Diagnostic and prognostic implications of peak leukocyte count in the intensive care unit

Nafeesa Alibhai[1]; Sameer Hirji (MD)[2]; Naheed Jivraj (MBBS, MSc)[3]; Bijan Teja (MD, MBA)[3]

[1]Specialization in Integrated Sciences: Genetics, Physiology, and Psychology, University of British Columbia, Vancouver, British Columbia, Canada
[2]Department of General Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

Abstract

Background: It is well established that leukocytosis is a predictor of infection and inflammation, and that leukopenia is a marker of immunocompromise. However, it is possible that the degree of leukocytosis may provide additional information to clinicians treating critically ill patients. Our aim was to determine if peak white blood cell (WBC) count could help clinicians in diagnosing patients' conditions and determining their prognoses.

Methods: This was a retrospective cohort study of six adult intensive care units (ICUs) at a US academic medical center. Patients admitted to an adult ICU between 2001 and 2012 were analyzed. Our primary aim was to determine which diagnoses were most commonly encountered in patients with different peak WBC counts during their stay. In our secondary analyses, we determined the length of stay and mortality associated with peak WBC count across diagnoses and used multiple logistic regression to determine whether peak WBC count was more predictive of mortality than other diagnostic and demographic variables.

Results: There were 45,340 patients in our cohort. There was substantial variation in the disease prevalence and risk of mortality across peak WBC count categories. Interestingly, the rate of *C. difficile* was substantially higher in patients with extreme leukocytosis (peak WBC ≥40,000; 12% compared to 1-2% in all other groups, $p<0.001$). In our multivariate regression, extreme leukocytosis was associated with very high mortality rates (adjusted odds ratio (aOR) 10.4, 95% CI: 8.5-12.7, $p<0.001$).

Conclusions: Degree of peak leukocytosis in critically ill patients provides valuable diagnostic and prognostic information. Having an understanding of the conditions associated with each category of peak WBC count can help clinicians in caring for patients in the intensive care unit. In particular, extreme leukocytosis signals a very high risk of mortality and may, in appropriate clinical contexts, indicate the need for more aggressive or urgent intervention.

Background

The white blood cell (WBC) count is among the most frequently ordered laboratory tests in medicine, having a long history and universal acceptance as a valuable investigative tool. The presence of leukocytosis often raises physicians' suspicion for infectious and inflammatory conditions.[1,2] In addition, a low leukocyte count leaves patients vulnerable to opportunistic infections, and signals to physicians that appropriate prophylaxis needs to be administered.[3] While the presence of leukopenia or leukocytosis is already valued by physicians, the implications of degree of leukocytosis in critically ill patients have not been fully investigated.

Among general medical ward patients, one study found that the likelihood of mortality was 1.4 and 2.3 fold higher for patients with leukocytosis and leukopenia, respectively.[4] Similarly, a study of patients in the emergency department at a single institution found that patients with extreme leukocytosis were more likely to suffer from infectious disease (74% vs. 48%), to be hospitalized (100% vs. 80%), and to die (32.1% vs. 12.7%).[5]

Additionally, a 2007 study performed by Halkes et. al demonstrated that it is not always appropriate to assume that extreme leukocytosis is caused by myeloproliferative disorders such as leukemia or lymphoma.[6] His study revealed other possible culprits, including leukemoid reactions, were the cause of this finding. Another study in 2006 performed by Lawrence et. al investigated patients in the emergency department and found that most patients with extreme leukocytosis had infections, and that they tended to have longer hospitalization and higher mortality.[5] The diagnostic and prognostic implications of degree of leukocytosis in the intensive care unit (ICU), however, require further investigation. In particular, this study was designed to more extensively study the diagnostic and prognostic implications of degree of leukocytosis in a large ICU cohort. Our hypothesis was that leukopenia and extreme leukocytosis would be associated with the highest mortality rates, and that certain conditions such as *C. Difficile* and pneumonia would be most strongly associated with extreme leukocytosis.

Corresponding Author:
Nafeesa Alibhai
alibhai.nafeesa@gmail.com

Methods

We retrospectively reviewed the Medical Information Mart for Intensive Care III (MIMIC-III) database, which comprises data from over 40,000 ICU admissions at Beth Israel Deaconess Medical Center (BIDMC) between 2001 and 2012.[7] Since the original MIMIC-III data collection did not impact patient safety and all data were deidentified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, the requirement for patient consent was waived by the Institutional Review Boards of BIDMC and the Massachusetts Institute of Technology.

We identified all patients admitted to adult ICUs. Patient demographics, laboratory values (e.g. peak WBC count, *C. difficile* testing results), International Classification of Diseases version 9 (ICD-9) codes and in-hospital outcomes were collected. Disease processes were grouped into the following subgroups: pneumonia and pneumonitis, urinary tract infection (UTI), *Clostridium difficile (C. difficile)*, other intra-abdominal process, other infectious process, myeloproliferative disorders, and other non-infectious process. ICD-9 codes were used for all diagnostic groups except for *C. difficile*, which was categorized based on *C. difficile* testing results.

In our primary analysis, we compared the rates of different diagnoses among patients with different peak WBC counts, categorizing patients as follows: leukopenia (peak WBC 4,000), physiologic leukocyte count (peak WBC 4,000-10,000), leukocytosis (peak WBC >10,000 and <40,000), and extreme leukocytosis (peak WBC ≥40,000). We determined which diagnoses were more likely to occur in patients within each group.

In our secondary analyses, we began by examining the ICU length of stay and mortality rate in each WBC count group across diagnostic categories. Additionally, we ran multiple regression including demographic variables (age, gender, race), diagnostic category variables (pneumonia and pneumonitis, UTI, *C. difficile*, other intra-abdominal process, other infectious process, and other non-infectious process) and peak leukocyte count variables, to determine which variables were most predictive of mortality via adjusted odds ratio (aOR). Values were negatively adjusted for each variable to compensate for the positive predictive value of possible confounders.

Finally, we outlined the most common diagnoses associated with each diagnostic subcategory in order to help clinicians think about specific conditions in their differential diagnoses.

Normally distributed continuous variables are expressed as mean ± standard deviation and are compared using Student's t-tests. Categorical variables are presented as frequencies and percentages and compared using $\chi 2$ tests. All statistical analyses were done using Stata (version 14.2, StataCorp LLC, College Station, TX) and $p < 0.05$ was the criterion for significance.

Results

Overall, there were a total of 45,635 adult hospital admissions in the MIMIC-III ICU database. Of these, 1,295 hospital admissions were excluded because of history of myeloproliferative disorder, resulting in a final cohort of 45,340 patients. Demographic and admission characteristics of the cohort by peak WBC category were summarized (Table 1). Disease prevalence in the final cohort was as follows: pneumonia (22%), urinary tract infection (14%), *C. Difficile* (2%), intraabdominal (13%), other infectious diseases (8%), and other non-infectious diseases (12%).

Table 1. Baseline Patient Characteristics

	Leukopenia (<4K)	Physiologic 4K-10K	Leukocytosis (10K-40K)	Extreme Leukocytosis (≥ 40K)	p
n (%)	860 (1.9%)	13,187 (29.1%)	30,756 (67.8%)	537 (1.2%)	
Age	58.6 ± 16.1	63.7 ± 17.6	64.2 ± 17.2	63.9 ± 16.8	<0.001
Male	484 (56.3%)	7,370 (55.9%)	17,372 (56.5%)	282 (52.5%)	0.22
Surgical[a]	173 (20.1%)	4,886 (37.1%)	17,240 (56.1%)	261 (48.6%)	<0.001
Ethnicity					
White	624 (72.6%)	9,457 (71.7%)	22,141 (72.0%)	388 (72.3%)	<0.001
Black	120 (14.0%)	1,689 (12.8%)	2,514 (8.2%)	49 (9.1%)	
Hispanic	39 (4.5%)	506 (3.8%)	1,035 (3.4%)	14 (2.6%)	
Other	48 (5.6%)	608 (4.6%)	1,563 (5.1%)	25 (4.7%)	
Unknown	29 (3.4%)	927 (7.0%)	3,505 (11.4%)	61 (11.4%)	
ICU Admission Planned	31 (3.6%)	1,213 (9.2%)	5,227 (17.0%)	38 (7.4%)	<0.001
Emergency	829 (96.4%)	11,969 (90.8%)	25,522 (83.0%)	497 (92.6%)	
ICU Length of Stay[b]	2.03 ± 2.04	2.36 ± 2.47	5.33 ± 7.45	12.82 ±14.97	<0.001

All values reported as n (%) or mean (SD)
[a]Admitted to surgical ICU
[b]For patients who were admitted to the ICU multiple times during a single hospital stay, the lengths of their ICUs were summed

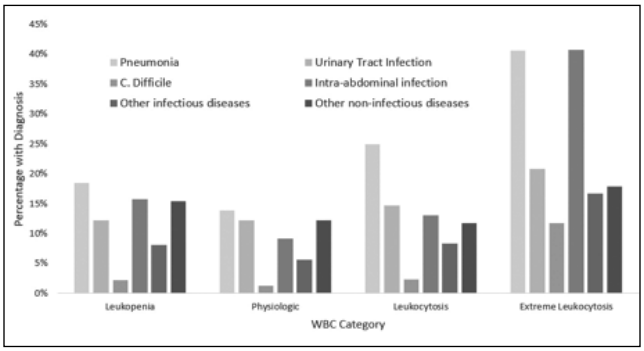

Figure 1. Percentage of patients in each peak WBC count category that had each diagnosis.
Note that total percentages may sum to more or less than 100% because individual patients could have more than one disease process or, rarely, no categorized disease process.

Primary Analysis

The primary analysis revealed the most common diagnoses associated with leukopenia, namely the percentage of patients with leukopenia who had a particular disease (Figure 1). These included pneumonia (18%), intra-abdominal infection (16%) and other non-infectious processes (15%). Patients with leukocytosis were most likely to have pneumonia (25%), urinary tract infection (15%) and other non-infectious processes (12%). Patients with extreme leukocytosis were most likely to have pneumonia (41%), intra-abdominal process (41%) and urinary tract infection (21%). The rate of *C. difficile* was substantially higher in patients with extreme leukocytosis compared to other groups (12% in patients with extreme leukocytosis, compared to 1-2% in all other groups, $p<0.001$).

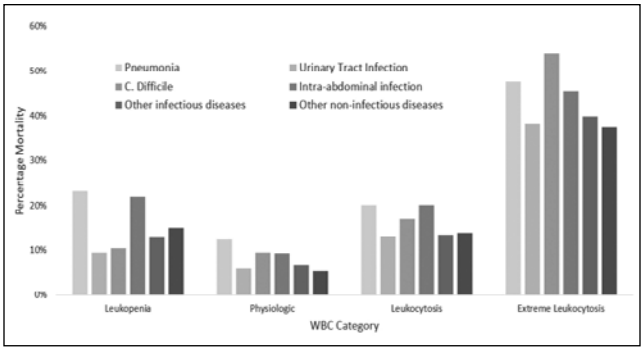

Figure 2. Mortality rates for patients with different disease categories by peak WBC count.
Note that total percentages may sum to more or less than 100% because individual patients could have more than one disease process or, rarely, no categorized disease process.

Secondary Analyses

The secondary analysis described risks of mortality across diagnostic and peak WBC count categories (Table 2). Odds ratios for patients with extreme leukocytosis were at least three times higher than those with leukopenia or leukocytosis across all diagnostic categories, reaching as high as 11.2 (95% CI: 5.5 – 22.9, P <0.001) for *C. difficile* (Table 2). Patients with extreme leukocytosis had substantially highest mortality rates across all diagnostic categories, reaching as high as 54% in patients with extreme leukocytosis and *C. difficile* (Figure 2).

Table 2. Odds Ratio for Mortality (compared to patients with normal WBC)

	Leukopenia (<4K)	Leukocytosis (10K-40K)	Extreme Leukocytosis (≥ 40K)
n (%)	860 (1.9%)	30,756 (67.8%)	537 (1.2%)
Pneumonia	2.1 (95% CI 1.4 - 3.1) P < 0.001	1.8 (95% CI 1.5 - 2.1) P < 0.001	6.4 (95% CI 4.7 – 8.6) P < 0.001
UTI	1.7 (95% CI 0.8 – 3.3) P < 0.001	2.4 (95% CI 1.9 – 3.0) P < 0.001	9.9 (95% CI 6.4 – 15.2) P < 0.001
C. Difficile	1.1 (95% CI 0.2 - 5.3) P < 0.001	2.0 (95% CI 1.1 - 3.4) P < 0.001	11.2 (95% CI 5.5 - 22.9) P < 0.001
Intraabdominal	2.7 (95% CI 1.7 - 4.3) P < 0.001	2.4 (95% CI 2.0 - 3.0) P < 0.001	8.1 (95% CI 5.8 - 11.3) P < 0.001
Other Infectious Diseases	2.1 (95% CI 1.0 - 4.5) P < 0.001	2.2 (95% CI 1.6 - 3.1) P < 0.001	9.5 (95% CI 5.7 - 15.8) P < 0.001
Other Non-Infectious Diseases	3.1 (95% CI 1.8 - 5.2) P < 0.001	2.9 (95% CI 2.3 - 3.6) P < 0.001	10.5 (95% CI 6.6 - 16.8) P < 0.001

All data presented as n (%) or odds ratio, 95% confidence interval, p value

Mean length of stay across diagnostic categories and white blood cell count categories (Table 3) was significantly longer for patients with extreme leukocytosis compared to other patient groups (p<0.01 for all diagnostic categories). Overall, length of stay was 8.4 days (95% CI: 7.9 - 9.0 days) longer for patients with extreme leukocytosis compared to patients without.

In our multiple regression analysis, we found that extreme leukocytosis was by far the most predictive variable of mortality. After factoring in the confounding effects of the other demographic variables (age, gender, race), diagnostic category variables (pneumonia and pneumonitis, UTI, *C. difficile*, other intra-abdominal process, other infectious process, and other non-infectious process) and peak leukocyte count variables, the adjusted odds ratio (aOR) for the predictive value of extreme leukocytosis was 10.4 (95% CI: 8.5 - 12.7, p<0.001). The next most predictive factor for mortality was leukopenia (aOR 3.1, 95% CI: 2.4 - 3.8, p<0.0001). Adjusted odds ratio for each variable is provided in Table 4.

Diagnoses most commonly encountered in each diagnostic category are presented in Table 5.

Table 3. Mean Length of Stay in Days

	Leukopenia (<4K)	Physiologic 4K-10K	Leukocytosis (10K-40K)	Extreme Leukocytosis (≥ 40K)
n (%)	860 (1.9%)	13,187 (29.1%)	30,756 (67.8%)	537 (1.2%)
Pneumonia	2.8 ± 3.1	4.0 ± 4.6	9.4 ± 10/7	18.0 ± 17.0
UTI	2.3 ± 2.1	2.9 ± 3.1	7.3 ±10.1	14.0 ± 16.3
C. Difficile	2.5 ± 2.7	3.7 ± 4.0	11.1 ± 12.7	14.0 ± 17.0
Intraabdominal	2.1 ± 2.4	2.8 ± 3.3	8.3 ± 11.4	16.2 ± 16.3
Other Infectious Diseases	2.7 ± 3.2	**3.2 ± 3.4**	9.1 ± 11.7	17.5 ± 18.7
Other Non-Infectious Diseases	2.4 ± 2.4	**2.6 ± 2.4**	5.8 ± 7.5	12.2 ± 14

All values reported as mean ± standard deviation

Table 4. Adjusted Odds Ratios for Mortality for All Variables Examined

	Adjusted Odds Ratio	95% Confidence Interval
Leukopenia	3.1	2.4-3.8
Leukocytosis	2.3	2.1-2.5
Extreme Leukocytosis	10.4	8.5-12.7
Pneumonia	2.4	2.2-2.5
UTI	0.8	0.8-0.9
C. Difficile	1.2	1.0-1.4
Intraabdominal	2.2	2.0-2.3
Other Infectious Diseases	1.1	1.0-1.3
Other Non-Infectious Diseases	1.0	0.9-1.1
Age	1.0	1.0-1.0
Male	0.9	0.9-1.0
Race: Black	0.9	0.8-1.1
Race: Hispanic	0.9	0.7-1.1
Race: Other	1.1	1.0-1.3
Race: Unknown	1.8	1.6-2.0

Table 5. Most Common ICD-9 Codes in Each Diagnostic Category

Diagnostic Group	Most Common ICD-9 Codes within Diagnostic Category
Pneumonia and pneumonitis (26 ICD-9 codes)	Pneumonia, organism unspecified Pneumonitis due to inhalation of food or vomitus Ventilator associated pneumonia Pneumonia due to Pseudomonas Methicillin susceptible pneumonia due to *S. aureus* Pneumonia due to other gram-negative bacteria Aspergillosis Empyema without mention of fistula Pneumonia due to Klebsiella pneumoniae Bronchopneumonia, organism unspecified Streptococcus pneumoniae pneumonia Bacterial pneumonia, unspecified Abscess of lung
Urinary tract infection (7 ICD-9 codes)	Urinary tract infection, site not specified Acute pyelonephritis without lesion of renal medullary necrosis Pyelonephritis, unspecified Infection and inflammatory reaction due to indwelling urinary catheter
Clostridium Difficile	Outcome confirmed by *C. difficile* toxin testing
Other intra-abdominal process (76 ICD-9 codes)	Acute and subacute necrosis of liver Acute pancreatitis Cholangitis Acute vascular insufficiency of intestine Perforation of intestine Peritoneal abscess Portal vein thrombosis Obstruction of bile duct Other diseases of spleen Spontaneous bacterial peritonitis Abscess of liver Other suppurative peritonitis Fistula of intestine, excluding rectum and anus Peritonitis (acute) generalized Ulcerative colitis, unspecified Acute cholecystitis Unspecified gastritis and gastroduodenitis, with hemorrhage
Other infectious process (38 ICD-9 codes)	Infection and inflammatory reaction due to other vascular device, implant, and graft Other and unspecified infection due to central venous catheter Acute and subacute bacterial endocarditis Cellulitis and abscess of leg, except foot Cellulitis and abscess of trunk Necrotizing fasciitis Cellulitis and abscess of upper arm and forearm
Other non-infectious process (26 ICD-9 codes)	Gout, unspecified Other pulmonary embolism and infarction Toxic encephalopathy Rheumatoid arthritis Tumor lysis syndrome Arterial embolism and thrombosis of lower extremity Immune thrombocytopenic purpura Other psoriasis

Discussion

Our data show that the degree of leukocytosis in critically ill patients provides valuable diagnostic and prognostic information. We found that patients in different peak WBC categories had substantially different disease patterns and prognoses. Extreme leukocytosis was predictive of substantially higher mortality across all disease categories, and in our multiple regression analysis, it was the single most important independent predictor of death, with odds ratio for mortality greater than 10-fold that of patients with normal leukocyte counts.

Traditionally, physicians are taught that leukocytosis should prompt investigations for infectious and inflammatory aetiologies, but little is taught about the value of peak WBC beyond the binary normal/abnormal test result. Here we present data demonstrating that the degree of leukocytosis in critically ill patients provides additional valuable information that clinicians can use.

The prognostic value of presenting WBC has been studied in ICU and non-ICU patient populations. One large study of ICU patients in two United Kingdom hospitals found that patients with WBC >25,000 on admission had much higher mortality than patients with normal admission WBC (35.2% vs. 18.9%). They also found that patients with WBC <4,000 on admission had significantly higher mortality, similar to our study.[8] On the other hand, a study of patients with infections on the surgical service at a single institution found that although patients with WBC >30,000 and WBC <3,000 had significantly higher mortality on preliminary analysis, this effect no longer reached significance when controlling for Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.[9] Of note, the APACHE II score provided four points for WBC ≥ 40,000, two points for WBC 20,000-39,999, and one point for WBC 15,000-19,999. It also provided up to four points for leukopenia.[10] The newer APACHE III and APACHE IV scoring systems only provide additional points for elevations in WBC up to 25,000.[11,12] Unlike the APACHE scores, which are meant to be calculated on admission to the ICU, our study was based on peak WBC count throughout the ICU stay, allowing us to benefit from information on the course of disease and corresponding WBC count.

Perhaps the most important strength of our study is the large sample size. This helped us to evaluate the epidemiology of relatively rare conditions such as*C. difficile*, which has a prevalence of only approximately 2% in the ICU,[13] as well as extreme leukocytosis, which we found had a prevalence of 1.1% in our cohort. This aslso helped us to obtain narrower confidence intervals on our estimates of mortality and length of stay differences between patient groups.

Additionally, the information in the MIMIC III database have been validated through the MIT-BIDMC collaboration,[7] strengthening our confidence in the integrity of the data.

One limitation of our study is that data were collected over a 12-year period, and some of the prevalence rates may have changed over time. Additionally, our data came from six ICUs at a single center, rather than from multiple centers. We feel, however, that prevalence of conditions such as *C. difficile* were similar in our cohort to other ICU cohorts,[13] and that mortality implications of *C. difficile* are likely generalizable to many other tertiary care center ICUs.

Conclusion

Degree of peak leukocytosis in critically ill patients provides valuable diagnostic and prognostic information. Clinicians in the ICU can benefit from deeper knowledge of which conditions are most commonly associated with each category of peak WBC count, and how peak WBC count impacts prognosis. In particular, extreme leukocytosis signals a very high risk of mortality and may, in appropriate clinical contexts, indicate the need for aggressive and/or urgent intervention.

Acknowledgements

We gratefully acknowledge the contributions of Ashton Anderson, Ph.D. for his assistance with the data analysis. This work was conducted with support from Harvard Catalyst.

References

1. Bulusu M, Narayan S, Shetler K, et al.. Leukocytosis as a harbinger and surrogate marker of Clostridium difficile infection in hospitalized patients with diarrhea. Am J Gastroenterol. 2000; 95: 3137-41.
2. Khanafer N, Toure A, Chambrier C, et al. Predictors of Clostridium difficile infection severity in patients hospitalised in medical intensive care. World J Gastroenterol. 2013; 19: 8034-41
3. Chu SY, Hanson DL, Ciesielski C, et al. Prophylaxis against Pneumocystis carinii pneumonia at higher CD4+ T-cell counts. JAMA. 1995; 273: 848.
4. Asadollahi K, Hastings IM, Beeching NJ, et al.. Leukocytosis as an alarming sign for mortality in patients hospitalized in general wards. Iranian journal of medical sciences. 2011; 36: 45-9.
5. Lawrence YR, Raveh D, Rudensky B et al. Extreme leukocytosis in the emergency department. QJM. 2007; 100: 217-23.
6. Halkes CJ, Dijstelbloem HM, Eelkman Rooda SJ, et al.. Extreme leucocytosis: not always leukaemia. Neth J Med. 2007; 65: 248-51.
7. Johnson AEW, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. Scientific Data. 2016; 3: 160035.
8. Waheed U, Williams P, Brett S, et al. White cell count and intensive care unit outcome. Anaesthesia. 2003; 58: 180-2.
9. Raymond DP, Crabtree TD, Pelletier SJ, et al. Extremes of white blood cell count do not independently predict outcome among surgical patients with infection. Am Surg. 2000; 66: 1124-30; discussion 30-1.
10. Knaus WA, Draper EA, Wagner DP, et al.. APACHE II: a severity of disease classification system. Crit Care Med. 1985; 13: 818-29.
11. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991; 100: 1619-36.
12. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006; 34: 1297-310.
13. Lawrence SJ, Puzniak LA, Shadel BN, et al. Clostridium difficile in the intensive care unit: epidemiology, costs, and colonization pressure. Infect Control Hosp Epidemiol. 2007; 28: 123-30.