The Role of Complete Blood Cell Count in Prognosis—Watch this Space!

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Abstract

Prognostic factors in cancer patients provide information about possible clinical outcomes and help classify patients into different risk groups. Treatment and clinical management decisions are often challenging, thus the availability of reliable and accessible prognostic markers is vital when designing treatment plans and discussing them with patients. This article discusses the prognostic value of the complete blood cell count components (i.e., white blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, hemoglobin level, and platelet count) in regard to clinical outcomes in patients with malignant disorders.

Keywords

Complete blood cell count, white blood cell count, hemoglobin level, platelet count, neutrophil count, lymphocyte count, monocyte count, survival, cancer, prognosis

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Prognostic factors of clinical outcomes in patients with cancer are a useful tool in the practice of medicine, especially in the fields of oncology and malignant hematology. A good prognostic factor should reflect the biology of its targeted disease, be inexpensive, reliable, reproducible, and standardized. Furthermore, a universal prognostic factor that can predict survival regardless of the type of cancer will help to simplify the management of cancer patients. In this article, we describe the undermined universal prognostic value of a low-cost, standardized, reliable, and reproducible prognostic factor in cancer: the complete blood cell (CBC) count and its components.

White Blood Cell Count

The absolute white blood cell (WBC) count obtained from the CBC count has been historically used as a marker of infection and inflammation. It is a widely available tool for clinicians to identify the presence of infection and monitor the patient's response to treatment, such as antibiotics. Nonetheless, the role of the WBC count has gone beyond the assessment of infectious processes and it has become an important prognostic measurement of outcomes in cancer treatment. The inflammatory process that takes place during cancer development and progression are, in part, reflected in abnormalities of the WBC count.

In hematologic malignancies, the WBC count is a prognostic factor for clinical outcomes included in international prognostic systems. For example, in advanced Hodgkin's lymphoma (HL), the International Prognostic Score (IPS) alerts cancer specialists of worse clinical outcomes in patients presenting with a WBC count ≥15,000/mm^3.[1] Another international prognostic system that associates a higher WBC count count with adverse clinical outcomes is the Mantle Cell Lymphoma International Prognostic Index (MIPI). The MIPI has been validated in several population-based cohorts, confirming that a high WBC count is a negative predictor of survival.[2,3]

In addition to hematologic malignancies, the WBC count has been reported to be of prognostic value in solid tumors. Pre-treatment leukocytosis, defined as a WBC count >10,000/µl, has been shown to be an independent prognostic factor of survival in cervical cancer patients.[4] In non-small cell lung cancer (NSCLC), the prognostic importance of the WBC count has been studied in patients before the initiation of systemic treatment and as a pre-operative measure, in both cases showing that an elevated WBC count is a significant predictor of overall survival (OS) and time to progression of disease.[5–7] Mandrekar et al.[5] developed a survival prediction model for newly diagnosed advanced-stage NSCLC that incorporates WBC count as one of the variables. Additionally, patients with metastatic melanoma who exhibit a high pre-treatment leukocyte count (>10 x 109/l) have poor clinical outcomes following biochemotherapy in both OS (hazard ratio [HR]=1.7; p=0.0005) and progression-free survival (PFS) (HR=1.5; p=0.008).[8]

Interestingly, 143,748 post-menopausal women were studied, as part of the Women Health Initiative, to determine the association of WBC count with the incidence of cancer and cancer mortality. The study concluded that within this population, women with higher WBC counts have an increased risk of developing invasive breast, colorectal, endometrial, and lung cancer, as well as a higher risk of overall mortality in breast and lung cancer.[9] As a biomarker of inflammation,

the WBC count is a simple test to roughly assess inflammation in patients with cancer.

Absolute Neutrophil Count

Many of the cells and mediators involved in the development of the systemic inflammatory response are also found in the microenvironment of tumors; it is believed that these factors support tumor growth and progression, affecting host antitumor activity, which underlies the importance of identifying markers associated with cancer-inflammatory response.[10,11] Neutrophils are central to this inflammatory response. The prognostic significance of the absolute neutrophil count (ANC) has been extensively studied, with evidence to suggest that blood neutrophils provide significant information when monitoring cancer progression, anticipating possible complications and assessing patient's tolerance to therapy.

The association between malignancies and inflammation has been extensively studied in cervical cancer, in part due to evidence linking this neoplasm with papillomavirus infection. One study analyzed the number and functions of neutrophils in healthy controls, patients with pre- or micro-invasive stages, and patients with invasive cervical cancer, reporting an association between neutrophilia and an advanced stage of cervical cancer as well as impaired neutrophil migration in the invasive cancer group.[12] These results suggest that the defective neutrophils are associated with tumor development and impaired host immune response. Another study in cervical cancer patients proposed a new prognostic marker multiplying the pre-treatment neutrophil and monocyte counts, and reported that those with an elevated value had a poor outcome.[13] A different study of 338 patients with stage III and IV NSCLC reported that pre-treatment elevated neutrophil counts (≥4,500 mm^{-3}) were significantly associated with decreased OS (p=0.0008) and PFS (p=0.024).[14] Furthermore, the role of the immune system in patients receiving immunotherapy has been assessed using the peripheral neutrophil count as a predictor of treatment response and survival in metastatic renal cell carcinoma and stage IV melanoma, consistently reporting that a high neutrophil count is an independent prognostic factor for short OS; however, these studies used different cutoff values to divide patients into high versus low neutrophil groups.[8,15,16]

It has been repeatedly shown in many types of malignancies that the neutrophil:lymphocyte ratio (NLR) is a prognostic marker of survival. In a study of patients with colorectal cancer (some who received palliative care only, others surgical resection, and another group that underwent surgical palliative care), an elevated pre-treatment NLR was associated with the worst OS, but this was not independent of stage.[17] Similarly, other studies confirmed that an elevated NLR prior to treatment is a useful predictor of survival in breast,[18] ovarian,[19] gastric,[20–22] colon,[23] lung,[24] and pancreatic cancer[25–27] (in these studies the cutoff value of NLR ranged from 2.5 to 5.0). In hepatocellular carcinoma, the prognostic significance of the NLR has not only been evaluated at diagnosis and pre-operatively, but also as a marker of tumor recurrence after liver transplantation.[28–31] Interestingly, a study that evaluated NLR patients with unresectable hepatocellular carcinoma who were treated with transarterial chemoembolization reported that patients with a NLR ≥3.3 before treatment had a worse OS (median survival of eight months versus 12 months for patients with a NLR <3.3; p=0.001). However, an increased NLR after treatment was associated with better outcome (p=0.006), suggesting that, in these patients, transarterial chemoembolization triggered an antitumor immune response through the mobilization of lymphoid and myeloid cells.[32]

It has also been reported that the NLR may provide useful information for prognostication in patients undergoing systemic cancer therapy. In a retrospective study of patients with malignant mesothelioma treated with systemic therapy, an NLR <5 was associated with a 10-month longer survival than an NLR ≥5 (16.7 versus 6.6 months); the study confirmed that NLR is an independent predictor of poor survival regardless of whether systemic therapy was the initial or subsequent treatment.[33] Similar results were obtained in a study that evaluated the prognostic significance of NLR in patients with advanced colorectal cancer treated with chemotherapy. In this study, an NLR ≤5 and combination chemotherapy were associated with improved PFS and OS.[34] Also, normalization of the NLR after one cycle of chemotherapy was a strong predictor of benefit from treatment, resulting in improved PFS. Moreover, the prognostic role of NLR was also validated in patients with pancreatic and colorectal liver metastasis treated with chemotherapy (the cutoff value for NLR used in these studies was 5).[35,36]

The neutrophil count has also been studied in hematologic malignancies, proving to be as strong a prognostic tool as in solid tumors. The International Prognostic Scoring System (IPSS), developed to evaluate outcomes in myelodysplastic syndromes, incorporated cytopenias as one of their prognostic parameters, considering patients with neutropenia as a negative factor for disease outcome.[37,38] Recently, the NLR at diagnosis was shown to be a prognostic factor for patients with diffuse large B-cell lymphoma (DLBCL) treated with combination chemotherapy. NLR ≥3.5 was associated with worse clinical outcomes (including reduced PFS and OS) when compared with patients with NLR <3.5. Another significant finding of this study was the association between B-symptoms (fever and night sweats) and a high NLR at diagnosis.[39] Clearly, the neutrophil count alone or the NLR provide inexpensive information regarding solid and hematologic malignancy outcomes that may guide treatment decisions.

Absolute Lymphocyte Count

The absolute lymphocyte count (ALC) has been studied in hematologic and solid malignancies as a marker of host antitumor immunity. Its prognostic significance has been evaluated during different clinical stages of cancer, including at diagnosis, at different phases of chemotherapy or radiation treatment, and after autologous stem-cell transplantation (ASCT). ALC is proven to be an independent prognostic factor for survival, independent of cancer type, and it is included in several validated prognostic scores, such as the IPS in advanced HL.[1]

Absolute Lymphocyte Count at Diagnosis

ALC at diagnosis can be considered a biomarker of immune status to the presence of a malignancy. Several studies have confirmed the utility of ALC in predicting survival in patients with lymphoma. One of the first studies to assess the prognostic role of ALC at the time of diagnosis involved 228 patients with follicular lymphomas and it reported that the OS was significantly better for patients with an ALC >1 x 10^9/l compared

with an ALC <1 x 10^9/l at diagnosis.[40] Decreased lymphocyte count at the time of diagnosis has also been reported to correlate with reduced OS in classical HL[41–43] and in DLBCL patients receiving chemotherapy.[44] In DLBCL, a low ALC has been identified as an adverse prognostic factor associated to inferior OS and confirmed to add additional prognostic information when compared to the International Prognostic Index (IPI), which is the standard tool used to predict outcomes in DLBCL.[42,43] Superior clinical outcome has also been reported in DLBCL patients who have an ALC >1 x 10^9/l at the time of first relapse.[45]

The status of the immune system at diagnosis has also been studied in patients with multiple myeloma (MM) through the analysis of the peripheral ALC. In a cohort of 537 patients with newly diagnosed MM, those with an ALC >1.4 x 10^9/l experienced a higher OS (65 months) when compared with patients with an ALC <1.4 x 10^9/l (26 months).[46] Similar results were reported using the ALC as a prognostic marker in myelodysplastic syndromes (ALC >1.2 x 10^9/l, median OS of 26.6 months versus ALC <1.2 x 10^9/l, median OS of 18.5 months; p<0.001).[47]

Absolute Lymphocyte Count Pre-Treatment and During Treatment

Prognostic markers for cancer patients who are receiving treatment are valuable tools for clinicians to make informed decisions and a useful way to stratify patients into groups who would likely benefit from a particular intervention. A recent study validated a prognostic score that included the lymphocyte count to asses survival in patients undergoing chemotherapy for advanced or metastatic cancer after first-line treatment.[48] The majority of patients included in this prospective study had primary breast, lung, or ovarian cancer and treatment after inclusion included chemotherapy, immunotherapy, radiotherapy, and supportive care. An ALC <700/µl was reported as an independent predictor of decreased survival in this cohort of metastatic patients.[48]

The role of ALC recovery after induction chemotherapy has been study in patients diagnosed with acute myelogenous leukemia.[49] The authors reported that in a cohort of 103 patients, subjects with an ALC ≥500 cells/µl at all time points (days 15, 21, and 28 after induction chemotherapy and before first consolidation chemotherapy) had a superior OS and leukemia-free survival. Another study showed that patients with DLBCL with confirmed relapse at follow-up had a lower ALC compared with those without evidence of relapse after receiving immunotherapy (R-CHOP).[50] Furthermore, the antitumor status of the host immune system evaluated through the peripheral ALC has also been assessed in patients receiving radioimmunotherapy,[51] treatment with cytotoxic T-lymphocyte antigen,[52] and chemoradiation[53] in both hematologic and solid malignancies, with a general consensus that a higher ALC is associated with better response to treatment and superior OS.

The above-mentioned studies suggest that lymphocytes have a role in the anticancer immunosurveillance of the host defense mechanism during chemotherapy, radiotherapy, and immunotherapy. Cancer clinicians should pay special attention to this CBC count parameter when making treatment decisions and should carefully monitor the host's immune status as a way to anticipate possible outcomes.

Absolute Lymphocyte Count in Autologous Stem Cell Transplant

Numerous studies have focused their attention on immune reconstitution after autologous hematopoietic stem cell transplantation (AHSCT) as treatment for malignant diseases. Early ALC recovery after AHSCT is considered a marker of post-transplantation immune recovery and is associated with prolonged survival. One of the first studies to assess the prognostic significance of ALC recovery after ASCT consisted of patients with MM and non-Hodgkin's lymphoma (NHL), using an ALC cutoff value of 500 cells/µl on Day 15 after transplant.[54] The data analyzed in this study showed that ALC ≥500 cells/µl on Day 15 after ASCT is an independent prognostic factor of OS and PFS (in MM, the median OS for patients with an ALC ≥500 cells/µl was 33 months versus 12 months for patients with an ALC <500 cells/µl [p<0.0001]; in NHL, the median OS for patients with an ALC ≥500 cells/µl was not reached versus six months for patients with an ALC <500 cells/µl [p<0.001]). Subsequently, two different studies in NHL and MM patients provided evidence in favor of the prognostic importance of ALC after ASCT by establishing that ALC on Day 15 is directly dependent on dose-infused autograft lymphocytes (r=0.71 for NHL; r=0.83 for MM) and influences survival.[55,56]

Over the years, many studies have validated the prognostic significance of early ALC recovery post-ASCT as an indicator of survival in multiple malignant hematologic conditions,[57–60] metastatic breast cancer,[61,62] and primary systemic amyloidosis,[63] concluding that a higher ALC on Day 15 post-transplant is associated with significantly improved clinical outcomes. Furthermore, new-onset lymphopenia (as measured by ALC) during routine follow-up after ASCT was identified as a simple marker to assess relapse in patients with DLBCL (patients with an ALC <1.0 x 10^9/l had a greater cumulative incidence of relapse).[64]

Absolute Monocyte Count

It has been postulated that monocytes promote tumor progression and support host antitumor immunity. Moreover, an increased monocyte count in the peripheral blood is considered a predictive factor of poor prognosis in cancer patients. Sasaki and colleagues[65,66] studied the pre-operative absolute monocyte count (AMC) in patients who had had liver resection due to hepatocellular carcinoma, as well as in patients who underwent hepatic surgery due to colorectal metastasis. They reported that a pre-operative AMC of ≥300/mm^3 was an independent prognostic indicator of tumor recurrence in cirrhotic patients with hepatocellular carcinoma. In the study of 97 patients with colorectal liver metastasis, univariate analysis showed that patients with a pre-operative monocyte count >300/mm^3 had a worse five-year cancer related survival when compared with patients with a monocyte count ≤300/mm^3 (p=0.04), but disease-free survival rates did not differ between both groups.[66] Elevated pre-operative monocyte counts in a multivariate analysis were found to be an independent prognostic factor for cancer-related survival.

Another study of patients with stage IV melanoma treated with interleukin-2-based immunotherapy identified elevated monocyte counts as a negative prognostic factor (HR=1.7; p<0.001).[16] A high peripheral AMC (alone or combined with neutrophil count) has also been associated with adverse outcomes in cervical and ovarian cancer.[13,67]

Table 1: Complete Blood Cell Count Components as Prognostic Factors in Cancer

Complete Blood Cell Count Component	Cancer	Effect on Outcome	
		Poor Prognosis	Superior Prognosis
White blood cell (WBC) count	Hodgkin's lymphoma[1]	High WBC count	Low/normal WBC count
	Mantle cell lymphoma[2,3]		
	Cervical cancer[4]		
	Non-small cell lung cancer[5–7]		
	Melanoma[8]		
	Breast cancer[9]		
Absolute neutrophil count (ANC)	Cervical cancer[12]	High ANC	Low/normal ANC
	Non-small cell lung cancer[14]		
	Renal cancer[15]		
	Melanoma[8,16]		
Absolute lymphocyte count (ALC)	Non-Hodgkin's lymphoma[40,42–45,50,51,54,55,59,60,64]	Low ALC	High ALC
	Hodgkin's lymphoma[41,58]		
	Multiple myeloma[46,54,56]		
	Myelodysplastic syndrome[47]		
	Breast cancer[48,61,62]		
	Lung cancer[48]		
	Ovarian cancer[48]		
	Acute myelogenous leukemia[49,57]		
	Melanoma[52]		
	Cervical cancer[53]		
Neutrophil:lymphocyte ratio (NLR)	Colorectal cancer[17]	High NLR	Low NLR
	Breast cancer[18]		
	Ovarian cancer[19]		
	Gastric cancer[20–22]		
	Colon/colorectal cancer[23,34,36]		
	Lung cancer[24]		
	Pancreatic cancer[25–27]		
	Hepatocellular cancer[28–32]		
	Mesothelioma[33]		
	Myelodysplastic syndrome[37,38]		
	Diffuse large B-cell lymphoma[39]		
Absolute monocyte count (AMC)	Hepatocellular cancer[65]	High AMC	Low AMC
	Colorectal cancer[66]		
	Melanoma[16]		
	Ovarian cancer[67]		
	Diffuse large B-cell lymphoma[43]		
	Hodgkin's lymphoma[41]		
Hemoglobin (Hgb) count	Cervical cancer[69–72]	Low Hgb count	High/normal Hgb count
	Ovarian cancer[73–76]		
	Endometrial cancer[77–79]		
	Esophageal cancer[80–84]		
	Lung cancer[5,7,85–90]		
Platelet count	Endometrial cancer[79,94]	High platelet count	Low/normal platelet count
	Ovarian cancer[95–97]		
	Esophageal cancer[98]		
	Gastric cancer[99]		
	Lung cancer[7,100–103]		
	Mesothelioma[104–107]		
	Primary myelofibrosis[108,109]	Low platelet count	Normal platelet count

The peripheral blood monocyte count has also been examined in hematologic malignancies, such as leukemia and lymphoma. In patients with DLBCL, an elevated AMC ≥630/µl at time of initial diagnosis was associated with inferior PFS and OS.[43] Furthermore, this study combined the ALC and monocyte count at diagnosis to evaluate the AMC:ALC ratio as a prognostic score and this new score was able to identify low-, intermediate-, and high risk patients. In addition, they were able to show that the AMC:ALC ratio provides additional prognostic information when compared with the IPI. Nonetheless, in classical HL, the peripheral blood lymphocyte:monocyte ratio at diagnosis was reported as a strong predictor of OS, PFS, and time to progression. This study was not only able to evaluate the prognostic

significance of the combined lymphocyte:monocyte ratio, but also reported that an AMC ≥900 cells/µl at diagnosis is an indicator of inferior survival and worse outcome.[41]

The above-mentioned studies provide evidence that monocytes are immunologically relevant host factors that can be routinely assessed through the CBC count to monitor patients' response to treatment and identify high-risk patients who are more likely to have adverse outcomes.

Hemoglobin Concentration

Anemia is a common morbidity encountered in cancer patients and, as a consequence, anemic patients suffer from shortness of breath, fatigue, and decreased energy, among other symptoms. Anemia can be a due to the malignancy itself or be a direct consequence of treatment, such as radiotherapy or chemotherapy. Therefore, the hemoglobin concentration in peripheral blood has also been studied as a prognostic factor in malignant disorders.

The role of hemoglobin levels in clinical outcomes has been extensively examined in gynecologic malignancies, such as cervical, ovarian, and endometrial cancer. In 1989, a retrospective study of 386 patients with advanced cervical carcinoma treated with radiotherapy established that anemic patients had a higher risk of treatment failure during treatment.[68] Subsequently, various studies have established an association between hemoglobin levels and survival in cervical carcinoma.[69–72] A retrospective review of 494 women with locally advanced cervical cancer treated with cisplatin and radiotherapy reported that low hemoglobin levels in the last part of treatment were predictive of disease recurrence and survival, whereas patients with a hemoglobin level <10.0 g/dl had a significantly lower PFS.[72] This study also reported that patients with large tumor size and higher stage of disease had lower hemoglobin levels at baseline, suggesting that hemoglobin is a tumor-related factor. Other cervical cancer studies have reported a relationship between baseline hemoglobin level and better response to chemotherapy,[69] as well as longer disease-free survival and OS in patients treated with radiotherapy who had a baseline hemoglobin level ≥12 g/dl.[71]

Similar results have been described for other solid malignancies, including ovarian,[73–76] endometrial,[77–79] esophageal,[80–84] and lung cancer,[5,7,85–90] reporting that a low hemoglobin count is an indicator of poor prognosis. The above-mentioned studies suggest that close attention should be paid to anemia before and during treatment, with the goal of maintaining adequate hemoglobin levels and, as a consequence, ideally improving cancer outcomes and quality of life.

Platelet Count

Angiogenesis is considered an essential step for tumor growth, progression, and metastasis. Vascular endothelial growth factor (VEGF) is a known potent stimulator of angiogenesis and, in addition, it has been demonstrated that platelets are a source of VEGF.[91] Hence, researchers have reported a strong positive correlation between VEGF serum concentration and platelet counts in cancer patients, as well as a worse prognosis in those patients with higher concentrations of serum VEGF per platelet count.[92,93]

The prognostic significance of the platelet count has been studied in several malignancies, yielding important information about clinical outcomes. Thrombocytosis has been associated with unfavorable prognosis or advanced disease in gynecological cancers,[74,94–97] esophageal carcinoma,[98] gastric cancer,[99] and lung cancer.[7,100–103] Most of these studies used different cutoff values to define thrombocytosis (ranging from 293 x 10^9/l to 400 x 10^9/l); however, a high platelet count was always identified as a negative prognostic factor. In surgically resected NSCLC, an increased pre-operative platelet count has consistently been associated with statistically significant reduced survival when compared with patients without thrombocytosis.[7,100,103]

The peripheral blood platelet count has also been investigated in patients with malignant mesothelioma. In 1989, Ruffie et al.[104] published one of the first studies to identify a platelet count ≥400,000/µl as a significant prognostic indicator of decreased survival in mesothelioma (p=0.001 in a multivariate analysis; n=328). These results were validated in subsequent studies that confirmed that a high platelet count is an indicator of poor clinical outcome.[105–107]

Recent studies have examined the prognostic role of the platelet count as an additional risk factor that should be added to the IPPS[108] and the Dynamic International Prognostic Scoring System (DIPSS)[109] for primary myelofibrosis (PMF). In these studies, researchers showed that a platelet count <100 x 10^9/l is an independent prognostic factor of survival in PMF patients, with a shorter median survival when this factor was added to the above-mentioned prognostic scores. In the DIPSS study, a platelet count <100 x 10^9/l was associated with inferior survival in both the training set (n=428) and the test set (n=365).[109] In addition, all 793 patients were assessed for leukemic transformation and the analysis identified a platelet count <100 x 10^9/l as an independent predictor of leukemia-free survival. Hence, it is likely that future prognostic models in PMF will include the platelet count as an important predictive parameter of clinical outcomes.

Conclusion

It is evident that components of the CBC count can provide valuable prognostic information in solid tumors and hematologic malignancies (summarized in *Table 1*) that are not only limited to survival predictions or assessment of disease progression, but also are important tools when evaluating response to treatment. Despite numerous studies to evaluate the prognostic significance of these factors and their potential clinical applications, in many cancers, these markers are still not routinely used in clinical practice as a tool to monitor disease progression or response to treatment. One reason is that most of the published studies were retrospective in nature. Additionally, many of them used different cutoff values for the prognostic analysis, complicating their interpretation. Thus, true assessment of the utility of the CBC count as an inexpensive, established, and globally accessible prognostic factor in many malignancies requires careful prospective studies. It is likely that future prospective studies examining the biology behind the prognostic value of the different components of the CBC count would later yield significant therapeutic progress and a thorough understanding of disease pathogenesis. ■

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