IJMS
Vol 36, No 1, March 2011

Brief Report

Leukocytosis as an Alarming Sign for Mortality in Patients Hospitalized in General Wards

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Abstract

There is some evidence that leukocytosis without infection is associated with increased hospital mortality, but data in this regard are very incomplete. This study was designed to investigate the relationship between leukocytosis at the time of admission and mortality among patients hospitalized in general wards. During July to Nov 2004, all deceased patients who had a white blood cell (WBC) count record for the first 24 hours of admission were selected as cases. Among survivors, twice the number of cases was selected as controls. Different levels of WBC counts were compared between cases and controls. Totally 1650 patients, including 550 deceased (cases) and 1100 survivors (controls) were analyzed. Of these, 876 (53%) were males and 774 (47%) females, and 42 (3%) were admitted to ICU, 1426 (86%) to medical and 182 (11%) to surgical wards. There was a significant difference between the mean age of deceased patients (78.0 years) and survivors (53.0 years) (P<0.0001). The median WBC for deceased and surviving patients was 9.4 and 11.4×10^9/l, respectively. Patients with a WBC $>10\times10^9$/l accounted for 804, among which 335 (42%) were deceased. Leukocytosis and leukopoenia were more frequent among the deceased patients compared to the survivors. The likelihood ratio for leukocytosis and leukopenia among the cases and controls was 1.4 and 2.3, respectively. Leukocytosis was identified as an alarming sign for mortality among patients admitted to general hospital wards at early stages of admission. A quick medical intervention for amendment of the causes related to leukocytosis should consequently reduce hospital mortality.

Iran J Med Sci 2011; 36(1): 45-49.

Keywords ● General hospital ● hospital mortality ● inpatient ● leukocytosis

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Received: 29 March 2010
Revised: 15 July 2010
Accepted: 18 July 2010

Introduction

The normal white blood cell (WBC) counts in peripheral blood is within a reference range from 4,300 to 10,800 WBC/mm^3. Leukocytosis is usually defined as a white blood cell count greater than 11,000/mm^3 (11×10^9/l).[1,2]

Two important pathophysiological mechanisms are involved in the etiology of leukocytosis.[3] These include a normal bone marrow response to external stimuli and a primary bone marrow disorder. Leukocytosis can occur in response to external stimuli including infection, inflammation, drugs, traumas, malignancies, ketoacidosis, poisoning, exercise and psychiatric disorders. Moreover, leukocytosis can also occur as a result of acute leukemias, chronic leukemias and myeloproliferative disorders.[1-4]

The identification of factors related to mortality in early admission of patients is interesting for health staff as well as patients and their families. There is some evidence that leukocytosis is associated with increased hospital mortality, however, data are very incomplete, or have focused on some certain diseases and certain specialties.[5-10] Moreover, in a previous study in 2002, in which the cases were matched with controls for age range, gender, hospital ward and date of admission, we showed that some laboratory variables were related to inpatient mortality. Nevertheless, a comprehensive study to examine the existence of such an association for patients admitted to hospital for general causes has not been performed.

This study was designed to investigate the risk of leukocytosis among patients admitted to hospitals for different conditions using unmatched controls. Moreover, it aimed at evaluating the epidemiological characteristics of this variable at the time of admission.

Materials and Methods

The study is a case control design using retrospective analysis of medical files of patients with and without leukocytosis. It was approved prospectively by both the Liverpool School of Tropical Medicine (LSTM) Research Ethics Committee, and Liverpool Research and Ethics Committee (LREC). Also, a data protection approval and an honorary research contract with Liverpool Royal University and Broadgreen Hospitals NHS Trust (RLBUHT) were obtained after gaining the ethics approval, to enable investigator access to patients' specific data within the hospital environment.

Using Epi-Stat function of Epi-info version 3.01, 2003, a power of 80%, a confidence interval of 95%, and case: control ratio of 1:2, a total number of 222 samples including 74 cases and 148 controls were calculated to be required for the study. We easily exceeded this minimum number by including all deceased patients in a five months period and twice their numbers as controls to increase the power of analysis for different variables.

All patients admitted to the Royal Liverpool University Hospital (RLUH) in a five-month period of 2004 (July-November), who died during hospitalization were chosen. Moreover, for each case two sequential surviving controls hospitalized in the same ward with the same date of admission were selected.

The setting chosen was an urban teaching hospital with one of the busiest accident and emergency departments in the United Kingdom. The hospital had the main medical wards with the exception of obstetrics, pediatrics, neurology and neurosurgery, and cardiothoracic surgery. It was one of the busiest hospitals in the north west of England for acute medical and surgical admissions (mean admission/day ~45 patients).[11]

Amongst the deceased patients, only 550 had laboratory tests performed in the first 24 hours after admission, but before any medical intervention. They were all selected, and two sequential controls (survivors) were selected for each case. The controls had been hospitalized in the same ward, and had the nearest admission time to that of the respective cases.

Leukocytosis was defined in accordance with the definition used by the RLUH laboratory and Oxford Textbook of Medicine, which states it as the raised number of various types of white blood cells including neutrophils, eosinophils, basophils, monocytes and lymphocytes (normal WBC=4–10×10^9/l).[7]

Data were entered into Statistical Package for Social Sciences (SPSS) version 12.0 (Chicago, IL, USA). They were analyzed using univariate analysis, likelihood ratio and Chi Squared tests. Likelihood ratios, which can be used for diagnostics purposes, were calculated as the proportion of leukocytotic patients who died divided by the proportion of leukocytotic patients who survived. The confidence intervals and P values associated with these ratios were obtained from the website http://statpages.org/ctab2x2.html. Mean and standard deviation were used where data followed normally distribution and median was used where data was skewed. Any difference between the deceased patients and survivors were computed with 95% confidence interval. A P value of ≤0.05 was considered statistically significant.

Results

As described in the methodology, patients' records for a 5-month period were analyzed. Between July and November 2004, there were 11944 patients admitted to the RLUH among which 11372 (95%) patients were discharged alive and 572 (5%) patients died during hospitalization. The number of male and female patients were 6078 (51 %) and 5866 (49%), respectively. The age (mean±SD) of survivors was 56.0±22.0 and that for the deceased patients was 78.0±13.0 years. Eighty four percent of the patients were admitted to the medical wards, 1% to the ICU, and the rest (15%) were admitted to the surgical wards. Deceased patients were significantly older than survivors (P<0.0001) and needed a longer hospitalization (19±24 vs. 8±16 days, P<0.0001) (table 1).

Table 1: The characteristics of patients who had laboratory tests done in the first 24 hours of admission and the wards to which they were admitted in the Royal Liverpool University Hospital between Jul-Nov 2004

	All	Survivors (%)	Deceased (%)	OR (CI)	P value
Frequency, n (%)	1650	1100 (67)	550 (33)	- -	
Age (mean±SD) in year	61.0±22.0	53.0±21.0	78.0±13.0	- -	0.0001
ICU, n (%)	42 (3)	19 (45)	23 (55)	2.4 (1.3-4.7)	0.006
Medical wards, n (%)	1426 (86)	957 (67)	469 (33)	0.98 (0.8-1.1)	0.8
Surgical wards, n (%)	182 (11)	124 (68)	58 (32)	0.9 (0.7-1.3)	0.8
WBC (median)	9.9×10^{9}/l	9.4×10^{9}/l	11.4×10^{9}/l	2.4 (1.04-5.7)	0.03
I/P in days (median)	4	2	9	9.0 (2.2-37.1)	0.001

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, I/P: in-patient days

Of 1650 (550 deceased cases and 1100 survivor controls) selected patients, 876 (53%) were males, 774 (47%) females, 42 (3%) admitted to ICU, and 1426 (86%) to medical, and 182 (11%) to surgical wards. The distribution of percentages of patients admitted to different wards of the hospital is shown in figure 1.

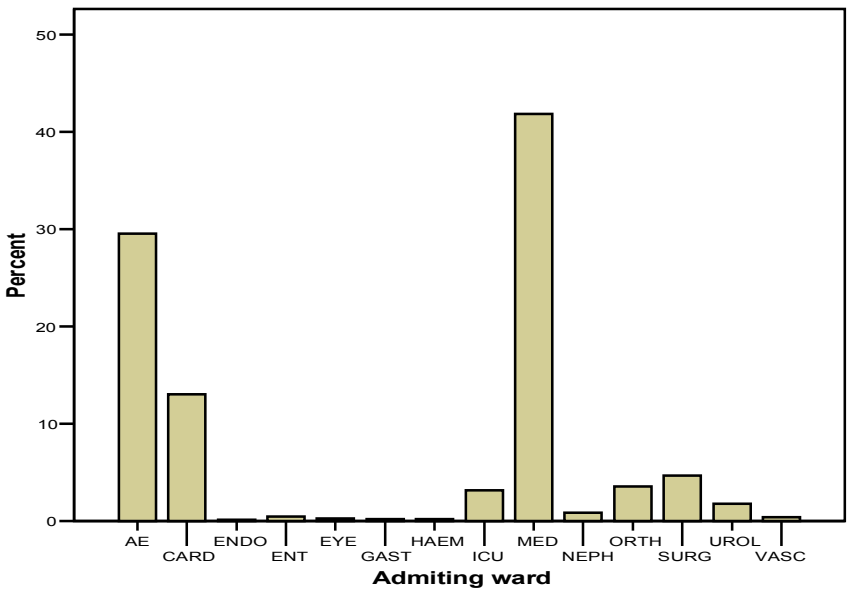
The median WBC count for the deceased and surviving patients was 11.4×10^{9}/l and 9.4×10^{9}/l, respectively (table 1), and there was a significantly difference between these groups (P=0.03).

The number of patients with a WBC count of $>10\times10^{9}$/l were 804, which comprised of 335 (42%) deceased cases and 469 (62%) matched controls (table 2).

The mean±SD age of all selected patients (cases and matched controls, n=1650) was 61.0±22.0 years. There was a significant (P<0.0001) difference between the age of deceased patients (78.0±13.0 years) and matched survivors (53.0±21.0 years). Deceased patients had a significantly (P<0.001) longer hospitalization than the survivors (9 vs. 2 days, (table 2).

The number of cases with leukocytosis (WBC counts $>10\times10^{9}$/l) were significantly (P=0.0001) more in deceased patients (335 out of 550) than that in surviving patients (469 out of 1100). Moreover, the number of cases with leuckopenia (WBC counts $<4\times10^{9}$/l) were significantly (P=0.002) more in deceased patients (14 out of 550) than that in surviving patients (12 out of 1100) (table 2).

The patients' ages were stratified into 3 strata including 20-49 years, 50-64 years, and ≥65 years, and the three strata were entered into the analysis. The number of cases in the surviving patients, which occurred in the first (20-49 years) and the second strata (50-64 years)



AE=Accident and emergency, CARD=Cardiology, ENDO=Endocrinology, ENT=Ear, Nose & Throat, EYE=Eye, Gast=Gastrointestinal, HAEM=Haematology, ICU=Intensive care unit, MED=Medical service, NEPH=Nephrology, ORTH=Orthopaedic, SURG=Surgery, UROL=Urology, VASC=Vascular

Figure 1: The distribution (in percentage) of all patients (deceased and matched controls, n=1650) who admitted to various wards of Royal Liverpool University Hospital between July to November 2004 and had laboratory test done in the first 24 hours of their admission.

Table 2: The frequencies of strata of WBC counts and age (in years) of deceased patients (n=550) and matching survivors (n=1100)

Variables	Ranges	Number (Percent)		Univariate Analysis	
		Deceased	Survivors	OR (95% CI)	P value
Leukocytes $\times 10^9$/l	>10	335 (61.00%)	469 (42.64%)	2.2 (1.8-2.7)	0.0001
	4-10	200 (36.37%)	617 (56.10%)	0.5 (0.4-0.6)	0.0001
	<4	14 (2.55%)	12 (1.10%)	3.6 (1.5-8.5)	0.002
Age (years)	20-49	27 (4.91%)	437 (39.73%)	9.04 (6.8-12.0)	0.0001
	50-64	35 (6.36%)	223 (20.27%)	3.9 (2.7-5.7)	0.0001
	≥65	487 (88.55%)	392 (35.64%)	13.5 (6.4-28)	0.0001

OR: Odds ratio, CI: Confidence interval of odds ratio, P: P values

were significantly higher than those occurring in the deceased patients (table 2). However, the number of cases from the deceased patients (n=487, 88.55%), which occurred in the third strata (≥65 years) was significantly higher than those from the surviving patients (n=392, 35.64 %) (table 2).

The number of deceased and surviving patients in subnormal (leukopenia), normal, and above normal (leukocytosis) ranges of WBC counts was used to calculate likelihood ratio for the two groups (table 3). The likelihood ratio for leukocytosis and leukopenia was 1.4 and 2.3, respectively. This indicated that these two abnormalities were about 1.4 and 2.3 times more likely to occur in deceased patients than in surviving patients (table 3).

Discussion

Most relevant studies have evaluated the effects of leukocytosis in varying hospital wards, age groups, special diseases, and have also used varying definitions.[5-10,12,13] The present study showed that more than one third (40%) of all patients admitted to a general hospital had a WBC >10×10^9/l.

There is a considerable evidence that leukocytosis may be an independent predictor for death at least for specific clinical outcomes.[5-10] One study,[14] has reported no significant relationship between leukocytosis and mortality, and only one study[6] has reported that the WBC count was an independent predictor of all causes of mortality. However, the current study shows that leukocytosis had a positive relationship with mortality in general hospitalized patients.

Mortality for patients with leukocytosis (WBC counts of >10×10^9/l) in this study was 8 %, which was less than that reported by Crabtree and others (18.6%).[10] This difference may be related to the special group of patients (patients with suspected infection in the surgical services) analyzed by these authors. There appears to be no report in the literature studying the relation between mortality and leukocytosis among patients admitted to various hospital wards.

In this study, the relationship between WBC count levels and mortality appeared as a "U" shape curve, showing an association between higher and lower levels of white blood cell count and mortality.

The strengths of this study were the selection of all patients admitted to various hospital wards, the recruitment of two controls per each case, and the use of a large number of patients in the dataset. The large datasets used in this study allowed us to get sufficient number of patients to investigate the effect of different levels of WBC (leukopenia, normal level and leukocytosis) on in-patient outcome. More intervention studies need to be performed to determine a causal association and whether the correction of abnormalities will improve outcomes.

Conclusion

The findings of the present study once again confirm leukocytosis as an alarming sign of death among hospitalized patients. Identifying leukocytosis as an alarming sign for mortality at early stages of admission, regardless of primary cause for patients' admission, could

Table 3: The likelihood ratios for different ranges of WBC counts in deceased (n=550) and surviving patients (n=1650)

	Range	Exposure	Mortality		LR*	95% CI	P value
			Yes	No			
Number of leukocytes ($\times 10^9$/l)	>10	+	335	469	1.4	1.3-1.6	0.0001
		-	214	629			
	4-10	+	200	617	0.65	0.6-0.7	0.0001
		-	349	481			
	<4	+	14	12	2.3	1.1-5.0	0.04
		-	535	1086			

CI: Confidence interval of likelihood ratio, LR*: Likelihood ratio of deceased patients compared with survivors

help health care staff to make a quick decision for the allocation of appropriate hospital ward (ITU, ICU, etc) and the application of appropriate treatment for patients. The correct and timely interventions should consequently reduce the hospital mortality.

Conflict of Interest: None declared

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