Introduction

A tumor refers to an abnormal tissue growth that usually lacks cysts and can be either benign or malignant. Tumors can be categorized into major liquid and solid tumor groups. Liquid tumors develop in the blood, bone marrow, or lymph nodes and encompass conditions such as leukemia, lymphoma, and myeloma. On the other hand, solid tumors refer to the growth of cancerous cells in solid masses within organ systems and can occur anywhere in the body.

While modern treatments have shown promising improvements in survival rates, it is important to note that they can also result in temporary side effects, probably including but not limited to nausea, vomiting, myelosuppression, fever, and neutropenia. Among the common symptoms in cancer patients are inflammation and fever, which can be caused by infection, drug reactions, blood transfusion, or even the tumor itself. Febrile neutropenia is a frequent complication of cancer treatments, including chemotherapy and radiation therapy. It poses a significant risk for the development of severe bacterial infections, which can have life-threatening consequences.

While published statistics, mortality occurs in 40% of patients experiencing severe neutropenia. However, it is essential to note that timely treatment can significantly reduce complications.

The Role of Inflammatory Indices in Predicting Infections and Guiding Treatment in Neutropenic Patients With Solid Tumors

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Abstract

Introduction: This study explores the link between inflammatory markers and hospital outcomes in febrile neutropenic patients with solid cancers—complication caused by systemic chemotherapy that can lead to hospitalization and requires timely diagnosis and treatment to reduce fatalities.

Methods: This study was conducted in 2017 at Vali-e-Asr Hospital in Birjand with 22 participants. Blood samples were collected to measure inflammatory indexes. The study documented various hospital outcomes, including duration of neutropenia and fever correction, length of hospital stays, ICU admission or mechanical ventilation, and mortality. Accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each marker.

Results: According to the findings, there was no significant difference in the mean duration of neutropenia, the duration of fever, or the length of hospital stay comparing procalcitonin (PCT; $P = 0.96$, $P = 0.36$, $P = 0.66$, respectively), polymorphonuclears (PMNs; $P = 0.11$, $P = 0.94$, $P = 0.52$, respectively), and erythrocyte sedimentation rate (ESR; $P = 0.41$, $P = 0.24$, $P = 0.17$, respectively). Further, the performance metrics calculated for PCT, ESR, and PMNs were an accuracy of 50%, 50%, and 40.90%, sensitivity of 88.8%, 100%, and 88.8%, specificity of 23.07%, 15.38%, and 7.6%, PPV of 44.4%, 45%, and 40%, and NPV of 75%, 100%, and 50%, respectively.

Conclusion: Our findings suggested that there was no significant relationship between inflammatory factors and hospital outcomes. However, further research is needed to explore the prognostic value of these markers in a larger and more diverse patient population.

Keywords: CRP, ESR, PCT, Fever, Neutropenia, Solid Tumors
Early diagnosis of bacterial infections in patients with febrile neutropenia can be challenging due to the unknown origin and the presence of only a few clinical symptoms such as fever, headache, and hypotension. Therefore, the identification of specific markers that indicate early infection is crucial. Given that infection is the primary cause of mortality and morbidity in these patients, numerous efforts have been made to identify laboratory parameters that can assist in diagnosing infections. One such parameter is C-reactive protein (CRP), which is often found to be elevated in the blood of cancer patients. However, different reports have suggested various cutoff values for CRP. In recent years, there has been growing interest in procalcitonin (PCT) as a potential marker for severe bacterial infection. PCT is a precursor peptide for the hormone calcitonin, and its levels can rise in response to bacterial infections. The use of PCT as a diagnostic marker has shown promise in distinguishing between bacterial and non-bacterial causes of inflammation or infection, especially in patients with febrile neutropenia. In addition, other inflammatory factors such as erythrocyte sedimentation rate (ESR) and leukocyte count can be effective in the early diagnosis of inflammation. The present study sought to investigate the prognostic values of PCT, CRP, ESR, white blood cells (WBCs), and polymorphonuclears (PMNs) in febrile neutropenic patients with solid tumors.

Methods
All solid tumor patients with neutropenic fever who had referred to Vali-e-Asr Hospital in Birjand in 2017 were examined in this study. This cross-sectional, descriptive-analytical study was conducted on patients with solid tumors whose fever and neutropenia were caused by chemotherapy. The headcount was used as the sampling method, and the study included all patients with fever and neutropenia caused by chemotherapy during 2017.

Participants were included in the study if they were 14 years of age or older and had not recently utilized antibiotics. Fever was defined as having an oral temperature of 38 °C or higher for at least one hour. Neutropenia, on the other hand, was defined as having an absolute neutrophil count lower than 500 cells/µL or a cell count below 1000 cells/µL with a predicted decline to less than 500 cells/µL. Before the commencement of the study, written informed consent was obtained from all participants who met the inclusion criteria. Blood samples were collected from the study participants, and their serum was analyzed to measure various parameters, including PMN count, CRP, PCT levels, ESR, and WBC counts. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PMN count, PCT levels, and ESR were evaluated as well. Broad-spectrum antibiotics from the beta-lactam family were administered after identifying patients with fever and neutropenia. Granulocyte colony-stimulating factor treatment was used for those with neutropenia below 500 cells/µL. The study evaluated the duration of fever correction, neutropenia correction, and hospitalization in these patients. The Mann–Whitney U test was employed to analyze the results, and a P value less than 0.05 was considered statistically significant.

Results
The present study was conducted on a cohort of 22 patients with solid tumor cancer who were receiving treatment at Vali-e-Asr Hospital in Birjand in 2017. Among the participants, 11 patients (50%) were men, and 11 patients (50%) were women. The average age of the participants in this study was 57.86 ± 15.41 years, with an age range of 37 years as the minimum and 82 years as the maximum. Among the participants, breast cancer was found to be the most prevalent type of cancer, with 7 patients (31.8%). Following breast cancer, lung cancer was the second most prevalent type, with 4 patients (18.2%) identified as having this condition.

The mean duration of neutropenia correction among the patients was found to be 2.39 ± 4.27 days. Additionally, the mean duration of fever correction was calculated to be 1.8 ± 2.27 days. The mean length of hospital stay was 5.46 ± 7.77 days.

All 22 patients in the study displayed abnormal WBC counts, with levels below 3000 cells/µL of blood. Abnormal PMN levels, defined as less than 1,500 cells/µL, were found in 20 out of 22 patients (90.9%). Only 2 patients (9.1%) had normal PMN levels exceeding 1500 cells/µL. ESR was normal in only 2 patients (9.1%), while 20 patients (90.9%) demonstrated elevated ESR levels. The results revealed that 4 patients (18.2%) had normal PCT levels (less than 0.05 ng/mL), and elevated PCT levels were detected in 18 patients (81.8%) participating in the study. In addition, all participants exhibited abnormal CRP levels. The normal range for CRP is typically less than 0.3 mg/dL, but in this study, CRP levels were greater than 60 mg/dL for all patients (Table 1).

Among the 22 patients, one person (4.5%) required intensive care unit (ICU) admission and showed abnormal

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Median, Quartile (25–75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>2.71 ± 4.85</td>
<td>15.67</td>
<td>0.04</td>
<td>0.05–0.1</td>
</tr>
<tr>
<td>CRP</td>
<td>43.81 ± 81.32</td>
<td>164</td>
<td>18</td>
<td>45–87</td>
</tr>
<tr>
<td>ESR</td>
<td>33.36 ± 61.5</td>
<td>143</td>
<td>20</td>
<td>38–54</td>
</tr>
<tr>
<td>WBC</td>
<td>714.11 ± 1106.81</td>
<td>2600</td>
<td>200</td>
<td>475–1577.5</td>
</tr>
<tr>
<td>PMN</td>
<td>536.75 ± 756.04</td>
<td>2269</td>
<td>10</td>
<td>394.75–1100</td>
</tr>
</tbody>
</table>

Note: SD: Standard deviation; PCT: Procalcitonin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell; PMNs: Polymorphonuclear.
PCT, ESR, and PMN results (PCT: 15.67 ng/mL, ESR: 71 mm, PMN: 1000/µL). One patient (4.5%) required mechanical ventilation and demonstrated abnormal PCT, ESR, and PMN results (PCT: 0.08 ng/mL, ESR: 71 mm, PMN: 1000/µL). In addition, two patients (9.1%) succumbed to their illness and passed away during the study period; one of them showed normal PCT levels, and the other had abnormal levels. Both cases had abnormal ESR (51 and 71 mm, respectively) and PMN (810/µL and 1000/µL, respectively) levels.

The results revealed no significant difference in the mean duration of neutropenia, the duration of fever, or the length of hospital stay comparing PCT ($P = 0.96$, $P = 0.36$, $P = 0.66$, respectively), PMN ($P = 0.11$, $P = 0.94$, $P = 0.52$, respectively), and ESR ($P = 0.41$, $P = 0.24$, $P = 0.17$, respectively) (Table 2).

To evaluate the effectiveness of the diagnostic test, multiple criteria were employed to distinguish between patients with favorable and unfavorable prognoses. These criteria encompassed various factors such as mortality, ICU admission, the requirement for mechanical ventilation, and hospital stays exceeding 7 days. Cases that fulfilled these criteria were classified as having an unfavorable prognosis, indicating a higher likelihood of adverse outcomes. Conversely, cases that did not meet these criteria were considered to have a favorable prognosis, suggesting a lower risk of complications. Out of the total 22 patients, it is noteworthy that 13 patients (59.09%) were grouped as having a favorable prognosis, while 9 patients (40.91%) were categorized as having an unfavorable prognosis.

Sensitivity, specificity, PPV and NPV of PMN count, PCT levels, and ESR were evaluated based on these categorizations. When comparing the results of the diagnostic test, it was found that out of the 22 patients, 3 had both a favorable prognosis and normal PCT levels, which can be considered true negatives. Additionally, 8 patients had both an unfavorable prognosis and normal PCT levels, indicating true positives. However, there were cases where the diagnostic test results did not align with the prognosis. Specifically, 10 patients had abnormal PCT levels despite having a favorable prognosis, resulting in false positives. Conversely, one patient had an unfavorable prognosis but exhibited normal PCT levels, leading to a false negative (Table 3). Based on the provided data, the calculated performance metrics for PCT as a diagnostic test include accuracy of 50%, sensitivity of 88.8%, specificity of 23.07%, PPV of 44.4%, and NPV of 75% (Table 4).

Nine patients were correctly identified with a positive ESR result and an unfavorable prognosis (True positives). Two patients were correctly identified with a negative ESR result and a favorable prognosis (True negatives). Moreover, 11 patients were incorrectly identified as having a positive ESR result and an unfavorable prognosis (False positives). The related data are presented in Table 3. Based on the given data, the performance metrics for ESR as a diagnostic test were calculated as an accuracy of 50%,

### Table 2. The Mean Duration of Neutropenia Correction, Fever Correction, and the Length of Hospital Stay and Inflammatory Indices

<table>
<thead>
<tr>
<th>All (N = 22)</th>
<th>PCT</th>
<th>ESR</th>
<th>PMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>The mean duration of neutropenia correction (days)</td>
<td>3.11 ± 4.50</td>
<td>2.26 ± 4.22</td>
<td>1.40 ± 3.00</td>
</tr>
<tr>
<td>The mean duration of fever correction (days)</td>
<td>1.00 ± 1.50</td>
<td>1.91 ± 2.44</td>
<td>0.00 ± 1.00</td>
</tr>
<tr>
<td>The mean length of hospital stays (days)</td>
<td>3.60 ± 7.00</td>
<td>3.59 ± 7.42</td>
<td>1.41 ± 4.00</td>
</tr>
</tbody>
</table>

Note: PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; PMN: Polymorphonuclear.

### Table 3. Frequency of People With Favorable and Unfavorable Prognoses Based on PCT, ESR, and PMNs

<table>
<thead>
<tr>
<th>All (N = 22)</th>
<th>PCT</th>
<th>ESR</th>
<th>PMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Favorable prognosis</td>
<td>3</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Unfavorable prognosis</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; PMN: Polymorphonuclear.

### Table 4. Sensitivity, Specificity, Positive and Negative Predictive Values of PMN Count, PCT Levels, and ESR

| | Accuracy | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value |
| | PCT | 50% | 88.8% | 23.07% | 44.4% |
| | ESR | 50% | 100% | 15.38% | 45% |
| | PMN | 40.90% | 88.8% | 7.6% | 40% |

Note: PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; PMN: Polymorphonuclear.
sensitivity of 100%, specificity of 15.38%, PPV of 45%, and NPV of 100% (Table 4).

Eight patients were correctly identified as having a positive PMN result and an unfavorable prognosis (True positives), while 12 patients were incorrectly identified as having a positive PMN result and a favorable prognosis (False positives). One patient was correctly identified as having a negative PMN result and a favorable prognosis (True negatives), while one patient was incorrectly identified as having a negative PMN result but actually had an unfavorable prognosis (False negatives). The results are provided in Table 3. Based on the provided data, the performance metrics for PMNs as a diagnostic test were an accuracy of 40.90%, sensitivity of 88.8%, specificity of 7.6%, PPV of 40%, and NPV of 50% (Table 4).

Discussion

The present study was conducted on 22 neutropenic patients with solid tumors who attended Vali-e-Asr Hospital in Birjand in 2017. The present study aimed to determine the prognostic values of inflammatory factors for solid cancers and the management of infections in febrile neutropenic patients. According to the results of our study, an abnormal level of PCT (exceeding 0.05 ng/mL) was detected in 81.8% of febrile neutropenic patients with solid tumors. In line with our results, Erten et al reported that the average PCT level in 36 patients was 1.33 ± 0.93, while another study by Massaro et al demonstrated a PCT level of 2.30 ng/mL in 355 febrile neutropenic patients. In our study, it was found that all participants had abnormal CRP levels exceeding 60 mg/dL. A study released by Meidani et al showed that the mean PCT level in 64 febrile neutropenic patients was 28.65 ± 2.68 ng/mL, while the CRP level was 159.48 ± 73.9. Additionally, another study conducted in 2014 on 86 febrile neutropenic patients found a mean CRP level of 11.4 ± 19.7 mg/dL. This is while, in another study, Magrini et al reported that out of 25 affected patients, only 14 cases had abnormal PCT levels, and 23 cases had abnormal CRP levels. The findings of another retrospective study on 286 cancer patients with febrile neutropenia in Korea revealed that 50 patients (17%) had abnormal PCT levels, and 103 patients (36%) had CRP levels of more than 6.0 mg/L. The duration of the disease and fever can certainly impact the levels of inflammatory parameters. It is worth noting that during the first 24–48 hours of inflammation, there may not be a significant increase in serum concentrations of CRP, while serum concentrations of PCT can start to rise within the first 3 hours after the onset of infection. This disparity in response time between CRP and PCT can be attributed to their different mechanisms of production and release in the body. However, an increased CRP level in febrile neutropenic patients has been confirmed in all these studies. Various studies have revealed that an elevated ESR can occur as a result of inflammation, infection, and systemic diseases. However, it is important to mention that an elevated ESR alone is not considered a specific diagnostic indicator for any particular disease. The level of ESR can vary depending on individual patient characteristics and conditions. In our study, it was observed that ESR was within the normal range for 2 patients (9.1%) based on their age, while it was abnormal for 20 patients (90.9%). Based on the findings of previous studies, it is evident that the relative frequencies of the mentioned parameters (PCT, CRP, and ESR) can vary across different studies due to the diverse underlying disorders observed in patients. However, it is crucial to highlight that PCT demonstrates higher specificity in detecting infections when compared to serum CRP and ESR. On the other hand, CRP levels increased in response to various conditions, including systemic inflammations, underlying disorders, and malignant diseases.

In addition, our findings indicated that all 22 patients had abnormal WBC counts, which were less than 3,000 cells/µL. Moreover, 20 patients (90.9%) had abnormal levels of PMN, with counts less than 1500 cells/µL. In a separate study conducted in Turkey, among 27 patients with febrile neutropenia, the mean WBC count was reported to be 510 ± 910 cells/µL, while the mean PMN count was 220 ± 230 cells/µL.

Based on our results, the mean duration of neutropenia, fever, and hospitalization was 2.39 ± 4.27, 1.8 ± 2.27, and 5.46 ± 7.77 days, respectively. Additionally, it was noted that out of the 22 patients, 1 (4.5%) required ICU admission, 1 (4.5%) required mechanical ventilation, and 2 (9.1%) passed away. However, Debian et al reported that 64% of patients required intubation and admission to the ICU. Tragically, within two months of the onset of symptoms, 23% of the patients had unfortunately passed away. Furthermore, their findings revealed that 22.8% of the patients had diabetes, 7.9% had kidney disease, and approximately 20% had pulmonary heart disease.

In a study by Ahn in Korea, which involved 355 febrile neutropenia patients with solid tumors, it was reported that 3% of the patients had unfortunately passed away. In another study in the United States, which focused on 104 febrile neutropenia children with cancer, Alexander et al concluded that one case of death occurred, while four individuals sadly passed away in the ICU. The variations in results across different studies can be justified due to various factors. Parameters such as the duration of neutropenia and fever correction, length of hospital stay, the need for mechanical ventilation, and the occurrence of death can all be influenced by factors such as the individual patient’s condition and underlying disorders, as well as the timely diagnosis and appropriate treatment they receive. Each patient’s unique circumstances and the management they receive play a crucial role in
determining the outcomes observed in different studies. It highlights the complexity of these conditions and the importance of personalized care and treatment for each patient.

Among the patients with abnormal PCT and ESR levels, one patient required ICU admission ($P > 0.05$). One patient who had abnormal PCT and ESR levels ($P > 0.05$) needed mechanical ventilation. Furthermore, it was observed that one patient who passed away had a normal PCT level, while another patient who died had an abnormal PCT level. Both cases had abnormal ESR and PMN levels. However, it is worth mentioning that the difference in ESR and PMN levels between those with normal levels and those with abnormal levels was not found to be statistically significant. Our study did not find a significant difference in the duration of neutropenia, fever, or hospital stay between patients with normal and abnormal ESR and PCT levels. However, further research and larger sample sizes may be needed to establish stronger significance. The results published in PCT and infection prediction in neutropenic patients can vary and sometimes be contradictory. The results of a study conducted by Carnino et al in Italy demonstrated higher PCT levels and lower PMN counts in hospitalized cancer patients. However, they concluded that PCT may not be considered a reliable predictive marker for infection in neutropenic patients. A study by Murat Sedef et al on 104 cancer patients with fever indicated a significant association between mortality rate and abnormal PCT levels ($> 2$ ng/mL), a reduced number of PMNs, and elevated CRP levels. These findings suggest that PCT, along with PMN count and CRP levels, may serve as important markers for predicting mortality in cancer patients with fever. In this study, although there was no correlation between PCT levels and length of hospital stay, the association with mortality highlights the potential clinical significance of PCT as a prognostic indicator in this patient population. Meidani et al evaluated 64 patients with febrile neutropenia and confirmed the significance of PCT and CRP as important diagnostic indicators of severe infection in this specific patient population. These discrepancies in findings could be attributed to various factors, such as differences in study design, patient populations, underlying conditions, and the specific methodologies used in each study. It highlights the complexity of the relationship between PCT, ESR, CRP levels, and infection prediction in neutropenic patients and suggests that further research is needed to better understand this association.

According to our study, along with others, both CRP and PCT were identified as important diagnostic indicators of infection in febrile neutropenic patients. However, it is important to highlight that they may not be considered the major prognostic and predictive indicators in these patients. In addition, our results showed that abnormal ESR and PCT levels may not serve as specific prognostic indicators for longer hospital stays.

Conclusion

No significant correlation was observed between the serum levels of PCT, CRP, or ESR and patient prognosis in our study. However, further research and larger sample sizes are probably required to establish stronger significance.

Authors’ Contribution

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Supervision: Ahmad Reza Sezbazi.

Validation: Azadeh Ebrahimzadeh.

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Writing-review & editing: Arezou Khorosjerdi.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Ethical Approval

The present study was performed after obtaining written consent, and approval was obtained from the Research Ethics Committee of Birjand University of Medical Sciences (IR.Bums.REC.1396.235). The present study received approval from the Research Ethics Committee of Birjand University of Medical Sciences (IR.Bums.REC.1396.235), and a written consent form was obtained from all patients for participation.

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