PERIODICUM BIOLOGORUM
VOL. 127, No 1–2, 157–161, 2025
DOI: 10.18054/pb.v127i1-2.36383

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Original research article

Association of low white blood cell counts, comorbidities, and pneumonia in the surgical intensive care unit

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Keywords: intensive care surgical; infections; sepsis; mechanical ventilation; outcomes

Abbreviations
CRP – C-reactive protein
MV – mechanical ventilation
OR – odds ratio
VAP – ventilation-associated pneumonia

Received May 6, 2025
Revised June 19, 2025
Accepted July 2, 2025

Abstract

Background and purpose: *After the start of the COVID-19 pandemic, emergency admissions to the intensive care unit (ICU) have increased. These patients are often in poor general condition with frequent infections, especially pneumonia. Leukopenia may be associated with infections and a poorer treatment outcome in ICU patients. The aim of this study is to investigate the association of leukopenia with pneumonia, length of mechanical ventilation, length of ICU stay, and mortality in the ICU.*

Materials and methods: *Comorbidity, frequency of pneumonia, and duration of mechanical ventilation (MV) were compared in patients with leukopenia (LP group; n = 58) and a control group (n = 282) of surgical ICU patients.*

Results: *Patients with LP were more likely to be female (55% vs. 31%, P = 0.002), had a higher prevalence of respiratory disease (38% vs. 15.9%), gastrointestinal disease (74% vs. 51) and sepsis (41: 19%%) in comparison to control (P<0.001). In the LP population, 39% of patients had pneumonia, whereas in the control population, the rate was 23.8% (P < 0.023). The median ICU stay was 6 (3-14) vs 3 (2-8) days, P < 0.001, and MV length was 47 (8.25-96) vs 13.9 (3.1-85.9) hours in LP and control patients.*

Conclusion: *Women and patients with respiratory and acute abdominal diseases are at higher risk of developing leukopenia. The incidence of sepsis and pneumonia is high in this population. Microbiological analysis of the causative agents of these infections must be performed promptly, and targeted antimicrobial treatment applied.*

INTRODUCTION

Leukopenia refers to a reduced level of leukocytes in the blood (less than 3400/mm^3). The etiology of leukopenia is diverse. Primary leukopenias are extremely rare, typically occurring in childhood, and are often the result of hereditary or developmental disorders. Secondary leukopenias are more common, which occur as a result of the patient's comorbidities, such as liver disease, autoimmune diseases, malignant diseases, after exposure to chemicals, but also medically induced as a result of chemotherapy and radiotherapy *(1)*.

Laboratory tests in intensive care units (ICU) will reveal the total leukocyte count, while a differential blood count will show whether the leukopenia is absolute or relative *(1)*. Leukocyte morphology can be

checked by peripheral blood smears. Bone marrow biopsy, HIV testing, and lymph node biopsy may also be used *(1)*.

Leukopenia itself is an asymptomatic disorder, as can be observed in patients undergoing anticancer chemotherapy, other medications such as antibiotics, or those with organ transplants *(2)*. However, due to impaired immune function, infections develop more frequently. Oral ulcerations are common and recur after resolution. Patients also have symptoms and signs suggestive of infection (tachycardia, fever, chills, rigors, and fatigue) and symptoms of the affected organ system.

Leukopenia may be a sign of a systemic infection, such as a fungal infection *(3)*. In patients with infections, leukopenia is associated with an increase in inflammatory parameters, especially CRP, and may be a sign of sepsis *(4)*. Comorbidities may further aggravate the outcomes of leukopenic patients. In numerous studies, such as one conducted by De-la-Rosa-Martinez and coworkers in patients with *Clostridioides difficile* infections in Mexico with a high Charlson comorbidity score, leukopenia has been associated with increased mortality (*5*).

Patients hospitalized in the Surgical Intensive Care Unit are often in extremely poor condition. It has been proven that such patients are more likely to suffer from nosocomial infections due to their acute illness and invasive procedures. Frequent infections in surgical patients in the ICU are pneumonia, which can be the reason for respiratory insufficiency and admission to the ICU, and mechanical ventilation-associated pneumonia (VAP) that occurs during >2 days of stay in the ICU (*6,7*). The occurrence of VAP poses a great threat to the ICU patients because it is associated with an increased risk of death within a year. In addition to mechanical ventilation, the increased risk is also brought about by a large number of visits during the ICU stay and a prolonged stay of the patient in the ICU (*8*). The hypothesis of this study is that leukopenia in the ICU will be associated with a higher incidence of pneumonia and specific demographic factors compared to patients with normal or elevated leukocyte counts *(9)*.

MATERIALS AND METHODS

The study was designed as a cross-sectional study with historical data. Data from the Hospital Information System was taken from consecutive leukopenic patients (LP Group, N= 58) who were hospitalized in the Surgical Intensive Care Unit of the Clinic for Anesthesiology, Resus-

Table 1. *Demographic characteristics of leukopenic patients admitted to the surgical intensive care unit (ICU) over a 2.5-year period and a control group of consecutive patients admitted to the ICU.*

Characteristics	Leukopenic (N=58)	Control group (N=282)	P
Age	69[70-77]	66 [58-73.75]	0.11
Sex, (Male : Female)	26 (45%): 32 (55%)	179 (63%): 103 (37%)	0.008
Elective / emergency	10 (17%): 48(83%)	133 (47%): 149 (53%)	<0.0001
Comorbidities Cardiac	19 (32.8%)	100 (35.5%)	0.154
Vascular	41 (70.7%)	192 (68.1%)	0,151
Respiratory	22 (37.9%)	50 (17.7%)	0.0006
Neurologic	23 (39.7%)	100 (35.5%)	0.545
Renal	18 (31%)	61 (21.6%)	0.123
Gastrointestinal	43 (74%)	149 (53%)	0.003
Hepatobiliary	8 (14%)	44 (16%)	0.727
Endocrine/metabolic	27 (47%)	79 (28%)	0.006
(Poly)trauma	12 (20.7%)	40(14.1%)	0.210
Coagulopathies	10(17.2%)	27 (9.6%)	0.087
Sepsis	24 (41%)	42 (15%)	<0.0001
Pneumonia	19 (33%)	49 (17%)	0.008
Peritonitis	11 (19)	25 (8.9%)	0.023
Re-operation	28(49%)	42 (15%)	< 0.0001

Nominal data were analyzed using the Chi-square test and continuous variables using the Mann-Whitney U test. Percentages were calculated as a proportion of the total number in each group. Statistically significant differences are in bold.

citation and Intensive Care of the Clinical Hospital Center Osijek for 2.5 years, between July 1, 2022, and December 30, 2024. Their data were compared with consecutive patients (Control Group, N=282) who were not leukopenic. The collected data included the age and gender of the patients, the number of days spent in the ICU, whether the patients underwent surgery, the time spent on mechanical ventilation, baseline leukocyte count, baseline C-reactive protein (CRP), and baseline procalcitonin. Data on patients' initial diagnoses and the most common infections were also collected and classified into the following categories: cardiovascular, vascular, respiratory, coagulopathy, polytrauma, neurological, renal, gastrointestinal, hepatobiliary diseases, urological, gynecological, psychiatric, and metabolic and endocrine disorders. Of the infections diagnosed during treatment, sepsis, pneumonia, and peritonitis were recorded as the most common infections in the ICU.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS). Continuous variables are presented as median and interquartile range [IQR], and categorical variables as absolute and relative frequencies. Categorical variables were analyzed using the chi-square test, and continuous variables using the Mann-Whitney *U* test. Association analysis was examined using Spearman's or Pearson's correlation. All P values are two-sided. Patients with missing data (PCT) were excluded from individual analyses. The difference of $P<0.05$ was considered statistically significant.

RESULTS

A total of 58 LP patients and 282 control patients were analyzed in a cross-sectional study with historical data. Correlation analysis confirmed a positive correlation between leukopenia and female gender (Spearman correlation coefficient $\rho = 0.143$, $P = 0.008$). Among comorbidities, a significant correlation was confirmed for gastrointestinal diseases ($\rho = 0.162$, $P = 0.003$), respiratory diseases ($\rho = 0.186$, $P = 0.001$), and metabolic and endocrine diseases ($\rho = 0.162$, $P = 0.00303$). Sepsis ($\rho = 0.252$, $P<0.001$), pneumonia ($\rho = 0.145$, $P = 0.008$), and peritonitis ($\rho = 0.123$, $P = 0.023$) were infections associated with leukopenia. Their frequency and demographic data are shown in Table 1.

There were significantly more women and emergency patients in the leukopenic group of patients than in the control population. A greater number of these patients had sepsis, pneumonia, and peritonitis on admission. There were significantly more respiratory, gastrointestinal, endocrine, and metabolic diseases than in the control population (Table 1). The duration of mechanical ventilation and laboratory parameters also differed among these patients (Table 2). Leukopenic patients had twice as long ICU stays and had higher mortality rate than the control group (Table 2).

A statistically significant negative correlation was noted between the length of stay in the ICU and the measured WBC in the leukopenic patient group, such that patients with lower leukocyte counts had significantly longer ICU stays (Pearson's $r = -0.313$, $P = 0.005$).

DISCUSSION

This study included 340 patients and confirmed that the outcomes of patients with leukopenia were markedly worse than those with normal or elevated leukocyte counts in the control group. It confirmed that there are significant differences between the two groups and in their demographic characteristics, as was also recorded in other studies *(9,10).*

Although the age of the patients did not differ significantly, the gender differences were statistically significant, with women representing 55% of the total leukopenic patient population, while, they make up only 37% of the total population. In contrast, men in the control group make up 63% of the patients, and among the leukopenic patients, only 45%. A similar finding was noted in the study by Khanafer et al., who also found a significantly higher number of women, with a ratio of 1.5 to 1, compared to men, in their analysis of leukopenic patients with pneumonia. Their patients were medical rather than surgical, and their population was significantly younger, with an average age of 22 years *(9).*

Table 2. *Laboratory parameters and outcomes of leukopenic patients and a control group of patients treated in the surgical intensive care unit.*

Characteristics	Control group (N=282)	Leukopenic (N=58)	P
White blood cells*	8.6 [6.5 – 11.9]	2.3 [1.5 – 2.6]	<0.0001
CRP in admission	67.6 [18 - 160.7]	85.5 [29.3 – 157.4]	0.286
PCT	1 [0.4 - 5.7]	15.4 [1.4 – 62.4]	0.002
Mechanical ventilation (hours)	9 [2 - 47]	47 [8.25 - 96]	<0.0001
ICU stay	3 [2-5]	6 [3-14]	<0.0001
ICU mortality	50 (17.7%)	23 (39.7)	0.0002

*The lowest value during the ICU was recorded. Data was analyzed using the Mann-Whitney U test. Statistically significant differences are in bold.

Regarding the comorbidities observed in the study, it was noted that the frequency of cardiovascular, neurological, and renal diseases was similar in both groups. However, gastrointestinal diseases were significantly different in both groups, as many as 71% of leukopenic patients had some gastrointestinal disease, such as gastritis, ulcer, GI tumors, or diverticulosis. The association of leukopenia with GI diseases is exceptionally high, as in the study by Khan et al. *(11).* In the analysis of patients who had leukopenia with anorectal abscesses, they found that in these patients leukopenia was an independent risk factor for other infectious complications such as pulmonary complications (Odds ratio, OR 5.65, P = 0.002), but also for reoperation (OR 1.80, P = 0.019), unplanned readmission (OR 2.20, P < 0.001), and death (OR 2.77, P = 0.046) *(11).*

In this study, we confirmed that the frequency of pneumonia was significantly different between the groups. Out of 282 patients in the control group, only 33 (12%) had pneumonia. On the other hand, out of 58 patients in the leukopenic group, as many as 18, or 31%, had pneumonia. Our research showed that pneumonia is more frequent in the leukopenic population of ICU patients compared to controls, but other infectious diseases, especially sepsis, are also significantly more common in this group, which could be caused by specific multiresistant microorganisms or multifocal infections *(10).*

A retrospective study by A. Stoclin et al, which included 3388 oncology patients hospitalized in the ICU, showed that recent leukopenia is a significant risk factor for the development of numerous infections, including VAP (ventilator-associated pneumonia) *(12).* Our study also showed that leukopenia prolongs the stay of patients in the ICU and the duration of mechanical ventilation. According to the work of L. Papazian et al., the occurrence of VAP is influenced not only by the total duration of mechanical ventilation but also by the length of stay in the ICU, which may explain our results, i.e., the more frequent occurrence of pneumonia in leukopenic patients. The same work also states that pneumonia occurs more frequently in trauma patients *(13).*

Unfortunately, there is limited research on the association between leukopenia and pneumonia in surgical intensive care units. Studies conducted in other populations also confirm our results. A study by Khan et al., analyzing early postoperative complications after incision and drainage of anorectal abscesses, showed that leukopenia is one of the factors contributing to a higher frequency of reoperations and to the more frequent occurrence of life-threatening complications, including pneumonia *(11).* Also, a review study by Lederer et al, which aimed to determine the outcomes of surgical patients who had preoperative leukopenia, showed that patients with preoperative leukopenia had a much higher risk of developing infectious diseases, not only caused by multiresistant pathogens, but also by opportunistic pathogens *(14).*

Leukopenia has also been shown to be a significant factor affecting the length of stay of the ICU patients, and the duration of mechanical ventilation. Leukopenic patients typically spent twice as long in the ICU as control patients, as was also observed in the study by Khan et al *(11).*

As in their study, our leukopenic patients were mechanically ventilated five times longer, with a median of 9 hours of mechanical ventilation in the control group and 47 hours in the leukopenic group *(11).*

Leukopenia is common in surgical oncology patients who have undergone preoperative chemotherapy. It has been shown that leukopenia itself, which is associated with chemotherapy in oncology patients, is not a factor directly associated with postoperative morbidity and mortality in adults *(15)*, or children *(16).* Therefore, in surgical patients, in addition to leukopenia, other inflammatory markers, such as CRP and PCT, should be considered *(17).* The occurrence of fever in the leukopenic population of oncology patients is considered an emergency and requires empirical use of antibiotics, and often antifungal therapy *(18).*

In our study, the mortality of leukopenic patients was high, as in most studies. Leukocytes play a key role in protecting the body from infectious agents, and any disturbance in their number and function should be taken seriously; timely interventions should be made when symptoms of the disease appear. Treatment of leukopenia is based on treating the underlying cause that led to it, and preventing infections that could occur as a result.

This study has some shortcomings. Due to the retrospective nature of the study, inflammatory markers often were not recorded, and the number of patients for individual analyses was significantly smaller than the total number of all patients in the study. In some patients, empiric antibiotic therapy was started after symptoms of inflammation were registered, and microbiological samples were not taken, so it was impossible to analyze the microbiological agents in all patients.

We can conclude that the most common cause of leukopenia in our surgical patients is sepsis, which is often of abdominal origin. However, another study that would examine isolated causative agents in individual groups of patients in more detail, and the use of antibiotics before the appearance of leukopenia, could provide more information about high-risk patients and the most common causative agents *(19).* Based on these data, at-risk patients could be identified, and targeted diagnostics and therapy could be started earlier.

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