neutrophils	CVRF CRP	0.17 0.013	0.029 0.0001	0.08	3.37
Lymphocytes	Age Gender CRP	0.094 0.006 0.012	-0.127 -0.219 -0.199	0.094	3.847
Monocytes	None	NS			

Eosinophils	None	NS			
Basophils	None	NS			

Associated factors: age, CVRF, sum of geriatric syndrome, sex, infection and CRP

3.4. Sex, age and CRP were significantly associated with a decreased lymphocyte counts.

We assessed the association between the dependent factors (lymphocyte count) and the independent factors (age, CVRF, sum of geriatric syndrome, sex and infection) **(see Table 8)**. Age and sex were significantly associated with a decreased lymphocyte count. As CRP was significantly associated with infection, we performed the same analyses adding CRP as an independent variable **(see Table 9)**. Age, sex and CRP were significantly associated with a decreased lymphocyte count.

4. Discussion

Increased WBCC and, primarily, neutrophil count are usually reliable markers of infection in the presence of inflammatory states [4,5]. However, in some patients, WBC and neutrophil counts do not increase during infection [7].

Our retrospective study in a geriatric population failed to demonstrate a correlation between infection and total or differential WBCC. The neutrophil/lymphocyte ratio was significantly associated with the presence of infection. However, it must be interpreted with caution. In our regression

231 analyses, we found a negative correlation between lymphocyte count and age. As both groups in this
232 study were significantly different in terms of age, it could be a bias.
233 WBCC and differential are also used for the differential diagnose between bacterial and viral infection.
234 Lymphocytosis and monocytes are commonly used for the diagnose of viral infection in contrast to a
235 high neutrophil count for bacterial infection[35]. In our study, none of the patients in either group
236 presented with an increased lymphocyte count. As this study included the winter season, it would be
237 surprising if there were no viral infections observed during the study. Therefore, lymphocyte count
238 also seems to be a poor marker for viral infection in geriatric patients[36].
239
240 In contrast, CRP was significantly correlated with the presence of infection and seems to be a
241 more reliable marker for infection than WBCC in geriatric patients.
242
243 Regression analyses found that CVRF and CRP were significantly associated with an increase of
244 neutrophils and WBCC, as previously reported[37,38]. Increased WBCC are associated with low-grade
245 inflammation and CV diseases.
246 The prevalence of inflammatory diseases such as chronic kidney disease, anemia and CV
247 diseases is higher in geriatric older individuals and could reflect a greater proinflammatory burden[26,37–
248 39]. In this study, 72% of patients in the group without infection and 62% of patients in the group with
249 infection had at least one CV diseases. Chronic kidney insufficiency and anemia were also prevalent
250 in this study. The prevalence of CKI with GFR classification G3 in the group with infection and in the
251 group without infection was 44.8% and 48%; for the GFR classification G4, it was 8.9% and 10%; and
252 for anemia, it was 19% and 12.5% respectively. These chronic diseases are associated with an
253 inflammatory state that could blunt the immune response of geriatric patients during infection. For
254 example, in rheumatoid arthritis, neutrophils have impaired function when exposed to proinflammatory

cytokines such as TNFα and IL-1β[40]. Several studies have shown that innate cells of geriatric individuals secrete decreased cytokine levels upon TLR stimulation compared to healthy old individuals [18,41,42]. The absence of pyrexia or increase of WBC/neutrophil counts during an infection also reflect the decreased resistance to stressors because of an “exhaustion” of the immune system. Could low grade inflammation in older individuals be responsible for altered immune function in our geriatric patients? Could these inflammatory triggers be responsible for increased cytokine secretion and WBC count at basal states and thus for a decrease in the stress response in our geriatric patients? Bruunsgaard has shown that geriatric patients presenting with pneumonia have a prolonged inflammatory response in comparison to young people[43]. One well-known characteristic of geriatric patients is the atypical presentation of diseases (with an absence of symptoms). This is responsible for a delayed diagnosis, treatment and worse prognosis. Our hypothesis is that chronic inflammation could delay the acute immune response within infection; then, the anti-inflammatory response, which must counteract the inflammatory response, is also blunted. This could be responsible for the prolonged inflammatory response, tissue damage and reduced physiological reserve after acute diseases in geriatric patients;

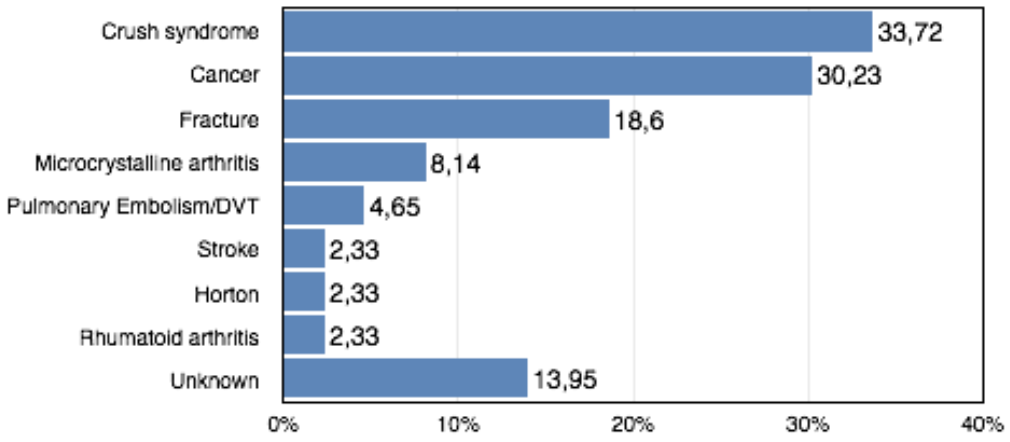
Factors other than CV diseases could also be responsible of this chronic inflammatory state, which could blunt the immune response, such as chronic infection including CMV[10], periodontitis[44], and alteration of the intestinal barrier[45]… Further studies are necessary to fully understand these mechanisms of immunosenescence.

Malnutrition is also prevalent in both groups (53%) and known to be correlated with altered immune function. Low MNA is associated with an increased risk of infection. Poor nutritional status is correlated with a low response to influenza and pneumococcal vaccination[46,47]. Cytokine production in response to TLR4 and TLR7/8 stimulation is reduced in older people with malnutrition[18]. However, in

our regression analyses, we found no association between malnutrition and WBCC. It would be interesting to further investigate functional properties of WBCC in these patients with nutritional deficiencies.

Our study is limited by its retrospective nature, the sample size and the lack of kinetic analyses of CRP and white blood cell levels during hospitalization. Almost 14% of inflammatory syndromes presented no obvious causes and could thus be due to viral infection (see figure 1).

Figure 1 represents the known causes of inflammatory syndrome in the subjects where no infection has been documented.



These observations deserve further prospective investigations comparing white blood cell and differential counts in healthy and frail older individuals presenting with an inflammatory syndrome with or without infection. It will be important to establish more reliable markers of infection in this geriatric population, such as CRP and band cell neutrophils. In critically ill patients, band cell neutrophils have diagnostic significance for sepsis, even in patients with a normal WBCC[48]. As with neutrophils, it has been proposed that evaluation of morphological changes of reactive lymphocyte affirm the differential diagnose for viral infection[36]. Other biomarkers have different cut-offs for aging and comorbidities,

such as troponin and Pro-Bnp[49,50]. Consequently, it would also be important to assess the normal value of total and differential WBCC in geriatric patients.

In conclusion, our observations suggest that – in a geriatric population - CRP are better predictive markers of infection than total/differential WBCC.

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