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Review Article

Is Absolute Lymphocyte Count Just Another Prognostic Factor in Cancer?

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The role of host immunity in cancer clinical outcomes has been wellestablished in animal models. In humans, the impact of the immune system as a therapeutic maneuver to treat malignancies has been proven by the development of graft-versus-tumor effect observed in the allogeneic stem cell transplantation. However, with few notable exceptions, no definitive conclusions have been reached as to the role of host immunity in humans and its impact on cancer outcomes. This article reviews the clinical evidence of how human immunity can affect cancer clinical outcomes using the absolute lymphocyte count as a surrogate maker of host immune competence.

1. Introduction

The concept of immune surveillance was originally proposed by Ehrlich in 1909 [1] and subsequently reintroduced by Thomas and Burnet [2] in the 1960s who argued that lymphocytes recognized and destroyed arising cancer cells. However, despite tumor immune surveillance, tumors do grow in the presence of a functioning immune system; thus, the concept of immune surveillance has been expanded to account for an ongoing dynamic interaction in which the host immune system is modified by the tumor and the tumor in turn is modified by the immune system (tumor immunoediting concept) [3].

The evidence of cancer immunosurveillance in animals model has been demonstrated in spontaneous tumor development in immunodeficient mice, carcinogen-induced tumors in immunodeficient mice, and to some extent in genetic tumor models in immunodeficient mice [3]. The evidence of cancer immunosurveillance in humans has been less convincing despite evidence of increased cancer risk in immunosuppressed patients, improved clinical outcomes in patients demonstrating lymphocyte tumor infiltration, as well as epidemiologic data suggesting decreased incidence of malignancies in patients with elevated baseline (homeostatic) levels of natural killer (NK) cells activity [3]. This article reviews published data regarding the absolute lymphocyte count, as a surrogate maker of host immunity, in clinical outcomes of patients with cancer, providing further clinical evidence of role of host immunity in cancer immunosurveillance, cancer survival, and cancer treatment efficacy.

2. Absolute Lymphocyte Count at Diagnosis

The original clinical setting in which the absolute lymphocyte count (ALC) was associated with survival in lymphomas was in Hodgkin's disease. The association of low ALC and poor clinical outcomes in patients with Hodgkin's disease was incorporated in the International Prognostic Factors Project on Advanced Hodgkin's Disease [1] currently utilized in clinical practice. More recently, ALC at diagnosis appears to also predict survival in patients with in diffuse large B-cell lymphoma (DLBCL) improving the prognostic ability of the International Prognostic Index [4–6], as well as in follicular lymphoma, augmenting the prognostic ability of the Follicular Lymphoma International Prognostic index (FLIPI) [7]. Using an ALC cut-off values of $1.0 \times 10(9)$/L, Ray-Coquard et al. [8] reported in a large cohort of 322 non-Hodgkin's lymphoma (NHL) patients poor clinical outcomes in patients with an ALC $< 1.0 \times 10(9)$/L. The median overall survival was 11.3 months for NHL patients with an ALC $< 1.0 \times 10(9)$/L compared with 94.3 months for NHL patients

with an ALC ≥ 1.0 × 10(9)/L. The median progression-free survival was 9.3 months for NHL patients with an ALC < 1.0 × 10(9)/L compared with 56.1 months for NHL patients with an ALC ≥ 1.0 × 10(9)/L. In multiple myeloma (MM), ALC at diagnosis is a prognostic factor for overall survival [9]. In myeloid disorders, a low ALC at diagnosis was recently identified by the International Prognostic Scoring System (IPSS) as an independent predictor of poor survival in myelodysplastic syndrome [10].

In addition, ALC at diagnosis has been demonstrated not only to be a prognostic factor of survival, but also a predictor of treatment (chemotherapy) efficacy in solid tumors. In breast cancer, women with an ALC ≥ 2.0 × 10^9/L at diagnosis had a superior 5-year survival for stage I (80%), stage II (63%), and stage III (53%) compared with breast cancer patients with an ALC < 2.0 × 10^9/L for stage I (74%), stage II (44%), and stage III (18%) [11]. In a large cohort of 287 hormone-resistant metastatic breast cancer patients, Ray-Coquard et al. [8] showed superior overall and progression-free survival for patients with an ALC ≥ 1.0 × 10(9)/L compared with those who did not prior to treatment [median overall survival: 13.6 months versus 9.5 months, $P < .0001$; and median progression-free survival: 8.5 months versus 6.8 months, $P < .0001$, respectively]. In a cohort of 113 women with metastatic or recurrent breast cancer, patients with a higher peripheral blood CD8 count experienced superior survival. With an average survival of 4.1 years, 72% of patients with a low CD8 count died compared with only 55% of patients with a high CD8 count ($P < .01$) [12]. Similarly, in pancreatic cancer, patients with an ALC < 1.2 × 10^9/L at diagnosis experienced a shorted survival compared with patients with an ALC ≥ 1.2 × 10^9/L [13]. Furthermore, pancreatic cancer patients with higher CD4 and CD8 tumor-infiltrating lymphocytes had better prognosis compared with those who did not [14]. Better clinical outcomes associated with high ALC have been also reported in gastric cancer [15, 16], head and neck cancer [15, 16], melanoma [15, 16], neuroblastoma [15–17], uterine cancer [15, 16], and soft tissue sarcoma [8].

3. Absolute Lymphocyte Count and Chemotherapy

Chemotherapy has been the main therapy for advanced cancer for the last 50 years, and one of the main side effects of the use of such cytotoxic agents is immune compromise/immune cytopenias. In the adult setting, we recently published that patients that maintained an ALC ≥ 500 cells/μL during induction chemotherapy for acute myelogenous leukemia (AML) experienced superior survival [18]. A similar observation was recently published in pediatric patients with AML and acute lymphoblastic leukemia (ALL). Pediatric AML with an ALC at day 15 ≥ 350 cells/μL after induction therapy experienced a 5-year overall survival of 85% [19]. Similarly, pediatric ALL patients with an ALC at day 15 ≥ 350 cells/μL after induction chemotherapy experienced a 6-year overall survival of 87% [19].

Pretreatment (prechemotherapy) peripheral blood ALC also appears to affect the efficacy of cancer chemotherapy in adult patients with metastatic solid tumors. In a cohort of 183 adult patients with metastatic solid tumors, patients with an ALC ≥ 1500 cells/μL had a higher objective response rate [43% (45/104)] compared with those with an ALC < 1500 cells/μL [10% (8/79)] ($P < .001$) [20]. In pediatric patients with Ewing sarcoma that achieved an ALC at day 15 after initial chemotherapy, treatment of ≥500 cells/μL had a 3-year overall survival of 68% compared with 32% for patients with an ALC < 500 cells/μL at day 15 after initial chemotherapy treatment [21, 22]. In NHL patients that relapse after standard chemotherapy, higher ALC at the time of relapse has been associated with better clinical outcome and survival after further treatment has been implemented after relapse [23, 24].

Pretreatment lymphopenia has been also associated with early death after chemotherapy. Ray-Coquard et al. [25] reported performance status and lymphopenia (<700 cells/μL) as the only two independent risk factors to predict early death after conventional chemotherapy, defined as death of the patient within 31 days following day 1 of chemotherapy administration, referred to as early death, resulting from either toxicity, disease progression or both. In 47% of the early death cases, the cause of death was due to progression of disease, suggesting that host immunity (i.e., lymphopenia) could have an impact on the efficacy of chemotherapy [25, 26].

4. Absolute Lymphocyte Count and Immunotherapy/Radioimmunotherapy

Anti-CD20 antibody (Rituximab) therapy has become the standard of care in the treatment of non-Hodgkin lymphoma. One of the mechanisms of action of rituximab is through antibody-dependent cellular cytotoxicity (ADCC). For this mechanism of rituximab to work, host immunity is relevant. Decaudin et al. showed that in 29 patients with follicular lymphoma treated with rituximab, response rate correlated with ALC at the time of rituximab therapy. The overall response rate was 75% when the ALC was >1000/μL and 33% when ALC was <1000/μL ($P < .02$) [27]. In a cohort of 79 patients with follicular lymphoma, we confirmed not only higher response rate, but also longer time to progression (TTP) with higher ALC at the time of single-agent rituximab therapy. In a cohort of 79 follicular patients, the complete response rate was 58% (23/40) for patients with an ALC ≥ 890 cells/μL compared with only 13% (5/39) for patients with an ALC < 890 cells/μL ($P < .0001$). The median TTP for patients with an ALC ≥ 890 cells/μL was 36.5 months compared with only 8.1 months for patients with an ALC < 890 cells/μL from the time of rituximab therapy ($P < .0009$) [28].

Radioimmunotherapy (RIT) delivers radiation to tumor cells using antibodies as carriers of radionuclides. Besides the cytotoxic radiation delivered to the tumor cells via antibody binding to tumor-specific or tumor-associated antigen, several immunologic-related mechanisms have been

attributed to RIT, including complement-mediated lysis [complement-dependent cytotoxicity (CDC)] and ADCC [29]. Thus, competent host immunity would be necessary for CDC and ADCC to work in RIT. In a cohort of 75 patients with follicular lymphoma and treated with single dose of ^{90}Y-Ibritumomab tiuxetan (Zevalin), we identified a higher complete response rate (66%) versus only 19% in patients with a higher pretreatment ALC (ALC $\geq 1.0 \times 10^9$/L). In addition, the 5-year progression-free survival from Zevalin treatment was 35% in patients with an ALC $\geq 1.0 \times 10^9$/L compared only with 5% in patients with an ALC $< 1 \times 10^9$/L prior to Zevalin therapy [30].

5. Absolute Lymphocyte Count and Immunomodulatory Drugs

One of the mechanisms attributed to Lenalidomide (Revlimid) is the ability to immunomodulate the host immunity system. In vitro studies have shown that Revlimid can trigger apoptosis in both hematological and solid tumor cells through natural killer (NK) activation [31]. Thus, ALC, as a surrogate marker of host immunity, should be a prognostic factor to assess response to Revlimid therapy. Two recent studies using Revlimid for the treatment of NHL identified the ALC at treatment as a prognostic factor for response to revlimid therapy. In one study, patients with an ALC $\geq 0.6 \times 10^9$/L had a 33% response rate compared with 0% response rate if the ALC $< 0.6 \times 10^9$/L to revlimid at the start of therapy [32]. In another study, the response rate to Revlimid in NHL patients with an ALC $\geq 0.6 \times 10^9$/L was 42% compared with only 9% in NHL patients with an ALC $< 0.6 \times 10^9$/L [33].

6. Absolute Lymphocyte Count and Targeted Therapy

Imatinib Mesylate (Gleevec) is considered the primary example of single-agent targeted therapy, inhibiting BCR-ABL kinase in chronic myeloid leukemia (CML). The experience from allogeneic stem cell transplantation and the efficacy of donor lymphocyte infusions would suggest that CML is the most susceptible of all leukemias to immune regulation [26]. A recent study showed that CML patients treated with imatinib who develop a bone marrow lymphocytosis (bone marrow lymphocyte count > 24% of involved field) appeared to experience improved clinical outcomes. A bone marrow lymphocytosis was associated with an 83% positive predictive value of achieving a complete cytogenetic response at 12 months and an 89% positive predictive value of achieving a major molecular response at 18 months of imatinib therapy [34]. This study suggests that bone marrow lymphocyte count in CML patients treated with imatinib could be used as a simple test to assess which CML patients will response to imatinib, as well as, that host immunity might have a relevant antitumor effect enhancing the efficacy of imatinib therapy in CML.

7. Allogeneic Graft Versus Tumor Effect

Barnes et al. described an immune-mediated graft-versus-tumor (GVT) effect after allogeneic stem cell transplantation (Allo-SCT), when mice injected with leukemia and treated with total body irradiation and syngeneic stem cell transplantation died of recurrent leukemia, whereas mice receiving All-SCT under same conditions survived longer without evidence of leukemia, while having developed in addition graft-versus-host disease (GVHD) [35]. The clinical evidence of GVT has been recognized based on indirect observations, such as: (1) anecdotal reports showing that sudden withdrawal of immunosuppression in relapsed patients post-Allo-SCT can reestablish complete remission, (2) increased relapse rates in patients receiving syngeneic marrow grafts compared with recipients of allogeneic grafts, (3) decreased relapse rates post-Allo-SCT in association with GVHD, (4) T-cell depletion of an allogeneic graft increases the risk of relapse, and (5) donor lymphocyte infusion induce complete remission after relapse following Allo-SCT. The recognition of the adoptive GVT effect provides the strongest clinical evidence of the ability of human, donor allo-reactive immune effector cells to eradicate tumor cells [36].

However, there is a fundamental problem observed when using Allo-SCT as an immunotherapeutic modality. The immune response seen after All-SCT is not tumor specific. The allo-reactive immunocompetent donor cells that produce GVT also target the host (GVHD). GVHD is a major toxicity of Allo-SCT and a major contributor to transplant-related mortality (TRM) [36]. Therefore, currently efforts are made to maximize GVT and minimize GVHD.

8. Absolute Lymphocyte Count Recovery Posttransplant

Several studies in the Allo-SCT setting have shown that higher absolute lymphocyte count (ALC) recovery post-Allo-SCT was associated with better clinical outcomes, suggesting that ALC could be used as a surrogate marker of immunity [37, 38]. To assess whether early ALC recovery has any prognostic ability post-autologous stem cell transplantation (ASCT), we analyzed the ALC at day 15 (ALC-15) post-ASCT in MM and NHL [39]. The median overall survival (OS) and progression-free survival (PFS) for the MM group were superior for patients with an ALC-15 $\geq$ 500 cells/μl versus an ALC-15 $<$ 500 cells/μL (33 months versus 12 months, $P < .0001$, and 16 months versus 8 months, $P < .0001$, respectively). In the NHL group, the median OS and PFS were also superior for patients with an ALC-15 $\geq$ 500 cells/μL versus an ALC-15 $<$ 500 cells/μL (not reached versus 6 months, $P < .0001$, and not reached versus 4 months, $P < .0001$, resp.). We subsequently reported similar superior survival with ALC-15 post-ASCT in multiple hematological malignancies [40–43] and metastatic breast cancer [44]. Several independent groups have confirmed our findings [45–50]. The superior survival observed for the first time with ALC-15 in different malignancies suggests not only a role of cancer immunosurveillance, but also that the patients' own (autologous) immune system post-ASCT has antitumor

activity that is not disease specific. In addition, the fact that none of these patients developed GVHD favors of a possible more-specific immune response against tumor (and not the host) in the post-ASCT setting. We confirmed the findings of ALC-15 as a prognostic factor for survival in APHSCT in a prospective study [51], in addition to identifying NK cells at day 15 post-APHSCT as the key lymphocyte subset conveying the superior survival observed with a faster immune recovery post-APHSCT.

9. Cut-Off Values of Absolute Lymphocyte Count and Absolute Lymphocyte Count Subsets

A limitation of the use of ALC as a prognostic factor is the fact that several studies have reported different cut-off values of ALC to use for survival analysis [4–11]. A standard ALC cut-off value would help clinicians to advise patients about prognosis. Despite the different ALC cut-off values, a common denominator is that lymphopenia has been associated with poor clinical outcomes. However, the heterogenous cut-off values of ALC suggest that ALC might not be the best surrogate marker of host immunity to understand the underling immunologic antitumor mechanism and, thus, explain the superior survival observed with higher ALC values. Thus, the study of the lymphocyte subsets is paramount to start to understand the pathogenic mechanism of the role of host immunity in cancer survival. For example, we recently reported a prospective study showing NK cells as the key lymphocyte subset conveying the improved survival post-APHSCT [51]. In the study, patients with an ALC $<$ 500 cells/μL at day 15 post-APHSCT, but with normal NK cells numbers, had a similar survival to patients with normal NK cells numbers and an ALC $\geq$ 500 cells/μL at day 15 post-APHSCT. This finding suggests in this specific clinical scenario that NK cells are a better surrogate marker of host immunity than ALC and provide a platform to study the NK cell anti-tumor mechanism in APHSCT. Plonquet et al. [52] reported that DLBCL patients and higher number of NK cells numbers at diagnosis had better treatment response and clinical outcomes compared with those who did not. These clinical observations suggest that new treatment modalities to enhance host immunity (i.e., NK cells) might improve survival in cancer patients. One of those new treatments that it is currently undergoing clinical trials is anti CD 137 monoclonal antibody [53, 54]. CD 137 is a surface glycoprotein that belongs to the tumor-necrosis factor receptor superfamily (TNFRSF) and is expressed by activated natural killer cells, T cells, and dendritic cells [53, 54]. In vivo studies have shown that anti CD137 enhances cytotoxicity of NK cells and induces a CD4+Th1 response [53]. Furthermore, anti CD137 effect of immunomodulation can be enhanced by depletion of regulatory T-cells (T-regs) [54], which has been associated with T-cell mediated immunosuppression and correlated with tumor progression in NHL patients [55]. Thus, new therapy to deplete or inhibit T-reg-might also enhance host anti-tumor immunity, translating into improved survival in cancer patients [56] .

Table 1: Clinical scenarios were absolute lymphocyte count has been associated with superior clinical outcomes.

Adult setting	References
At diagnosis	
Breast cancer	12,13
Colon cancer	21
Gastric cancer	16,17
Head and neck cancer	16, 17
Lung cancer	21
Pancreatic cancer	14,15
Hodgkin Disease	4
Melanoma	16, 17
Myelodysplastic syndrome	11
Multiple myeloma	10
Neuroblastoma	16, 17, 18
Non-Hodgkin lymphoma	5, 6, 7, 8
Soft tissue sarcomas	9
Uterine cancer	16, 17
Standard chemotherapy	
Acute myelogenous leukemia	19
Immunotherapy/radio-immunotherapy	
Follicular lymphoma	29, 31
Targeted therapy (Gleevec)	
Chronic myelogenous leukemia	35
Immunomodulation (Revlimid)	
Non-Hodgkin lymphoma	33, 34
Autologous stem cell transplantation	
Acute myelogenous leukemia	41
Amyloidosis	42
Hodgkin Disease	42, 51
Multiple myeloma	40, 47, 48
Non-Hodgkin lymphoma	40, 44, 47, 50, 51
Breast cancer	45, 49
Ovarian cancer	46
Pediatric setting	
Standard chemotherapy	
Acute lymphoblastic leukemia	20
Acute myelogenous leukemia	20
Ewing sarcoma	22, 23

10. Neutrophil/Lymphocyte Ratio

Inflammation has been associated as a triggering factor for cancer development and progression [57–59]. The neutrophil count, as a surrogate marker of inflammation, has been studied as a prognostic factor for survival in cancer. Several studies have demonstrated poor clinical outcomes in patients with high pretreatment neutrophil counts in solid tumors, including lung cancer [60], renal cancer [61], and melanoma [62]. In addition, several studies have looked into the combination of the neutrophil and

lymphocyte count (neutrophil/lymphocyte ratio) which has a prognostic marker of survival in solid tumors [60, 63]. Patients with high neutrophil/lymphocyte ratio experienced poor prognosis in lung cancer and colorectal cancer [60, 63]. This index has been also studied in a reverse fashion (lymphocyte/neutrophil ratio); lower scores have been identified as an increasing independent predictor of death [64]. These clinical observations suggest that high neutrophil count, as a surrogate marker of inflammation, might have an immunosuppressive effect on the host immunity, translating into poor clinical outcomes. In vitro studies have supported this hypothesis as they have shown that neutrophils suppressed the cytotoxic activity of immune effector cells, and the degree of suppression correlated with the number of neutrophils [60].

11. Absolute Lymphocyte Count and Clinical Applications

The majority of prognostic factors fulfilled their purpose in predicting clinical outcomes once they are identified. However, few prognostic factors not only are able to predict future clinical outcomes, but also are the platform to develop therapeutic interventions. One example of a prognostic factor currently used to predict survival and was the starting point to develop a specific treatment to target this prognostic factor is the epidermal growth factor (EGF) receptor HER2 in HER2-positive breast cancer, using monoclonal antibody (e.g., Trastuzumab [Herceptin]) or a small-molecule tyrosine kinase inhibitor (e.g., lapatinib) [65]. Thus, is ALC just a predictor of clinical outcomes or both: a predictor of clinical outcomes and a platform to develop therapeutic interventions?

The discovery of absolute lymphocyte count at day 15 (ALC-15) as a prognostic factor for survival after APHSCT led to identify what factors affected ALC-15 recovery post-APHSCT. The sources of lymphocyte recovery post-APHSCT can be divided into two categories: (a) the host and (b) the stem cell autograft [36]. From the host, lymphocyte sources include host stem cells and host lymphocytes surviving the high-dose chemotherapy. The host stem cells surviving high-dose chemotherapy most likely do not contribute to ALC-15 recovery post-APHSCT because without stem cell graft support these patients remain myelosuppressed for prolonged period of time. To identify host lymphocytes is difficult in comparison with Allo-SCT where the development of mixed chimerism in Allo-SCT allows discrimination of host versus donor lymphocytes. Such discrimination is not possible in APSHCT in the absence of marking studies of graft lymphocytes.

The second possible source of lymphocytes recovering post-APHSCT is the autograft. From the autograft, lymphocyte could originate form: (1) infused stem cells (CD34), or (2) infused autograft lymphocytes collected at the same time with stem cells [47]. In our institution, as in many others, patients' autografts used for APHSCT do not undergo any additional processing beyond cryopreservation, so that what is collected (CD34 ± lymphocytes) is infused back to the patient. In order to understand the impact of the autograft on post-APHSCT lymphocyte reconstitution, we evaluated the impact of infused CD34 and/or lymphocytes from the autograft on the kinetics of post-APHSCT lymphocytes recovery. We reported no correlation between the amount of CD34 stem cells infused and ALC-15. However, a strong positive correlation was identified between the autograft lymphocyte content (autograft absolute lymphocyte count, A-ALC) and ALC-15. Patients that were infused with autografts containing higher A-ALC recovered greater numbers of lymphocytes by day 15 (ALC-15) and experienced significant improved clinical outcomes in the setting of NHL and MM post-APHSCT [66]. Superior survival was observed in patients infused with an A-ALC $\geq 0.5 \times 10^9$ lymphocytes/kg. This finding was been recently confirmed by other investigators. These data suggest that the stem cell autograft in APHSCT should not only be viewed only for "bone marrow rescue" procedure to harvest CD34 stem cells necessary for hematologic engraftment, but also as an adoptive immunotherapeutic strategy in which autograft lymphocyte content directly influences tumor-related clinical outcomes in a number of different clinical settings.

The association between A-ALC and ALC-15 provides the first clinical evidence of an autologous GVT effect as the infusion of autograft lymphocytes has a direct impact not only on immune reconstitution, but also on survival post-APHSCT, similar to the GVT effect observed in the Allo-SCT from the infused donor immune effector cells. Therefore, factors that can be manipulated during stem cell collection to maximize A-ALC collection could be used as immunotherapeutic strategies to improve immune recovery and survival post-APHSCT. One of those factors is the apheresis instruments. Apheresis instrument settings have been designed to optimize CD34 collection and not A-ALC. However, we compared the A-ALC content of autograft collected by three different apheresis instruments (COBE Spectra, Fenwal CS 3000, Baxter Amicus) using manufacturer recommended settings. It was interesting to discover that different instruments harvested significantly different numbers of lymphocytes (A-ALC). The differences in A-ALC content impacted ALC-15 and survival in these patients. These data suggest that apheresis machines could be optimized to harvest not only enough CD34 for hematologic engraftment, but also lymphocytes for immunologic engraftment. By manipulating the mononuclear cell band during the centrifugation process of the apheresis machine, we have shown that we can collect higher numbers of naïve T-cells and NK cells, affecting the lymphocyte recovery post-APHSCT [67]. Recently, we have shown that early NK cell recovery post-APHSCT is the key immune effector cells affecting survival post-APHSCT. Thus, the enrichment with NK cells by manipulating apheresis machine settings may establish a more immunocompetent autograft to use as an adoptive immunotherapeutic strategy in APHSCT. These observations, starting with the ALC-15, then the association of A-ALC and ALC-15, followed by the discovery that apheresis instruments can be modified to enhance A-ALC

collection, have led to development of a randomized, double-blind phase III clinical trial currently in progress. In this study, patients are randomized to undergo peripheral blood stem cell collections using "standard" versus "modified" apheresis settings adjusted for improved A-ALC content. The goal of the study is to ascertain the impact of the two apheresis strategies on clinical outcomes (relapse rates at 1 year posttransplant) in patients with relapsed non-Hodgkin's lymphoma.

12. Conclusions

With the advent of new technological advances (e.g. microarray gene expression analysis), it is important to recognize that low cost, standardized, routinely used tests such as a complete blood cell count (CBC) can still provide useful information regarding the behavior of different malignancies, as well as serve as a platform for the development of therapeutic interventions aimed at improving clinical outcomes. In this article, we reviewed the reported data regarding the use of ALC, a component of a CBC, as a prognostic factor for survival in cancer and prognostic factor to develop cancer treatments (see Table 1).

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