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Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women

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Abstract

Increasing evidence demonstrates that inflammation is associated with many pathophysiologic processes and mortality in older adults. Increase in total white blood cell (WBC) counts is recognized as an important cellular marker of systemic inflammation. However, relationships of total WBC and individual differential counts with mortality in older adults, particularly in older women, have not been adequately evaluated. To address this important question, we obtained baseline total WBC and differential counts and 5-year all-cause mortality of 624 community-dwelling women age 65–101 in the Women's Health and Aging Study cohort, excluding those with WBC counts above the normal range. Using Kaplan–Meier survival and Cox proportional hazard regression analyses, and adjusting for age, race, body mass index, smoking, and education, we identified that baseline higher total WBC, higher neutrophil, or lower lymphocyte counts were independently associated with increased mortality. No significant associations of eosinophil, monocyte, or basophil counts with mortality were observed. These results suggest that beyond acute bacterial infection, changes in counts of baseline total WBC and its specific subpopulations predict increased mortality in older women. They provide a basis for further investigation into the role of *leukocytes* in age-related inflammation and its associated adverse outcomes in older adults.

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Keywords: Total WBC count; Neutrophils; Lymphocytes; Predictive value; All-cause mortality; Older women

1. Introduction

A large body of evidence demonstrates that age-related inflammatory phenotype, as marked by elevated levels of interleukin-6 (IL-6) or C-reactive protein (CRP), is associated with many pathophysiologic processes and mortality in older adults (Ershler et al., 2000, 1997; Ferrucci et al., 1999; Harris et al., 1999; Ikeda et al., 2001; Taaffe et al., 2000; Volpato et al., 2001). Increase in peripheral white blood cell (WBC) count is recognized as an important cellular marker of systemic inflammation, primarily due to acute bacterial

infection. Several studies in middle-aged populations have demonstrated that high total WBC count is associated with increased risk for cardiovascular disease (CVD), decline in lung function, as well as coronary, cancer, and all-cause mortality (Grau et al., 2004; Lee et al., 2001; James et al., 1999; Chan-Yeung et al., 1988; Gillum et al., 1993; de Labry et al., 1990; Grimm et al., 1985). However, the relationships of counts of total WBC and its subpopulations with mortality in older adults, particularly in older women, have not been closely examined. In addition, total WBC count above the clinically defined normal range was not excluded in the studies cited above, leaving acute bacterial infection as a potential major contributor to all-cause mortality. Furthermore, our recent data from the Women's Health and Aging Studies (WHAS) have shown direct in vivo associations of total WBC and specific differential counts with circulating IL-6 levels, the hallmark of the age-related inflammatory phenotype (Leng et al., 2005). Hence, evaluating the relationships of total and differential WBC counts with

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mortality in older women, will help to advance our understanding of the role of *leukocytes* in the age-related inflammatory phenotype and its associated adverse health outcomes in this growing and highly vulnerable population.

This study, was designed to test our hypothesis that baseline total and specific differential WBC counts are associated with increased mortality in community-dwelling older women, excluding potential effects from acute bacterial infection. In the WHAS cohort, we examined the relationships of baseline total WBC and differential (neutrophil, lymphocyte, eosinophil, monocyte, and basophil) counts with 5-year all-cause mortality in community-dwelling women aged 65 years and older.

2. Methods

2.1. Study population

The Women's Health and Aging Studies (WHAS) I is a cohort study of the causes and course of disability among moderately to severely disabled women aged 65 years and older living in the community. The study design and data collection methods of the WHAS I have been described in detail elsewhere (Fried et al., 2000; Guralnik et al., 1995). Briefly, of 5316 community-dwelling women screened from Medicare beneficiaries in Baltimore, Maryland, 1409 were eligible for the study based on study entry criteria. One thousand and two women (71% of those eligible) agreed to participate in the study. The Johns Hopkins University institutional review board approved the study, and all participants gave informed consent.

Blood samples were obtained in 791 participants. Among them, 646 had blood samples sent for total and differential WBC counts. Eight participants who died right after study enrollment and four with missing data on education (indicator for socioeconomic status, an important potential confounding factor for mortality) were excluded. To minimize potential influence of acute bacterial infection, nine participants with total WBC more than $11 \times 10^3/\text{mm}^3$ or percentile of neutrophils more than 80% at baseline were excluded from the analysis. One additional subject with an influential outlier monocyte count (likely due to technical error) was also excluded, yielding a final sample size of 624 subjects for this study.

2.2. Measurements of total and differential WBC counts

Total and differential WBC counts were obtained using a Coulter counter in a well-standardized commercial laboratory in Teterboro, NJ.

2.3. Mortality follow-up

Vital status was obtained through follow-up interviews with proxies, obituaries, and matching with the National Death Index over a 5-year period.

2.4. Statistical analysis

Summary statistics were constructed for comparing baseline characteristics of the original WHAS I cohort ($N=1002$) with a subset of 624 women used in our analyses. P -values for testing the differences between the 624 women with the 378 women who were excluded for reasons detailed above in the Methods were calculated using the χ^2 test for categorical variables and analysis of variance (ANOVA) for continuous variables. Baseline distributions of total and differential WBC counts were summarized using mean, standard deviation, and by 5, 25, 50, 75, and 95th percentiles. To assess potential effect of documented history of hematologic malignancy (leukemia or lymphoma) or treatment with radiation and/or chemotherapy, data on baseline WBC counts and mortality in a subset of 26 participants with these conditions were compared with that of 598 remaining subjects for significant group differences. Kaplan–Meier survival curves were used to compare all-cause mortality across the 5 years of follow-up by tertiles of total and differential WBC counts at baseline; the log rank test was used to test the hypothesis that at least one of the survival curves differs from the others. The Cox proportional hazards models were used to study relationships of baseline total and differential WBC counts with 5-year all-cause mortality, adjusting for race, smoking status, and education. We used age as the time scale with age 65 as the time origin to take into account the left-truncated (i.e. delayed entry) and right censored survival data. This approach has also been shown to be more robust to age-related confounding and yield more clinically relevant and age-specific results (Lamarca et al., 1998). The confounding or mediating effect of body mass index (BMI) was explored in a subset of 582 women with complete BMI measurements. Two sets of Cox models were employed in all analyses: one with total and differential WBC counts modeled as continuous predictors to maximize power, and the other using tertiles derived from the baseline data for more straightforward clinical interpretation. For the former, a quadratic term was added into the model where there was a clear indication of non-linear association. We checked the assumptions of the Cox models that we fit by using Martingale residuals for validating functional form for the predictors, deviance residuals for identifying poorly predicted subjects, deviance and score residuals for identifying influential observations, and Schoenfeld residuals for checking proportionality assumption. STATA 7.0 was used for model estimation and diagnostics.

3. Results

Baseline demographic and clinical characteristics of all study participants in the WHAS I cohort and 624 participants included in this study are summarized in Table 1. Compared to the 624 subjects included in

Table 1
Selected characteristics of participants evaluated within WHAS I cohort

Characteristics	WHAS I (N=1002)	Study sub-sample (N=624)	P*
	Mean (SD)	Mean (SD)	
Age (years)	77.7 (7.8)	77.6 (7.7)	.6
Race (% white)	71.2%	71.2%	1.0
Education (% high school grad)	9.7 (3.6)	9.7 (3.7)	.7
Smoking status (% of current or previous smokers)	46.8%	47.4%	.5
BMI (kg/m ²)	28.3 (6.8)	28.9 (6.8)	<.001
Total # medical diagnoses	4.0 (1.7)	4.0 (1.7)	1.0
Self-reported health (%)			
Excellent or very good	18.5%	17.6%	<.02
Fair or good	64.0%	67.7%	
Poor	17.4%	14.6%	

P-values were calculated for comparing 624 subjects who were included in this study with 378 subjects who were excluded for reasons detailed in Section 2 above.

the analysis, the 378 participants who were not included (either did not provide blood samples or were excluded due to early death, possible acute infection, or missing covariates) had lower BMI and poorer self-reported health status. There was no significant difference in age, race, education, cigarette smoking, or total number of medical diagnoses between the two groups.

The mean, median, and percentile range of total WBC and each of the WBC differential counts (neutrophil, lymphocyte, eosinophil, monocyte, and basophil) for the study population are summarized in Table 2. At the end of 5-year follow-up, 28% (n = 175) women in our study sample died.

To determine the predictive value of baseline total and differential WBC counts for future mortality, the Kaplan–Meier survival curves across tertiles of total WBC and each of the WBC differential counts were examined. Fig. 1 shows the Kaplan–Meier survival functions as a function of age, stratified by tertiles of total WBC, neutrophil, lymphocyte, and eosinophil counts. There was a significant difference in mortality between women with low and high/mid total WBC counts (<5.6 × 10³/mm³ vs >7.0 × 10³/mm³ or 5.6–7.0 × 10³/mm³, p = .03, Log-rank test). Similarly, women with high neutrophil counts (>4430/mm³) had higher mortality than those with mid or low neutrophil counts (3230–4430/mm³ or <3230/mm³) (p < .01). On the other hand, women with low lymphocyte counts (<1540/mm³) had higher mortality compared to those with mid or high lymphocyte counts (1540–2040/mm³ or >2040/mm³)

(p = .02). No significant mortality difference was observed across the tertiles of eosinophil (p = .64, Fig. 1), monocyte or basophil counts (data not shown).

The relationships of total WBC and each of the WBC differential counts with mortality were subsequently assessed using Cox proportional hazards regression analyses, adjusting for age, race, smoking status, and education as confounding factors. Table 3 summarizes fully adjusted mortality hazard (MH) and 95% confidence interval (95% CI) for each of the total and differential WBC counts stratified by tertiles. Consistent with the findings from Kaplan–Meier survival analyses, high counts of both total WBC and neutrophils were associated with increased risk for mortality. Neutrophil counts appeared to have a step-wise significant increase in mortality hazard across tertiles and have an overall greater mortality hazard than total WBC counts. Again, low lymphocyte counts were associated with increased mortality hazard, with the lowest mortality hazard for the mid tertile. No significant changes in mortality hazard were observed across tertiles of eosinophil, monocyte, or basophil counts (Table 3).

We further investigated these relationships using total and differential WBC counts as continuous variables to maximize power and, more importantly, to explore potential threshold relationships. Consistent with the results from analyses stratified by tertiles, total WBC and neutrophil counts were positively associated with mortality (Hazard Ratio [HR] = 1.1 for every 10³ increase in total WBC count with 95% confidence interval [CI] = 1.01–1.20, p = .03 and

Table 2
Mean, median, and percentiles of total and differential WBC counts

Study variable	Mean (SD)	5 (%)	25 (%)	Median	75 (%)	95 (%)
Total WBC (10 ³ /mm ³)	6.5 (1.7)	4.0	5.2	6.3	7.5	9.8
Neutrophils (1/mm ³)	3971 (1394)	2036	2913	3805	4806	6654
Lymphocytes (1/mm ³)	1837 (622)	892	1397	1792	2189	2945
Eosinophils (1/mm ³)	149 (108)	38	77	119	195	352
Monocytes (1/mm ³)	449 (184)	183	315	425	550	810
Basophils (1/mm ³)	49 (29)	10	28	42	61	111

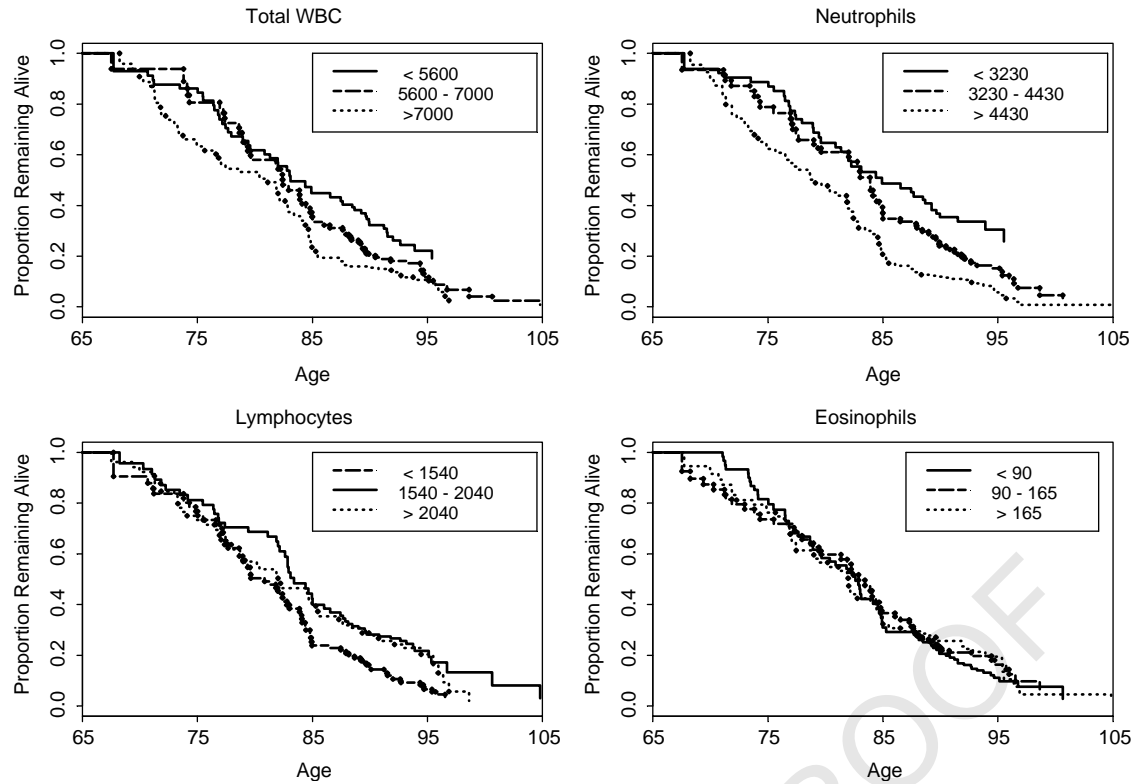


Fig. 1. Age-specific survival stratified by tertiles of baseline counts of total WBC ($p=.03$, Log-rank test), neutrophils ($p<.01$), lymphocytes ($p=.02$), and eosinophils ($p=.64$).

HR=1.2 for every 10^3 increase in neutrophil count with 95% CI=1.10–1.34, $p<.01$, respectively). Lymphocyte counts had statistically significant non-linear association with mortality, with both high and low levels of lymphocyte associated with increased mortality ($p<.01$ for the quadratic term). No significant associations of eosinophil, monocyte, or basophil counts with mortality were detected.

To examine potential confounding or mediating effect of BMI, similar analyses were carried out in a subset of 582 women with complete BMI measurements. BMI as a categorical variable (<18.6, 18.6–26.0, or >26.0 kg/m^2) was added to the Cox proportional hazards model. The results were not changed from the data presented in Table 3 and to that from the regression analysis described above (data not shown). Similar results were also obtained when BMI was added as a continuous variable in these analyses (data not shown).

To assess potential influence of documented history of hematologic malignancy (leukemia or lymphoma) or treatment with radiation and/or chemotherapy, data on baseline WBC counts and mortality in a subset of 26 participants with these conditions were compared with that of 598 remaining subjects. No significant differences in death rate, baseline total or individual differential WBC counts, or survival function were detected between the two groups (data not shown).

4. Discussion

In this study, we have demonstrated that high total WBC, high neutrophil counts, and low lymphocyte counts at baseline each are associated with increased risk for 5-year all-cause mortality in community-dwelling older women, adjusting for age, race, BMI, smoking status, and education.

Previous studies have suggested baseline total WBC count as an important predictor for subsequent CVD incidence and mortality, decline in lung function, cancer mortality, and all-cause mortality (Grau et al., 2004; Lee et al., 2001; James et al., 1999; Chan-Yeung et al., 1988; Gillum et al., 1993; de Labry et al., 1990; Grimm et al., 1985). However, these studies were performed in middle-aged populations, mostly in middle-aged men, except one that focused on men aged 64–84 years (Weijenberg et al., 1996). In addition, these studies did not exclude subjects with elevated total WBC count that was above the routinely defined normal range for potential acute bacterial infection in clinical settings. The present study specifically focused on community-dwelling women aged 65–101 years after exclusion of those who had total WBC count exceeding the clinically defined normal range. Additional analyses were performed to examine and exclude potential confounding effects of BMI or history of hematologic malignancies, radiation therapy, and/or chemotherapy.

Table 3
Adjusted mortality hazard and 95% confidence interval (95% CI) of total and differential WBC Counts for 5-year (using age) all-cause mortality

WBC variables	Mortality hazard	95% CI		P*
Total WBC (10 ³ /mm ³)				
<5.6	1.0			
5.6–7.0	1.42	0.96	2.09	.08
>7.0	1.55	1.05	2.29	.03
Neutrophils (1/mm ³)				
<3230	1.0			
3230–4430	1.60	1.05	2.45	.03
>4430	2.24	1.48	3.38	<.01
Lymphocytes (1/mm ³)				
<1540	1.65	1.15	2.38	<.01
1540–2040	1.0			
>2040	1.20	0.81	1.78	.36
Eosinophils (1/mm ³)				
<90	1.0			
90–165	0.84	0.58	1.21	.34
>165	0.84	0.58	1.20	.34
Monocytes (1/mm ³)				
<350	1.0			
350–500	0.89	0.61	1.31	.56
>500	1.03	0.71	1.49	.88
Basophils (1/mm ³)				
<32	1.0			
32–53	1.03	0.71	1.49	.88
>53	1.00	0.69	1.45	0.99

Adjusted for age, race, smoking status, and education.

Few studies have examined the relationships of differential WBC counts with mortality. A recent study of participants in the trial of Clopidogrel versus Aspirin in patients at Risk of Ischemic Events (CAPRIE), including young male and female patients (aged 21 years and above), has demonstrated that baseline total WBC as well as neutrophil counts are independent predictors of recurrent ischemic events and vascular death (Grau et al., 2004). Data of 105 healthy older men from the Baltimore Longitudinal Study of Aging (BLSA) have shown that there is a significantly lower lymphocyte count within 3 years of death when compared with 5 or 10 years before death (Bender et al., 1986). Among patients requiring hemodialysis, it has been reported that reduced lymphocyte and elevated neutrophil counts are associated with increased risk for mortality (Reddan et al., 2003). To the best of our knowledge, this is the first to report significant associations of total as well as specific differential WBC counts with increased mortality in community-dwelling older women. The significance of evaluating individual differential WBC counts is evident by the fact that they represent distinct WBC subpopulations with specific functions in the inflammation and immune systems. In addition, neutrophil and lymphocyte counts appear to have opposite effects. Therefore, the simple summation of all the differential counts may result in decreased sensitivity of total WBC count. Supportive of this, neutrophil count appeared to have

much stronger association with mortality than total WBC count (Fig. 1 and Table 3).

Possible biologic mechanisms underlying the observed associations are likely complex. *Leukocytes* may well be the cellular component of the age-related inflammatory phenotype, leading to adverse health outcomes including mortality in older adults (Brod, 2000; Plackett et al., 2004). They produce inflammatory mediators, such as IL-6, and therefore, contribute to the age-related inflammatory phenotype and its clinical consequences in older adults (Ershler and Keller, 2000). This is supported, at least in part, by our recent findings that total WBC and specific differential counts have significant associations with circulating IL-6 levels in the same cohort of community-dwelling older women (Leng et al., 2005). In addition, neutrophils produce oxidation metabolites and free radicals that cause oxidative damage to multiple tissues and organ systems and these processes are associated with increased risk of mortality (Babior, 1978; Fridovich, 1978). Lymphocytes are important circulating immune cells that play a critical role in maintaining immune function and regulating inflammation. The association of low lymphocyte counts with increased risk for mortality is likely due to age-related immunosenescence (Remarque and Pawelec, 1998; Pawelec et al., 2002). However, alternative mechanisms such as clinical or subclinical diseases that cause elevated total WBC count and changes in differential counts and lead to increased mortality are also plausible.

This study has several limitations. About a third of the WHAS I participants were not included in this study due to either unavailable blood sample or missing data, and these participants had lower BMI and reported worse health than did those included in the study. However, the identified associations of WBC counts with mortality were not appreciably affected by adjusting for BMI and self-reported health status (data not shown). Therefore, it seems unlikely that the incomplete assessment of the entire WHAS I cohort qualitatively invalidates our findings. In addition, although we vigorously excluded participants with values of WBC counts above the clinically defined normal range, potential contributions from infections, particularly chronic infections, that did not cause the WBC count to rise above the normal range could not be eliminated. Similarly, potential contributions from other diseases, such as CHD, were not considered in our analyses. However, since this study was designed to evaluate the prognostic value of baseline WBC counts for future mortality, we did not intend to adjust for potential effects from these clinical conditions. Despite these limitations, results from this study do support our original hypothesis and suggest that, despite exclusion of those with total WBC counts above the normal range, baseline total and specific differential WBC counts are significantly associated with increased 5-year all-cause mortality in community-dwelling older women. These findings provide a basis for further investigations into

561 the roles and mechanisms of *leukocytes* that contribute to
 562 adverse health outcomes in this vulnerable population.

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