Clinical Investigation

White Blood Cell Subtypes Are Associated with a Greater Long-Term Risk of Death

after Acute Myocardial Infarction

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We evaluated the association between white blood cell counts and long-term mortality rates in 2,129 patients (mean age, 65.3 ± 13.5 yr; 69% men) who had survived acute myocardial infarction. We obtained white blood cell counts and differential counts of white blood cell subtypes within the first 72 hours of hospital admission. The primary outcome was all-cause death at 1, 5, and 10 years after acute myocardial infarction.

In regard to death in the long term, we found significant negative linear associations (lymphocytes), positive linear associations (neutrophils and the neutrophil-to-lymphocyte ratio), and nonlinear U-shaped associations (basophils, eosinophils, monocytes, and total white blood cell count). After multivariate adjustment for the Soroka Acute Myocardial Infarction risk score, lymphocytes (strongest association), neutrophil-to-lymphocyte ratio, and eosinophils were independently associated with death for up to 10 years after hospital discharge. The independent associations weakened over time.

We conclude that lymphocyte count, neutrophil-to-lymphocyte ratio, and eosinophil count are independently and incrementally associated with death in the long term after acute myocardial infarction. ***(Tex Heart Inst J 2017;44(3):176-88)***

Key words: *Biomarkers/blood; coronary disease/blood; leukocyte count; models, statistical; multivariate analysis; myocardial infarction/blood/mortality; predictive value of tests; risk assessment/methods; survival analysis; time factors*

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Long-term risk stratification after acute myocardial infarction (AMI) is of great importance, because the benefits of costly interventions and medical treatments are greatest in patients who are at higher risk.[1] Evidence indicates that inflammation plays a crucial role in the atherosclerotic process, from its initiation, progression, plaque destabilization, triggering of an acute coronary event, and infarction size, to recuperation after AMI has occurred.[2-4] Moreover, it has been postulated that the greater the inflammatory response during the acute phase of AMI, the greater the proinflammatory activity during chronic (stable) phases of the disease.[5] Several inflammatory biomarkers (such as C-reactive protein and lipoprotein-associated phospholipase A_2) have been identified as important for risk stratification after AMI.[6,7] The circulating white blood cell (WBC) count and differential counts are simple, inexpensive-to-test, and readily available inflammatory markers[8] that have been associated with event rates in patients with coronary heart disease.[9,10] In addition, investigators have related high WBC count to death after AMI.[11,12] Moreover, Taglieri and colleagues[13] have reported that WBC count is an independent predictor of 3-year death in patients with non-ST-segment-elevation acute coronary syndrome (ACS), yet this predictor did not add prognostic information beyond the Global Registry of Acute Coronary Events (GRACE) score. However, prognosis was usually evaluated for a relatively short time in most studies. Investigators have often included WBC count without subtypes, included only a few subtypes, or applied incomparable methodologies. The independent prognostic value of WBC count and its subtypes, adjusted to other risk factors, has been debatable, and its evaluation as part of post-AMI prognostication has not been performed often.

We investigated the association of total and differential WBC counts in regard to long-term mortality rates (at 1-, 5-, and 10-yr follow-up) and evaluated the latter values as incremental predictors with use of a validated prognostic tool: the Soroka Acute Myocardial Infarction (SAMI) score, which integrates cardiovascular risk factors and affective comorbidities into an index score.[14,15]

Patients and Methods

Study patients were enrolled from the SAMI project database as previously described.[15] Of the 2,772 original patients discharged from a tertiary medical center with the diagnosis of AMI from 2002 through 2004, 643 were excluded. Hence, 2,129 patients were included in the current study (Table I). Reasons for exclusion were for clinical evidence of cancer (324), chronic inflammatory diseases (224), systemic infection that occurred during the index hospitalization (21), and autoimmune disease or other conditions that affect WBC count (51). In addition, we excluded 72 patients whose in-hospital stays were shorter than 3 days, and 10 whose WBC results were missing.

Our local ethics committee approved the study, which was performed in accordance with the Helsinki declaration.

Data obtained from the hospital's computerized information systems included demographic and clinical characteristics, cardiovascular risk factors and comorbidities, interventions administered as AMI treatment, and ancillary test results, as previously mentioned.[14] Death data were obtained from the Ministry of the Interior Population Registry.

We retrospectively obtained total WBC counts and peripheral differential leukocyte counts from within 72 hours of patient admission. These laboratory tests were performed with use of an ADVIA® automated hematology analyzer (Siemens Healthcare GmbH; Erlangen, Germany). For each differential leukocyte count, the neutrophil-to-lymphocyte ratio (NLR) was calculated.

Our study's follow-up period lasted up to 10 years from the patients' hospital discharge after AMI. We determined that 1,273 patients (59.8%) survived 10 years and that 856 patients (40.2%) died. For those 856, follow-up ranged from 5 to 3,628 days (9.9 yr). The median follow-up period for the entire study cohort was 8.1 years. The primary outcome was all-cause death at 1, 5, and 10 years.

Statistical Analysis

Statistical analysis of the data was performed with use of SPSS version 20 (IBM Corporation; Endicott, NY). The investigated WBC variables—total WBC count, and differential counts of WBC subtypes: neutrophils, lymphocytes, monocytes, eosinophils, basophils, and NLR—were categorized according to their quartiles (Q1–Q4). Categorizations were made separately for each period of analysis after the event (24, 24–48, and 48–72 hr) and for men and women. Univariate analysis included calculation of mortality rates for the investigated follow-up periods in the quartiled categories and their comparison with use of the χ^2 test. In addition, the relationships between the WBC count and outcomes were evaluated with use of generalized estimating equations with logit link function, considered to be repeated measures of laboratory data. The modeling was performed separately for each WBC subtype and follow-up period, and it was presented in 2 steps. During the first step, the values of the quartiles were included in the models as categorical variables and odds ratios; 95% confidence intervals and *P* values for death were calculated, with use of the lower quartile as a reference group. In step 2, WBC quartiles were included in multivariate models that comprised significantly predictive values for each period. Multivariate analysis (including the investigated WBC variables in the same model) was not performed, because of high correlation between those counts. For each test, $P \leq 0.05$ was considered statistically significant. The presence of a linear or J- or U-shaped association was first evaluated by examination of the mortality graphs for quartiles of every investigated WBC variable. Because the data regarding these variables were expressed by an ordered variable comprising only 4 categories, a quadratic (or higher-power function) test of curvature in the association was not possible. Accordingly, tests of model effects (Wald χ^2) were used to examine departure from a linear association. The latter tests compared a model in which the WBC variables were entered as 3 indicator variables with a model in which the variable was entered as a score. A nonlinear association is a better description of the relationship than is a linear association when a small *P* value results. This means that entering the data as categories (indicator variables) describes the association between WBC variables and the outcomes more accurately.

When nonlinear associations were indicated, the differences of the models' coefficients for the relationships of Q1 and Q4 with the outcomes were evaluated. A U-shaped association was defined when no significant difference in association strength between these quartiles was found. A stronger relationship of Q4 when compared with Q1 indicated a J-shaped association, and a stronger relationship of Q1 when compared with Q4 was defined as a reversed J-shaped association.

Evaluation of the incremental prognostic effect of the cell types over the SAMI score was performed by means of receiver operating characteristics analysis, and the net reclassification improvement method for a model-improvement evaluation was applied. This method[16] evaluated the change in predictive ability of the model after inclusion of an additional predictor. In this approach, the reclassification of subjects to the risk groups is performed by adding a marker to a model, separately for patients with and without outcome. In the current study, the patients were stratified into 3 equal-sized risk categories on the basis of the results of SAMI models (for each follow-up period). The reclassification was performed by adding the different WBC-subtype variables (such as eosinophils, lymphocytes, and NLR) to the existing SAMI models.

TABLE I. Baseline Characteristics and Deaths in the 2,129 Patients during the Follow-Up Periods

Variable	Value	Prevalence	Deaths		
			1 Yr	5 Yr	10 Yr
Demographic characteristics					
Age (yr)*	<65	1,010 (47.4)	26 (2.6)[a]	75 (7.4)[a]	134 (13.3)[a]
	65–75	540 (25.4)	55 (10.2)	152 (28.1)	262 (48.5)
	>75	571 (26.8)	143 (25)	340 (59.5)	459 (80.4)
	Unknown	8 (0.4)	—	—	—
Sex	Male	1,471 (69.1)	122 (8.3)[a]	325 (22.1)[a]	493 (33.5)[a]
	Female	658 (30.9)	102 (15.5)	243 (36.9)	363 (55.2)
Religion	Jewish	1,787 (83.9)	199 (11.1)[b]	508 (28.4)[a]	761 (42.6)[a]
	Muslim (Bedouin)	234 (11)	21 (9)	49 (20.9)	81 (34.6)
	Other or unknown	108 (5.1)	4 (3.7)	11 (10.2)	14 (13)
Cardiovascular risk factors					
Hypertension	Yes	1,069 (50.2)	125 (11.7)[c]	319 (29.8)[a]	486 (45.5)[a]
	No	1,060 (49.8)	99 (9.3)	249 (23.5)	370 (34.9)
Dyslipidemia	Yes	1,384 (65)	97 (7)[a]	271 (19.6)[a]	452 (32.7)[a]
	No	480 (22.5)	53 (11)	157 (32.7)	221 (46)
	Unknown	265 (12.4)	—	—	—
Diabetes mellitus, all forms	Yes	699 (32.8)	102 (14.6)[a]	246 (35.2)[a]	371 (53.1)[a]
	No	1,430 (67.2)	122 (8.5)	322 (22.5)	485 (33.9)
Diabetes mellitus without recorded renal or peripheral circulation manifestations	Yes	604 (28.4)	77 (12.7)[b]	192 (31.8)[b]	298 (49.3)[a]
	No	1,525 (71.6)	147 (9.6)	376 (24.7)	558 (36.6)
Peripheral vascular disease	Yes	293 (13.8)	54 (18.4)[a]	138 (47.1)[a]	194 (66.2)[a]
	No	1,836 (86.2)	170 (9.3)	430 (23.4)	662 (36.1)
Smoking	Yes	880 (41.3)	52 (5.9)[a]	133 (15.1)[a]	216 (24.5)[a]
	No	1,249 (58.7)	172 (13.8)	435 (34.8)	640 (51.2)
Renal diseases*	Yes	492 (23.1)	107 (21.7)[a]	243 (49.4)[a]	345 (70.1)[a]
	No	1,624 (76.3)	116 (7.1)	324 (20)	507 (31.2)
	Unknown	13 (0.6)	—	—	—
Obesity*	Yes	416 (19.5)	23 (5.5)[a]	68 (16.3)[a]	131 (31.5)[a]
	No	1,713 (80.5)	201 (11.7)	500 (29.2)	725 (42.3)
Cardiac history					
Chronic ischemic heart disease	Yes	1,598 (75.1)	134 (8.4)[a]	366 (22.9)[a]	577 (36.1)[a]
	No	531 (24.9)	90 (16.9)	202 (38)	279 (52.5)
PCI	Yes	258 (12.1)	26 (10.1)[c]	65 (25.2)[c]	109 (42.2)[c]
	No	1,871 (87.9)	198 (10.6)	503 (26.9)	747 (39.9)
CABG	Yes	168 (7.9)	23 (13.7)[c]	72 (42.9)[a]	105 (62.5)[a]
	No	1,961 (92.1)	201 (10.2)	496 (25.3)	751 (38.3)
Prior myocardial infarction	Yes	392 (18.4)	70 (17.9)[a]	158 (40.3)[a]	210 (53.6)[a]
	No	1,737 (81.6)	154 (8.9)	410 (23.6)	646 (37.2)
Other cardiac conditions					
Mitral or aortic valve disorders	Yes	345 (16.2)	58 (16.8)[a]	134 (38.8)[a]	201 (58.3)[a]
	No	1,784 (83.8)	166 (9.3)	434 (24.3)	655 (36.7)
Cardiomegaly	Yes	171 (8)	25 (14.6)[c]	59 (34.5)[b]	94 (55)[a]
	No	1,958 (92)	199 (10.2)	509 (26)	762 (38.9)
Congestive heart failure	Yes	205 (9.6)	51 (24.9)[a]	126 (61.5)[a]	165 (80.5)[a]
	No	1,924 (90.4)	173 (9)	442 (23)	691 (35.9)
Atrial fibrillation or flutter	Yes	280 (13.2)	63 (22.5)[a]	138 (49.3)[a]	198 (70.7)[a]
	No	1,849 (86.8)	161 (8.7)	430 (23.3)	658 (35.6)
Characteristics of AMI event					
AMI type	STEMI	1,381 (64.9)	125 (9.1)[b]	316 (22.9)[a]	501 (36.3)[a]
	NSTEMI	748 (35.1)	99 (13.2)	252 (33.7)	355 (47.5)
Underwent angiography	Yes	1,376 (64.6)	71 (5.2)[a]	219 (15.9)[a]	376 (27.3)[a]
	No	753 (35.4)	153 (20.3)	349 (46.3)	480 (63.7)
CAD on angiography (n=1,376)	None or insignificant	57 (4.1)	2 (3.5)[b]	5 (8.8)[a]	7 (12.3)[a]
	1-vessel	317 (23)	7 (2.2)	22 (6.9)	45 (14.2)
	2-vessel	394 (28.6)	21 (5.3)	59 (15)	102 (25.9)
	3-vessel or left main coronary artery	608 (44.2)	41 (6.7)	133 (21.9)	222 (36.5)

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TABLE I cont'd. Baseline Characteristics and Deaths in the 2,129 Patients during the Follow-Up Periods

Variable	Value	Prevalence	Deaths		
			1 Yr	5 Yr	10 Yr
Intervention for AMI*	Conservative	961 (45.1)	172 (17.9)[a]	406 (42.2)[a]	569 (59.2)[a]
	CABG	990 (46.5)	47 (4.7)	141 (14.2)	242 (24.4)
	Thrombolytic therapy or PCI	178 (8.4)	5 (2.8)	21 (11.8)	45 (25.3)
Underwent echocardiography	Yes	1,605 (75.4)	138 (8.6)[a]	354 (22.1)[a]	560 (34.9)[a]
	No	524 (24.6)	86 (16.4)	214 (40.8)	296 (56.5)
Echocardiographic results (n=1,605)					
Severe LV dysfunction*	Yes	168 (10.5)	42 (25)[a]	87 (51.8)[a]	114 (67.9)[a]
	No	1,437 (89.5)	96 (6.7)	267 (18.6)	446 (31)
Concentric or significant LV hypertrophy*	Yes	73 (4.5)	12 (16.4)[b]	30 (41.1)[a]	42 (57.5)[a]
	No	1,532 (95.5)	126 (8.2)	324 (21.1)	518 (33.8)
LV dilation	Yes	56 (3.5)	17 (30.4)[a]	29 (51.8)[a]	41 (73.2)[a]
	No	1,549 (96.5)	121 (7.8)	325 (21)	519 (33.5)
Elevated LV filling pressure	Yes	180 (11.2)	29 (16.1)[a]	80 (44.4)[a]	116 (64.4)[a]
	No	1,425 (88.8)	109 (7.6)	274 (19.2)	444 (31.2)
Moderate or severe mitral regurgitation*	Yes	80 (5)	24 (30)[a]	40 (50)[a]	51 (63.8)[a]
	No	1,525 (95)	114 (7.5)	314 (20.6)	509 (33.4)
Moderate or severe pulmonary hypertension*	Yes	67 (4.2)	19 (28.4)[a]	39 (58.2)[a]	50 (74.6)[a]
	No	1,538 (95.8)	119 (7.7)	315 (20.5)	510 (33.2)
Left atrial dilation	Yes	231 (14.4)	38 (16.5)[a]	97 (42)[a]	139 (60.2)[a]
	No	1,374 (85.6)	100 (7.3)	257 (18.7)	421 (30.6)
Significant right ventricular dysfunction	Yes	197 (12.3)	32 (16.2)[a]	70 (35.5)[a]	99 (50.3)[a]
	No	1,408 (87.7)	106 (7.5)	284 (20.2)	461 (32.7)
Moderate or severe tricuspid regurgitation	Yes	79 (4.9)	20 (25.3)[a]	41 (51.9)[a]	57 (72.2)[a]
	No	1,526 (95.1)	118 (7.7)	313 (20.5)	503 (33)
Laboratory results					
Plasma sodium (mEq/L)*	<135	499 (23.4)	83 (16.6)[a]	173 (34.7)[a]	262 (52.5)[a]
	≥135	1,621 (76.1)	141 (8.7)	395 (24.4)	593 (36.6)
	Unknown	9 (0.4)	—	—	—
Plasma potassium (mEq/L)	>5.1	448 (21)	82 (18.3)[a]	171 (38.2)[a]	252 (56.3)[a]
	≤5.1	1,672 (78.5)	142 (8.5)	397 (23.7)	603 (36.1)
	Unknown	9 (0.4)	—	—	—
Other conditions					
Anemia*	Yes	848 (39.8)	140 (16.5)[a]	326 (38.4)[a]	460 (54.2)[a]
	No	1,272 (59.7)	84 (6.6)	241 (18.9)	395 (31.1)
	Unknown	9 (0.4)	—	—	—
Gastrointestinal hemorrhage*	Yes	52 (2.4)	15 (28.8)[a]	27 (51.9)[a]	35 (67.3)[a]
	No	2,077 (97.6)	209 (10.1)	541 (26)	821 (39.5)
COPD*	Yes	164 (7.7)	50 (30.5)[a]	98 (59.8)[a]	126 (76.8)[a]
	No	1,965 (92.3)	174 (8.9)	470 (23.9)	730 (37.2)
Alcohol or drug addiction*	Yes	26 (1.2)	6 (23.1)[b]	8 (30.8)[c]	11 (42.3)[c]
	No	2,103 (98.8)	218 (10.4)	560 (26.6)	845 (40.2)
Schizophrenia or psychosis*	Yes	32 (1.5)	6 (18.8)[c]	17 (53.1)[b]	25 (78.1)[a]
	No	2,097 (98.5)	218 (10.4)	551 (26.3)	831 (39.6)
Neurologic disorders*	Yes	49 (2.3)	17 (34.7)[a]	29 (59.2)[a]	36 (73.5)[a]
	No	2,080 (97.7)	207 (10)	539 (25.9)	820 (39.4)

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LV = left ventricular; NSTEMI = non-ST-segment-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment-elevation myocardial infarction

*Soroka Acute Myocardial Infarction (SAMI) score component

[a] $P < 0.001$
[b] $0.001 \leq P < 0.05$
[c] $P > 0.05$

Data are presented as number and percentage. $P \leq 0.05$ was considered statistically significant.

Results

Study Population and Deaths. The study population consisted of 2,129 AMI patients discharged from the hospital. Their mean age was 65.3 ± 13.5 years, 69% were men, and 65% had sustained an ST-segment-elevation myocardial infarction (STEMI). The numbers and percentages of deaths were 224 (10.5%) at 1 year, 568 (26.7%) at 5 years, and 856 (40.2%) at 10 years. Table I shows deaths during the follow-up periods, in accordance with the patients' baseline characteristics. For each follow-up period, the mean SAMI scores were significantly higher in those who died than in survivors: at 1 year, 8.19 ± 3.53 versus 1.88 ± 4.43; at 5 years, 7.02 ± 3.78 versus 0.91 ± 3.95; and at 10 years, 6.22 ± 3.13 versus 0.99 ± 2.83 (P <0.001 for each).

WBC Variables. During the first 72 hours after patients' admissions with AMI, 5,461 results of WBC tests were collected: 2,546 tests in the first 24 hours, 1,868 during hours 24–48, and 1,047 during hours 48–72. The number of tests per patient ranged from 1 to 11; 50% of the patients had at least 2 tests performed. Table II shows total and differential WBC counts by quartile.

Association between WBC Variables and Death. Table III shows 1-, 5-, and 10-year deaths according to the WBC variables. When we applied generalized estimating equation methodology (Table IV), a significant linear association was found between lymphocytes, neutrophils, NLR, and long-term death risk. For lymphocytes, a higher quartile was associated with a lower mortality rate, whereas for NLR, higher mortality rates were found as the quartiles increased. A significant nonlinear association was found between the numbers of basophils, eosinophils, and monocytes (at 1 and 5 yr), the total WBC count (at 5 and 10 yr), and death in the

TABLE II. White Blood Cell Measurements by Quartile

Variable	Q1	Q2	Q3	Q4	Total
Total WBC count (×10³/μL)					
No. of tests	1,365	1,358	1,372	1,366	5,461
Range	0.16–7.94	7.12–9.82	8.72–12.5	11.24–47.8	0.16–47.8
Mean ± SD	6.44 ± 1.04	8.64 ± 0.58	10.63 ± 0.83	15.23 ± 3.48	10.24 ± 3.75
Median	6.64	8.64	10.55	14.23	9.5
Differential WBC count					
Neutrophils (×10³/μL)					
No. of tests	1,354	1,367	1,363	1,372	5,456
Range	0–5.34	4.67–7.09	6.15–9.5	8.34–37.3	0–37.3
Mean ± SD	4.07 ± 0.81	5.89 ± 0.51	7.72 ± 0.75	12.26 ± 3.41	7.5 ± 3.55
Median	4.22	5.9	7.62	11.31	6.69
Lymphocytes (×10³/μL)					
No. of tests	1,384	1,374	1,352	1,346	5,456
Range	0–1.26	1.14–1.79	1.61–2.55	2.16–17.4	0–17.4
Mean ± SD	0.87 ± 0.25	1.47 ± 0.16	2.03 ± 0.21	3.28 ± 1.13	1.9 ± 1.07
Median	0.91	1.46	2.01	2.98	1.72
Monocytes (×10³/μL)					
No. of tests	1,426	1,349	1,338	1,343	5,456
Range	0–0.43	0.36–0.56	0.47–0.73	0.64–3.5	0–3.5
Mean ± SD	0.31 ± 0.08	0.47 ± 0.05	0.61 ± 0.06	0.93 ± 0.26	0.58 ± 0.27
Median	0.33	0.46	0.61	0.86	0.53
Eosinophils (×10³/μL)					
No. of tests	1,493	1,363	1,292	1,308	5,456
Range	0–0.06	0.04–0.13	0.09–0.23	0.16–1.87	0–1.87
Mean ± SD	0.03 ± 0.02	0.09 ± 0.02	0.15 ± 0.03	0.34 ± 0.19	0.15 ± 0.15
Median	0.02	0.08	0.15	0.29	0.11
Basophils (×10³/μL)					
No. of tests	1,675	1,317	1,292	1,171	5,455
Range	0–0.02	0.01–0.03	0.04–0.06	0.05–1.19	0–1.19
Mean ± SD	0.01 ± 0.01	0.02 ± 0.01	0.05 ± 0.01	0.1 ± 0.07	0.04 ± 0.05
Median	0.01	0.03	0.04	0.08	0.03
Neutrophil-to-lymphocyte ratio					
No. of tests	1,356	1,354	1,373	1,372	5,455
Range	0–2.59	2.36–3.96	3.68–7.18	6.03–657.75	0–657.75
Mean ± SD	1.83 ± 0.46	3.06 ± 0.38	4.85 ± 0.79	13.47 ± 20.32	5.82 ± 11.17
Median	1.87	3.04	4.73	9.91	3.76

Q = quartile; WBC = white blood cell

TABLE III. Deaths by Quartile in Association with White Blood Cell Count Variables

WBC Variable	Follow-Up (yr)	Q1	Q2	Q3	Q4	*P* Value
Total WBC count	1	150 (11)	141 (10.4)	142 (10.3)	180 (13.2)	0.062
	5	386 (28.3)	331 (24.4)	343 (25)	412 (30.2)	0.001
	10	588 (43.1)	526 (38.7)	495 (36.1)	607 (44.4)	<0.001
Differential WBC count						
Neutrophils	1	128 (9.5)	128 (9.4)	154 (11.3)	202 (14.7)	<0.001
	5	342 (25.3)	307 (22.5)	373 (27.4)	449 (32.7)	<0.001
	10	532 (39.3)	488 (35.7)	551 (40.4)	641 (46.7)	<0.001
Lymphocytes	1	276 (19.9)	163 (11.9)	106 (7.8)	67 (5)	<0.001
	5	591 (42.7)	370 (26.9)	284 (21)	226 (16.8)	<0.001
	10	802 (57.9)	586 (42.6)	450 (33.3)	374 (27.8)	<0.001
Monocytes	1	175 (12.3)	126 (9.3)	129 (9.6)	182 (13.6)	0.001
	5	407 (28.5)	334 (24.8)	326 (24.4)	404 (30.1)	0.001
	10	574 (40.3)	516 (38.3)	527 (39.4)	595 (44.3)	0.009
Eosinophils	1	222 (14.9)	138 (10.1)	117 (9.1)	135 (10.3)	<0.001
	5	476 (31.9)	333 (24.4)	308 (23.8)	354 (27.1)	<0.001
	10	673 (45.1)	520 (38.2)	482 (37.3)	537 (41.1)	<0.001
Basophils	1	228 (13.6)	131 (9.9)	133 (10.3)	120 (10.2)	0.003
	5	504 (30.1)	322 (24.4)	323 (25)	321 (27.4)	0.002
	10	765 (45.7)	491 (37.3)	474 (36.7)	481 (41.1)	<0.001
Neutrophil-to-lymphocyte ratio	1	73 (5.4)	97 (7.2)	180 (13.1)	262 (19.1)	<0.001
	5	242 (17.8)	286 (21.1)	398 (29)	545 (39.7)	<0.001
	10	407 (30)	465 (34.3)	588 (42.8)	752 (54.8)	<0.001

Q = quartile; WBC = white blood cell

Data are presented as number and percentage. $P \leq 0.05$ was considered statistically significant.

long term. The associations were U-shaped for monocytes and total WBC count, J-shaped for neutrophils (fitting the linear and J-shaped models), and reversed J- or U-shaped for basophils and eosinophils. U-shaped relationships mean that both low and high counts (for example, for leukopenia and leukocytosis) are associated with higher mortality rates. The association between cell count and death was strongest for lymphocytes and NLR, and seemed to decrease upon longer follow-up periods for most cells. We found no significant difference in the prognostic ability of any test according to any time of analysis after admission within 72 hr. Moreover, we evaluated the relationship between WBC values on the day of the test (days 1–3) and outcome. There were no significant differences in regard to outcome, nor did WBC value on a particular day prove to be a significant independent predictor of death.

On multivariate modeling (Table V), only eosinophils, NLR, and lymphocytes maintained independent prognostic significance, and the relationship was stronger for shorter periods: eosinophils for up to 1-year risk of death, NLR for up to 5-year risk, and lymphocytes for up to 10-year risk.

Incremental Values to the SAMI Score. When eosinophils, lymphocytes, and NLR were entered separately into the multivariate predictive models, the area under the curve increased moderately for all 3 periods (more prominently in shorter periods) (Table VI). Net reclassification improvement analysis (Table VII) yielded significant improvements in the SAMI models after the addition of the variables. The extent of improvement was from 2% to 11%, with a trend toward greater improvement in the shorter follow-up periods.

Discussion

Our main and novel findings are as follows: 1) significant nonlinear associations between basophils, eosinophils, monocytes, total WBC count, and death—reversed J- or U-shaped for the first two and U-shaped for the others—whereas for lymphocytes, neutrophils, and NLR, the relationships between the cell counts and death were strongly linear. 2) Lymphocytes, followed by NLR, were the strongest predictors of long-term death after AMI. 3) High eosinophil levels were strongly and independently associated with 1-year death after AMI. 4) The independent post-AMI association of WBC subtypes and death seemed to weaken as the follow-up period lengthened. 5) When incorporated into the SAMI comprehensive score index and adjusted for other independent risk factors, lymphocytes (up to 10 yr), NLR (up to 5 yr), and eosinophils (up to 1 yr) maintained independent associations with death. Furthermore, their incorporation into the SAMI

TABLE IV. Relative Risk of Death during Each Follow-Up Period

WBC Subtype	Follow-Up (yr)		Quartile*			Model Effect for Association (*P* Value)	
			2	3	4	Linear	Nonlinear
Basophils	1	OR	0.701	0.728	0.725	0.023	0.01
		95% CI	0.553–0.888	0.562–0.944	0.547–0.96		
		P value	0.003	0.017	0.025		
	5	OR	0.752	0.774	0.877	0.128	0.005
		95% CI	0.633–0.894	0.644–0.931	0.726–1.06		
		P value	0.001	0.007	0.176		
	10	OR	0.707	0.689	0.829	0.011	<0.001
		95% CI	0.605–0.826	0.583–0.814	0.698–0.986		
		P value	<0.001	<0.001	0.034		
Eosinophils	1	OR	0.645	0.57	0.659	0.009	0.001
		95% CI	0.494–0.842	0.426–0.762	0.473–0.918		
		P value	0.001	<0.001	0.014		
	5	OR	0.691	0.669	0.793	0.039	0.001
		95% CI	0.565–0.845	0.539–0.829	0.63–0.997		
		P value	<0.001	<0.001	0.047		
	10	OR	0.752	0.725	0.849	0.1	0.004
		95% CI	0.626–0.902	0.596–0.882	0.688–1.047		
		P value	0.002	0.001	0.125		
Lymphocytes	1	OR	0.54	0.342	0.21	<0.001	<0.001
		95% CI	0.419–0.697	0.252–0.464	0.147–0.3		
		P value	<0.001	<0.001	<0.001		
	5	OR	0.494	0.357	0.271	<0.001	<0.001
		95% CI	0.409–0.598	0.288–0.442	0.212–0.345		
		P value	<0.001	<0.001	<0.001		
	10	OR	0.54	0.362	0.279	<0.001	<0.001
		95% CI	0.45–0.647	0.296–0.443	0.224–0.349		
		P value	<0.001	<0.001	<0.001		
Monocytes	1	OR	0.736	0.763	1.121	0.491	0.005
		95% CI	0.559–0.971	0.574–1.013	0.823–1.525		
		P value	0.03	0.062	0.469		
	5	OR	0.824	0.807	1.077	0.611	0.006
		95% CI	0.687–0.988	0.663–0.981	0.86–1.349		
		P value	0.036	0.031	0.518		
	10	OR	0.919	0.965	1.181	0.112	0.059
		95% CI	0.78–1.083	0.805–1.155	0.961–1.45		
		P value	0.315	0.695	0.113		

Continues on next page

model resulted in significantly improved predictive ability.

Total WBC Count and Death. Previous investigators have reported an association between elevated total WBC counts and death rates after myocardial infarction.[11-13] In these studies, elevated WBC counts were associated with reduced epicardial patency and a greater likelihood of thrombus formation at the site of the ruptured plaque, suggesting that an elevated WBC count is a marker of a hypercoagulable or prothrombotic state.[11] However, these associations often were not significant after adjustment for other risk factors.[17,18] Moreover, other investigators concluded that WBC count is not associated with major adverse cardiac events (MACE) or severity of coronary atherosclerosis in patients with ACS. Similarly, Toor and colleagues[19] studied preprocedural total and differential WBC counts of patients admitted for elective or urgent percutaneous coronary intervention (PCI) and found only a univariate significant association between total WBC count and long-term risk of death. These findings are consistent with the current study: there is only a partial univariate (nonlinear) association and there is no significant independent association between total WBC count and long-term risk of death. The discrepancies between studies might stem from different methodologies and outcomes, insufficient risk-factor adjustments, or confounding of associations resulting from a true association between WBC subtypes (such as neutrophils or lymphocytes) and the outcome. Thus, the U-shaped relationship observed between total WBC count and death, especially leukopenia and death, might be attrib-

TABLE IV cont'd. Relative Risk of Death during Each Follow-Up Period

WBC Subtype	Follow-Up (yr)		Quartile*			Model Effect for Association (*P* Value)	
			2	3	4	Linear	Nonlinear
Neutrophils	1	OR	0.99	1.22	1.654	0.003	0.009
		95% CI	0.736–1.33	0.889–1.674	1.169–2.339		
		P value	0.944	0.218	0.004		
	5	OR	0.857	1.115	1.439	0.001	<0.001
		95% CI	0.695–1.056	0.893–1.392	1.126–1.84		
		P value	0.148	0.337	0.004		
	10	OR	0.858	1.048	1.355	0.002	<0.001
		95% CI	0.716–1.028	0.862–1.275	1.086–1.691		
		P value	0.097	0.635	0.007		
Total WBC count	1	OR	0.938	0.935	1.229	0.281	0.265
		95% CI	0.711–1.239	0.678–1.289	0.871–1.734		
		P value	0.654	0.682	0.24		
	5	OR	0.817	0.845	1.095	0.281	0.025
		95% CI	0.667–1.003	0.675–1.058	0.855–1.403		
		P value	0.053	0.143	0.471		
	10	OR	0.835	0.746	1.057	0.878	0.001
		95% CI	0.695–1.004	0.609–0.913	0.844–1.323		
		P value	0.055	0.004	0.63		
Neutrophil-to-lymphocyte ratio	1	OR	1.356	2.652	4.148	<0.001	<0.001
		95% CI	0.979–1.878	1.929–3.645	2.959–5.816		
		P value	0.067	<0.001	<0.001		
	5	OR	1.233	1.879	3.034	<0.001	<0.001
		95% CI	1.007–1.509	1.519–2.324	2.395–3.842		
		P value	0.043				
	10	OR	1.22	1.747	2.828	<0.001	<0.001
		95% CI	0.024–1.453	1.45–2.103	2.227–3.512		
		P value	0.026	<0.001	<0.001		

CI = confidence interval; OR = odds ratio; WBC = white blood cell

*Quartile 1 was the reference group for each investigated WBC variable.

$P \leq 0.05$ was considered statistically significant.

uted to the associations of several cell subtypes (such as lymphocytes) and death. Nevertheless, similar U-shaped associations between WBC counts and death were reported in other medical circumstances as well.[20]

Eosinophils and Death. Toor and colleagues[19] prospectively studied the preprocedural total and differential WBC counts of patients admitted for elective or urgent PCI, as a predictor of the risk of all-cause death. The authors showed that increased eosinophil count was associated with a lower risk of death at 6 months after PCI and a higher risk of death upon long-term follow-up (up to 74 mo).[19] These results are largely consistent with our findings in the current study: increased eosinophil count was independently associated with lower 1-year mortality rates. We did not find an association between a higher eosinophil count and a greater risk of death (despite a trend of increase in Q4 vs Q3). This disparity might result from different cohorts (high-risk vs low-to-intermediate risk in the current study vs that of Toor and colleagues), study methodology, or a competing pathophysiologic mechanism. Toor and colleagues[19] suggested that eosinophils were associated with regulation of the inflammatory response, which might be protective by limiting myocardial tissue injury. The latter could be mediated by the expression of immunosuppressive cytokines (interleukin-10, -4, and -3) and by being a source of trophoblastic beta 1-glycoprotein, affecting the activity of regulatory T cells by eosinophils, and thus contributing to the resolution of acute inflammation.[19,21,22] On the other hand, eosinophils can increase the risk of thrombus formation by increasing platelet activation and aggregation.[23]

Neutrophils and Death. Neutrophils are the first leukocytes to be found in the damaged myocardial area (within 1–3 d) and are removed from myocardial tissue after phagocytizing débris.[24] The distinct presence of neutrophils in atherosclerotic plaques underlying AMI[25] strongly suggests that neutrophils play a role in mediating the destabilization of atherosclerotic plaques.[26] In a systematic review, including 21 studies and more than 34,000 patients, a significant relationship between clinical outcomes and neutrophils, measured as abso-

TABLE V. Adjusted Relative Risk of Death during Each Follow-Up Period

WBC Subtype	Follow-Up (yr)		Quartile*			Model Effect for Association (*P* Value)	
			2	3	4	Linear	Nonlinear
Total WBC count	1	OR 95% CI *P* value	1.042 0.742–1.463 0.813	1.16 0.8–1.683 0.434	1.098 0.722–1.668 0.663	0.587	0.773
	5	OR 95% CI *P* value	0.872 0.68–1.118 0.281	1.036 0.792–1.356 0.796	1.021 0.735–1.418 0.901	0.682	0.476
	10	OR 95% CI *P* value	0.962 0.753–1.229 0.757	0.967 0.739–1.266 0. 809	1.319 0.976–1.783 0.071	0.372	0.449
Differential WBC count							
Neutrophils	1	OR 95% CI *P* value	1.212 0.858–1.712 0.276	1.272 0.876–1.845 0.206	1.311 0.86–1.998 0.208	0.232	0.54
	5	OR 95% CI *P* value	0.956 0.743–1.23 0.728	1.148 0.878–1.501 0.314	1.136 0.823–1.568 0.438	0.293	0.419
	10	OR 95% CI *P* value	0.982 0.773–1.248 0.78	1.162 0.896–1.507 0.258	1.305 0.967–1.759 0.081	0.052	0.573
Lymphocytes	1	OR 95% CI *P* value	0.747 0.558–1.001 0.05	0.598 0.423–0.845 0.004	0.514 0.339–0.779 0.002	0.001	0.006
	5	OR 95% CI *P* value	0.643 0.504–0.821 <0.001	0.628 0.481–0.819 0.001	0.678 0.502–0.915 0.011	0.007	0.002
	10	OR 95% CI *P* value	0.753 0.589–0.962 0.023	0.696 0.529–0.916 0.01	0.819 0.609–1.102 0.187	0.138	0.365
Monocytes	1	OR 95% CI *P* value	0.803 0.616–1.047 0.105	0.839 0.639–1.101 0.206	0.911 0.672–1.234 0.546	0.615	0.374
	5	OR 95% CI *P* value	0.843 0.683–1.041 0.112	0.814 0.641–1.033 0.09	0.902 0.673–1.21 0.491	0.452	0.27
	10	OR 95% CI *P* value	0.986 0.8–1.214 0.894	1.145 0.897–1.461 0.277	1.228 0.935–1.613 0.14	0.091	0.456

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lute count, relative count, or NLR, was reported in 17 studies.[27] More specifically, several investigators showed that neutrophils measured within 24 hours after symptom onset were long-term predictors of death after AMI and ACS.[27-29] Conversely, Zouridakis and associates[30] found no correlation between neutrophils and clinical outcomes (death after hospital discharge meshed with other clinical outcomes). In the current study, an increased neutrophil count (especially in Q4) was associated with higher long-term mortality rates in the univariate analysis, but not in the multivariate analysis. Thus, it seems that the incorporation of neutrophils was not additive to the parameters of the SAMI score.

Lymphocytes and Death. Lymphocyte count, and particularly the CD4+ number, represent the regulatory arm of the immune system and have a pivotal role in modulating the inflammatory response at various stages of the atherosclerotic process.[31,32] Mor and colleagues[33] found a decrease in the number and suppressive function of naturally occurring $CD4^+CD25^+$ regulatory T cells in acute phases of ACS, which supports a potential role for regulatory cells in atheroprotection. In addition, lymphocytes infiltrating the ischemic and reperfused myocardium express interleukin-10 and might substantially aid healing by modulating the mononuclear cell phenotype and inducing the expression of tissue inhibitor of metalloproteinase-1.[34] Blum and co-authors[35] reported that lymphocytopenia and low CD4 cell numbers with inversion in the CD4/CD8 ratio are associated with MI. Furthermore, patients with the lowest

TABLE V cont'd. Adjusted Relative Risk of Death during Each Follow-Up Period

WBC Subtype	Follow-Up (yr)		Quartile*			Model Effect for Association (*P* Value)	
			2	3	4	Linear	Nonlinear
Eosinophils	1	OR	0.724	0.732	0.682	0.054	0.129
		95% CI	0.526–0.997	0.522–1.026	0.465–0.999		
		P value	0.048	0.07	0.049		
	5	OR	0.767	0.863	0.876	0.475	0.336
		95% CI	0.59–0.998	0.657–1.132	0.656–1.169		
		P value	0.048	0.287	0.368		
	10	OR	0.869	0.899	0.991	0.96	0.419
		95% CI	0.668–1.131	0.689–1.173	0.747–1.314		
		P value	0.296	0.433	0.947		
Basophils	1	OR	0.873	0.923	0.799	0.224	0.45
		95% CI	0.661–1.153	0.685–1.242	0.579–1.104		
		P value	0.339	0.595	0.173		
	5	OR	0.966	1	1.014	0.876	0.985
		95% CI	0.773–1.026	0.796–1.257	0.805–1.277		
		P value	0.76	0.997	0.907		
	10	OR	0.857	0.856	0.949	0.538	0.156
		95% CI	0.693–1.059	0.688–1.065	0.758–1.187		
		P value	0.153	0.163	0.645		
Neutrophil-to-lymphocyte ratio	1	OR	1.153	1.766	1.962	<0.001	0.002
		95% CI	0.799–1.662	1.224–2.547	1.306–2.948		
		P value	0.447	0.002	0.001		
	5	OR	1.047	1.218	1.399	0.019	0.254
		95% CI	0.828–1.323	0.946–1.567	1.034–1.891		
		P value	0.702	0.126	0.029		
	10	OR	1.011	1.062	1.291	0.105	0.669
		95% CI	0.806–1.268	0.835–1.351	0.961–1.734		
		P value	0.922	0.622	0.09		

CI = confidence interval; OR = odds ratio; WBC = white blood cell

*Quartile 1 was the reference group for each investigated WBC variable.

$P \leq 0.05$ was considered statistically significant.

TABLE VI. Incremental Predictive Ability of White Blood Cell Subtypes Over the SAMI Score: ROC Curve

Score[a]	Follow-Up Period (yr)		
	1[b]	5[b]	10[c]
SAMI score	0.857 (0.844–0.87)	0.86 (0.85–0.871)	0.881 (0.872–0.89)
SAMI + eosinophils	0.858 (0.845–0.871)	0.861 (0.851–0.872)	0.882 (0.872–0.892)
SAMI + lymphocytes	0.861 (0.848–0.873)	0.863 (0.852–0.873)	0.883 (0.874–0.892)
SAMI + NLR	0.861 (0.848–0.874)	0.862 (0.852–0.873)	0.882 (0.873–0.891)

NLR = neutrophil-to-lymphocyte ratio; ROC = receiver operating characteristic; SAMI = Soroka Acute Myocardial Infarction

[a]Data are presented as a C-statistic, ROC curve value, and 95% confidence interval.
[b]Classical SAMI score
[c]Adapted SAMI score

CD4 counts, and those whose CD4 counts did not return to normal in subsequent days, were more likely to have repeat infarctions and to die.

Potential causes of lymphopenia in AMI are an abruptly increased level of corticosteroids[36] and an increase in lymphocyte apoptosis in the context of uncontrolled immune-system activation.[37] Horne and coworkers[18] reported lymphocytes to be an independent predictor of death and of myocardial infarction in patients with or at high risk of coronary artery disease. Similarly, Zouridakis and associates[30] reported a significant inverse relationship between clinical outcomes

TABLE VII. Incremental Predictive Ability of White Blood Cell Subtypes upon Net Reclassification Improvement

Score[a]	Follow-Up Period (yr)		
	1[b]	5[b]	10[c]
SAMI + eosinophils	0.11 (<0.001)	0.06 (<0.001)	0.02 (0.01)
SAMI + lymphocytes	0.09 (<0.001)	0.05 (<0.001)	0.02 (0.04)
SAMI + NLR	0.11 (<0.001)	0.04 (<0.001)	0.03 (0.002)

NLR = neutrophil-to-lymphocyte ratio; SAMI = Soroka Acute Myocardial Infarction

[a]Data are presented as net classification improvement value and *P* value.
[b]Classical SAMI score
[c]Adapted SAMI score

$P \leq 0.05$ was considered statistically significant.

and lymphocyte count in patients with unstable angina pectoris. Nunez and colleagues[38] found that a low lymphocyte count obtained within the first 96 hours after STEMI predicted a recurrent post-discharge AMI (median follow-up period, 36 mo). Khandaker and coauthors[39] reported that an elevated lymphocyte count before PCI was independently associated with lower rates of death, cardiac death, and death or MI over a median follow-up period of 5.1 years. When these last authors compared lymphocyte counts to those of neutrophils, myocytes, and total WBC in the same model, the preprocedural lymphocyte count most strongly predicted death.[39] Consistent with these reports, we found that the lymphocyte count was the strongest independent predictor of long-term death after AMI. Conversely, Huang and colleagues[29] did not find a significant correlation between lymphocyte count and MACE in ACS patients, although the count did predict stenosis greater than 75% on coronary angiography. This discrepancy with the current study could result from different outcomes (MACE vs death), inclusion criteria (ACS vs AMI), and smaller study groups that precluded statistical significance.

Neutrophil-to-Lymphocyte Ratio. The NLR measured within the first days has been a strong predictor of short- and long-term death after ACS.[19,40,41] Huang and colleagues[29] reported that NLR was only slightly higher in patients with MACE after a median follow-up period of 21 months after ACS. In the current study, NLR was strongly associated with post-AMI death in the 3 evaluated follow-up periods. However, when adjusted for the SAMI risk score, only Q4 compared with Q1 had significant predictive validity for 5-year death, and no significant relationship between NLR and the outcome at 10-year follow-up was found.

Strengths and Limitations of the Study

The strengths of the current study are its relatively long follow-up period and a large study group. Results from the first 72 hours were analyzed rather than those upon admission or in the first 24 hours only; we think that this is more applicable clinically. We analyzed a wide variety of WBC subtypes, using a separate (yet similar) statistical model for each one rather than dividing them into quartiles according to cell type; we think that this enables appropriate comparisons between all subtypes and generalizes the usability of our results. In contrast, some limitations should be mentioned. First, this was an observational study that was not designed to examine the mechanisms underlying the associations that were found. Second, it was not possible to differentiate the cause of death as cardiac or noncardiac from the database of deaths, and data on cardiovascular outcomes other than death were not available. Third, no measurements of other inflammatory factors such as C-reactive protein or proinflammatory cytokines were available for comparison. Fourth, post-hospital-discharge information potentially influencing prognosis was missing (medical therapy, compliance with therapy, medical evaluation, and so forth). Fifth, it would have been of substantial clinical value to use the GRACE or Thrombolysis in Myocardial Infarction score as well; however, this was not possible. Sixth, because we wanted to focus on long-term prognosis, only hospital survivors were included in our study.

Conclusions

Lymphocytes, eosinophils, and NLR were strongly and independently associated with long-term risk of death in a large cohort of patients with AMI who were discharged from the hospital; lymphocytes had the strongest association. The strength of these associations weakened as the follow-up duration lengthened. The incorporation of these markers into a multivariate predictive model (SAMI score) had a significant effect on its predictive ability. Hence, analysis of these simple, inexpensive-to-test, universally available inflammatory markers might provide some pathophysiologic insights into the mechanisms related to the long-term outcomes of AMI patients and improve long-term stratification of patient risk. This

would aid better selection of AMI patients for various treatments and interventions.

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