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Mini review

Unlocking the potential: Harnessing biomarkers commonly used in clinical practice to predict complications and outcomes in febrile neutropenia

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Summary. Febrile neutropenia (FN) is a frequent and serious complication in cancer patients undergoing standard therapy. Its incidence ranges widely, from 10% to 50% in patients with solid tumors and up to 80% in those with hematological malignancies. FN significantly impacts patient outcomes, often necessitating dose reductions or delays in cancer treatment, which can adversely affect overall survival. The mortality rate associated with FN is substantial, between 10% and 30%. Given its profound impact, early identification of patients at high risk for adverse outcomes is crucial. The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a useful tool for stratifying FN risk but has limitations, including subjectivity and difficulty in emergency settings. Biomarkers such as procalcitonin and C-reactive protein (CRP) have demonstrated potential in predicting FN complications. Procalcitonin, in particular, has shown superior performance over the MASCC score in predicting bacteremia and mortality in FN patients. CRP, while useful, is less effective than procalcitonin in certain contexts. Moreover, malnutrition, common in cancer patients, may also influence FN outcomes. Albumin, a marker for nutritional status, correlates with inflammation and malnutrition and may hold promise for FN prediction. Emerging ratios, such as the procalcitonin to albumin ratio (PAR) and the CRP to albumin ratio (CAR), have shown efficacy in predicting complications in various conditions but have not yet been explored in FN. This review emphasizes the urgent need for further research to validate these biomarkers and their ratios in FN, potentially leading to better risk stratification and management strategies, thereby improving patient outcomes.

Keywords: albumin, C-reactive protein, febrile neutropenia, prediction, procalcitonin.

INTRODUCTION

Febrile neutropenia (FN) frequently occurs as a complication in cancer patients undergoing standard therapy (DE Castro Carpeño et al. 2015). The incidence of FN varies widely. It can vary from 10% to 50% in patients with solid tumors, and up to 80% in those with hematological malignancies (Klastersky 2004; DE Castro Carpeño et al. 2015). The impact of FN can differ based on individual patient factors and the characteristics of the underlying disease (DE Castro Carpeño et al. 2015). Key factors influencing the severity of FN include patient age, the presence of comorbidities, the type of carcinoma (CA), and the stage of cancer. Mortality rates associated with FN are significant. They range from 10% to 30% (Al-Tawfiq et al. 2019; Parodi et al. 2019; Weerasubpong et al. 2019; Sereeaphinan et al. 2021).

However, mortality is not the sole concern associated with FN. The presence of FN often necessitates reductions in cytostatic doses or delays in treatment cycles, which can negatively impact the efficacy of cancer treatment and overall patient survival rates. These complications underscore the need for prompt hospitalization and intensive care for FN patients.

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Given the seriousness of FN and its potential consequences, it is crucial to identify patients at higher risk for adverse outcomes. The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a valuable tool for stratifying outpatients with FN (Bhardwaj et al. 2021). The MASCC score consists of several components: 1) Burden of illness or symptom severity, as determined by the attending physician at presentation (None: 5 points, Moderate: 3 points, Severe: 0 points); 2) Hypotension, defined as systolic blood pressure <90 mmHg (Yes: 0 points, No: 5 points); 3) Active chronic bronchitis, emphysema, decreased FEV, or the need for oxygen therapy, corticosteroids, and/or bronchodilators (Yes: 0 points, No: 5 points); 4) Type of cancer (Solid tumor: 4 points, Hematologic without prior fungal infection: 4 points, Hematologic with prior fungal infection: 0 points); 5) Dehydration requiring IV fluids (Yes: 0 points, No: 5 points); 6) Status at onset of fever (Outpatient: 3 points, Inpatient: 0 points); 7) Age (<60: 2 points, ≥60: 0 points). This index helps clinicians identify patients at increased risk of developing complications, thereby guiding decisions on treatment, the necessity for intravenous antibiotic therapy, and hospitalization needs (Chaftari et al. 2021). However, the MASCC score includes a subjective component—the burden of illness—whose interpretation can vary significantly among physicians based on their experience (Chaftari et al. 2021). Additionally, calculating the MASCC index can be challenging in intensive care or emergency settings (Chaftari et al. 2021). Moreover, 9% to 15% of patients categorized as low-risk by the MASCC index still develop serious complications (Virizuela et al. 2016). Therefore, there is a pressing need for a more objective, straightforward, and accurate method for classifying the risk in FN patients.

Given the profound impact of FN on the treatment and prognosis of carcinoma patients, accurately predicting its complications and outcomes is critically important. Numerous studies have focused on the potential of biomarkers to forecast FN-related complications, with a particular emphasis on inflammation-related markers. In light of these considerations, this mini-review aims to summarize the most important crucial data regarding commonly used biomarkers in clinical practice, particularly those associated with inflammation, and their relevance in predicting FN outcomes.

BIOMARKERS IN PREDICTION OF FN COMPLICATIONS

Regardless of hospital setting, blood samples from patients suspected of developing FN are typically taken immediately when the diagnosis is proposed. This prompt action is essential for measuring the neutrophil count, which is crucial for confirming an FN diagnosis. Additionally, several other biomarkers are measured, such as C-reactive protein (CRP) and procalcitonin, both of which are indicators of inflammation (Đukić et al. 2022). These routinely taken biomarkers have potential in predicting the development of FN complications and outcomes.

A study by Yadav et al. (2021) demonstrated that procalcitonin is a useful marker for predicting bacteremia, outperforming the MASCC risk score for this purpose. This study also indicated that procalcitonin could be used for predicting mortality in patients with FN. Similarly, a study by Ahn et al. (2013), investigating the use of procalcitonin for predicting septic shock, found that procalcitonin performed better than the MASCC score. Both studies also showed that adding procalcitonin to the MASCC risk index score improves its performance in stratifying patients at risk of developing complications. In another study focusing on the prediction of bloodstream infections (BSI) in patients with FN, procalcitonin emerged as a better predictor of BSI than the MASCC score (Chaftari et al. 2021). Additionally, this study showed that procalcitonin is a good predictor of the length of hospital stay.

Similar to procalcitonin, CRP levels can also be used to predict FN complications and outcomes. Elevated CRP levels are an independent predictor of poor outcomes in cancer patients with FN (Ahn et al. 2011). Interestingly, although CRP is a useful marker for predicting FN outcomes, studies have shown that procalcitonin performs better, particularly in predicting bacteremia (Shilpakar et al. 2019).

Given the widespread issue of malnutrition among carcinoma patients and its adverse effect on prognosis (Arends 2024), there is significant interest in exploring whether biomarkers related to malnutrition can also predict FN outcomes and complications. Albumin, a frequent marker of nutritional status (Keller 2019), is also commonly used to detect malnutrition in CA patients (Enkobahry et al. 2023). Furthermore, albumin levels have been linked to predicting malnutrition within this patient group (Yan et al. 2022). Notably, albumin levels reflect both malnutrition and inflammation, with low serum albumin indicating severe inflammation (Soeters et al. 2019). Low serum albumin is often associated with severe inflammation, as albumin is a negative acute-phase reactant. During inflammatory responses, the liver shifts its production focus from albumin to acute-phase proteins like CRP and fibrinogen, which help in managing infection, injury, or stress. Consequently, serum albumin levels drop, leading to hypoalbuminemia. This decrease in albumin can be linked to increased capillary permeability, leading to its loss from the bloodstream, and reduced synthesis due to cytokine activity, such as interleukin-6 (IL-6). Given its dual role in representing both malnutrition and inflammation—two crucial factors in cancer and FN—it is

essential to examine its potential in predicting FN outcomes and complications. Further research in this area could provide valuable insights, potentially improving FN management strategies and enhancing patient care (Dimitrijević et al. 2024). In contrast to CRP and procalcitonin, there is currently insufficient clinical research to support the use of this biomarker in predicting FN complications and outcomes. This highlights the urgent need for further studies to explore and validate the potential of this biomarker, given its importance in improving patient care and outcomes.

In recent years, several clinical trials have explored the procalcitonin (PCT) to albumin ratio (PAR) and the C-reactive protein (CRP) to albumin ratio (CAR) as predictive markers for various diseases and their complications. The PAR has demonstrated its effectiveness as a biomarker for identifying sepsis in neonates with pneumonia (Li et al. 2023), urosepsis, and uroseptic shock, as well as for predicting mortality in intensive care unit (ICU) patients with sepsis (Luo et al. 2018). Similarly, the CAR has proven useful in predicting mortality among critically ill patients, with higher CAR levels being associated with increased mortality rates in the ICU (Park et al. 2018). Additionally, elevated CAR levels are independent predictors of both the presence and severity of neonatal sepsis and a risk factor for sepsis in adults with severe burn injuries (Li et al. 2021; Yu et al. 2021). However, these relatively new biomarker ratios have not yet been investigated for their potential in predicting FN outcomes and complications. It is crucial that future research explores the utility of PAR and CAR in this field to enhance the prediction and management of FN complications. There are several tools that can predict the development of sepsis, such as the sepsis index, monocyte distribution width, and others (Agnello et al. 2021; Hausfater et al. 2021). Although these two have been validated in certain conditions, they cannot be used in FN due to a lack of universal standardization and the need for broader adoption in clinical practice for sepsis prediction.

Apart from the biomarkers mentioned, several others could potentially be used to predict febrile neutropenia outcomes and complications. One standout is presepsin, a biomarker that, while not yet universally standardized or widely adopted in clinical practice, shows promise (Piccioni et al. 2021). We can speculate that presepsin could also be useful in predicting FN outcomes and complications due to its ability to diagnose sepsis early, which is a serious health risk in people with FN. Due to its role in indicating malnutrition, prealbumin, similar to presepsin, could be considered for predicting FN complications if it becomes a standard of care in clinical settings.

CONCLUSIONS

In summary, febrile neutropenia (FN) is a significant complication in cancer patients, with its incidence and severity influenced by various patient and disease factors. While the MASCC risk index remains a valuable tool for risk stratification, its limitations highlight the need for more objective and reliable methods. Biomarkers such as procalcitonin and CRP have shown promise in predicting FN outcomes, particularly in identifying severe complications like bacteremia and septic shock. Additionally, the potential of malnutrition-related biomarkers, especially albumin and its ratios with procalcitonin and CRP, warrants further investigation.
The current evidence underscores the importance of promptly measuring these biomarkers to improve FN management. However, the existing research is insufficient to fully validate their predictive capabilities, especially in the context of FN. Therefore, further studies are crucial to explore and confirm the utility of these biomarkers in predicting FN complications and outcomes. Advancing our understanding in this area could lead to better risk stratification, more tailored treatments, and ultimately, improved patient care and survival rates for those affected by this serious condition.

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