ORIGINAL RESEARCH ARTICLE

RELATIONSHIP BETWEEN POSSIBLE INDICATORS OF DISEASE SEVERITY AND TREATMENT OUTCOMES IN HODGKIN LYMPHOMA

[1]Madu AJ, [2]Korubo K, [1]Okoye H, [3]Ugwu N, [1]Duru A, [1]Ugwu AO, [4]Efobi C, [5]Madu K, [6]Nnabugwu I,[7] Madu F.

[1]Department of Haematology and Immunology, University of Nigeria Enugu Campus. Nigeria. [2]Department of Haematology, University of Port Harcourt, Rivers State, Nigeria. [3]Department of Haematology and Immunology, Ebonyi State University Abakaliki, Nigeria. [4]Department of Haematology, Nnamdi Azikiwe University Anambra State, Nigeria. [5]Department of Orthopedics, National Orthopedic Hospital Enugu, Nigeria. [6]Department of Urology, University of Nigeria Enugu Campus, Nigeria. [7]Department of Business Management, University of Nigeria Enugu Campus, Nigeria.

Corresponding Author:
Dr. AJ. Madu,
Department of Haematology and Immunology, University of Nigeria Enugu Campus, Nigeria
E-mail: anazoeze.madu@unn.edu.ng

ABSTRACT

Aims and objectives:
To assess the relationship between some possible indicators of disease severity and the treatment outcomes in Hodgkin lymphoma.

Materials and Methods:
This was a prospective study of patients histologically diagnosed with Hodgkin lymphoma from July 2016 to July 2019 in three tertiary hospitals in Nigeria.

Results:
The patients included 20 males and 20 females, aged 17 to 76 years. Median values at diagnosis were; haemoglobin concentration (Hb) varied from 9.5g/dL (range 10, 95% CI), leucocyte count was 7.5 x 10^9 /L (range 32.2, 95% CI), absolute neutrophil count (ANC) was 4.3x 10^9 /L (Range 29.4, CI 95%), platelet count was 238 x 10^9/L (Range 474, CI 95%). Two (5.4%) patients were positive for HIV. Splenomegaly was seen in (8/33) 24.2 % of the patients at diagnosis. Neither age nor spleen size were noted to be associated with survival (r = -0.146; p= 0.474 and r =0.043; 0.967, respectively). Nodular sclerosis HL was the most prevalent (50%), with higher mortality (p=0.001). The mean absolute neutrophil count (ANC) at diagnosis was 4.3±7.8 x 10^9/L and was related to an increased risk of death (F = 585.9; p = 0.002). The mean haemoglobin concentration at diagnosis was 9.5 ± 2.5 g/dL and this had a direct relationship with the duration of survival (r = 0.637; p = 0.011). Twenty patients (57.1%) had Ann-Arbor Stage IV disease, while 5 (12.5%) had B symptoms. The relationship between ANC and duration of follow-up was not significant. Combination chemotherapy - ABVD, was used in 75% of the patients out of which 20% relapsed or failed treatment. High serum conjugated bilirubin and alkaline phosphatase were associated with poorer outcomes (r = -0.593; p=0.018 and r = -0.753; 0.019, respectively).

Conclusion:
At presentation, haemoglobin concentration had a direct relationship with the duration of survival, while a high absolute neutrophil count and the nodular sclerosis HL subtype were associated with higher risk of death. There is, therefore, a need for more studies to corroborate these findings in larger patient groups.

Keywords:
Hodgkin lymphoma, prognosis, treatment outcome, absolute neutrophil count, survival

INTRODUCTION

Hodgkin lymphoma (HL) includes a subgroup of malignancies involving the lymphoid tissues and specifically the lymph nodes, showing the characteristic CD30 positive giant Reed-Steinberg cells. It was first described by Thomas Hodgkin in 1832 in Guys Hospital, London.[1,2] The presence of Epstein Barr virus, also seen in endemic Burkitt's lymphoma, has been discovered in about 40% of the cases.[3,4] The incidence of HL is less than 1% of all cancers in the United Kingdom and very rare in Asia, however it is commoner in North America, Australia and Europe. It has been observed to have a higher incidence in Western countries and westernized populations, including those that migrate to these regions.[5] There has been an observed changing pattern of the disease across different countries and tribes, pointing towards interplay between genetics and the environment with regards to the disease aetiology.[6,7]

The disease usually presents as lymphadenopathy, with or without other constitutional symptoms. HL has a male preponderance and occurs more in adolescents and young adults-median age 22 years. Based on the histology findings the World health organization (WHO) has classified the disease into; a classical and non-classical type.[8] The non-classical lymphocyte predominant HL is rare and accounts for 9.4% and 5.3% of HL in adult and children, respectively. Poor prognostic risk factors include; raised erythrocyte sedimentation rate (ESR), age ≥ 50 years, bulky, mediastinal or extra-nodal disease, presence of B symptoms, and involvement of >3 lymph node regions.[9]

Radiotherapy for Stages I and II disease and systemic chemotherapy for the later stages have been the mainstay of treatment. In the past few years, a lot of advances have been made in the area of immunotherapy and overall management of HL. Late presentation and non-availability of PET (positron emission tomography) scan, important in disease monitoring as well as the high cost of treatment have a deleterious impact on treatment outcome.[10,11]

Neutropaenia at presentation is usually due to bone marrow infiltration or myelosuppression and can either worsen or develop during the course of chemotherapy, the degree at this time being determined by the type and duration of the chemotherapy.[12] The impact of some blood parameters in determining treatment outcome has been investigated in several previous publications.[13,14] Tumour staging is done in an attempt to stratify risk and predict disease course. Also, sub-classes of Hodgkin lymphoma have been associated with variations in prognosis, thus the non-Classical HL is usually thought to connote poor prognosis. Other adverse clinically relevant events include occurrence of splenomegaly which is an indirect indicator of tumor bulk as well as number and constitution of cycles of chemotherapy received.

Patients with low ANC are at risk of infections and are more likely to have adjusted dose or truncated chemotherapy cycles, they may be prone to disease progression or resistance as a result thereby affecting the response to treatment and disease prognosis. More so, there are many subtypes of HL and the prognosis depends of the type. To determine the HL subtypes, one may often times require some advanced technology and ancillary studies, which may be lacking in some developing countries as evidenced by higher frequency of unclassified HL documented in a review of HL cases in developing world.[10] Consequently, there is need to use a simplified inexpensive marker to predict disease outcome, which is sensitive to all subtypes.[9]

The impact of neutrophil count, spleen size, stage and age as indicators of both direct and indirect tumor burden was assessed in this study. The aim was to determine the effect of some possible indicators of severity at time of presentation and during treatment on patient outcome and disease prognosis. Choice and duration of chemotherapy also affects treatment outcome and are influenced by neutrophil count as well as haemoglobin (Hb) concentration. These were also assessed

as independent determinants of treatment outcome/survival.

MATERIALS AND METHODS

This was a retrospective study involving three tertiary health institutions in Nigeria (University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla, University of Port Harcourt Teaching Hospital (UPTH) Rivers State and Federal Teaching Hospital Abakiliki (FETHA) Ebonyi State) that included patients diagnosed with HL between April 2016 and May 2019. The case notes of patients were used to obtain information on the demographic data as well as the Ann- Arbor stage (obtained from information on the clinical features noted at presentation and splenic size; the chest X ray and ultrasound findings; and bone marrow biopsy histology was used to rule out Stage IV disease). The histological subtype, Hb concentration, leucocyte count, absolute neutrophil count (ANC), platelet count on admission were also recorded. The drug regimen used, the number of cycles received and duration from diagnosis to last visit were also retrieved. Information on whether the patients are alive or dead (mortality) as at the time of collation of this result was also noted. The duration of survival was taken to be the period from diagnosis till date of death (for patients who were reported to be dead or died in the facility), while patients who were lost to follow up were not included in this analysis.

The data was obtained from all patients diagnosed histologically with Hodgkin lymphoma in the centers involved. This was analyzed using SPSS 20.0 and the relationship between these parameters were assessed using log rank and correlation tests (Kendall tau_b). Ordinal and nominal variables were assessed using Chi square and Fischer's Exact test to evaluate relationships. The values were taken to be significant if p value was less than 0.05. Frequencies were expressed as percentages and presented in tables and charts.

Ethical approval was obtained from the Health Research and Ethical Review Boards of the facilities involved in the study.

RESULTS

In this study, 40 patients were recruited over the 3-year interval; UNTH - 17, UPTH – 16 and FETHA -7. This consisted of 20 males and 20 females aged 17 to 76 years, with a median age of 32 years. Figure 1 shows a plot of the age distribution of the patients that indicates a possible bi-modal peak. The HIV status was recorded in 37 patients and observed to be positive in 2 (5.4%). Splenomegaly was seen in (8/33) 24.2 % of the patients at diagnosis while 25 of them had no palpable spleen. The mean spleen size was 2.8±5.6 cm.

The median Hb concentration varied from 9.5g/dL (range 10, 95% CI) at diagnosis to 11 (range 11, 95% CI) and 11.3 g/dL (range 9.7, 95% CI) at 6 and 12 months respectively, while the leucocyte count was 7.5 x 10^9 /L (range 32.2, 95% CI) at diagnosis and 6.0 x 10^9 /L (range 18.7, 95% CI) and 3.75 x 10^9/L (range 13.9, 95% CI) at 6 and 12 months respectively. The median absolute neutrophil count (ANC) was also found to vary from 4.3x 10^9 /L (Range 29.4, CI 95%) to 3.59 x 10^9 /L (Range 3.2, CI 95%) and 1.73 x 10^9 /L (Range 9.0, CI 95%) at 6 and 12 months respectively, while the platelet count was 238 x 10^9/L (Range 474, CI 95%), 280 x 10^9 /L (Range 600, CI 95%) and 195 x 10^9/L (Range 324, CI 95%) at the same points of assessment respectively. When weighted by the subtypes of Hodgkin lymphoma and the absolute neutrophil count at diagnosis being taken as the dependent variable, the analysis of variance (ANOVA) showed the leucocyte count at diagnosis was a significant predictor of mortality (dead/alive); F = 585.198, p=0.002 However, the ANC at diagnosis did not show a significant relationship with the duration of follow up (r = 0.588; p=0.219). Figure 2 shows the Hb and absolute neutrophil count at diagnosis as well as total number of cycles received by patients in the various disease stages.

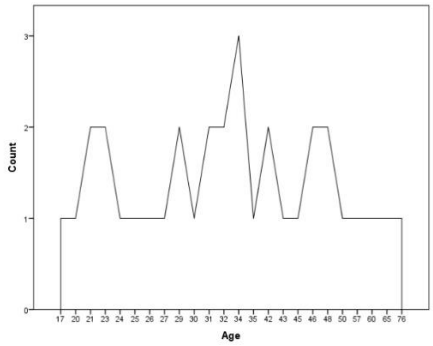


Figure 1. Age distribution among the observed patients with Hodgkin lymphoma

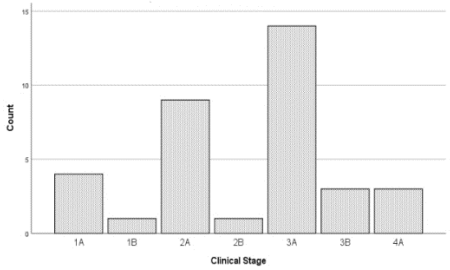


Figure 2. Ann-Arbor Stage of patients diagnosed with Hodgkin Lymphoma

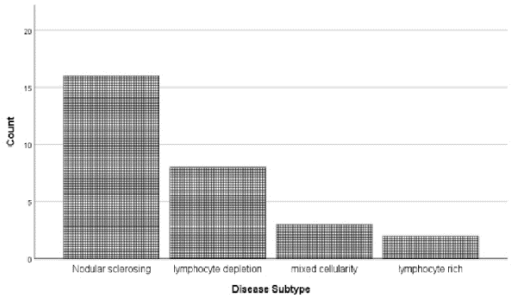
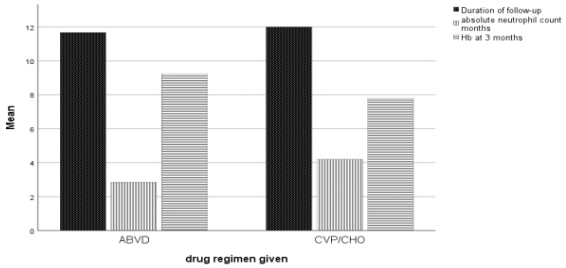
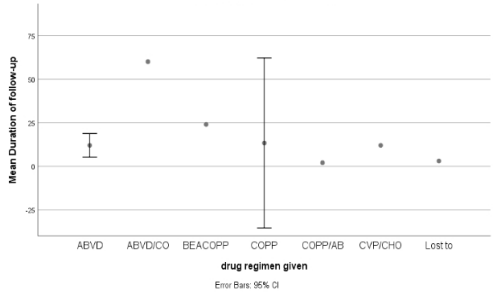


Figure 3. Frequency of the various histological types of Hodgkin lymphoma



ABVD= Adriamycin, Bleomycin, Vinblastine and Dacarbazine; CVP/CHO= Cyclophosphamide, Vincristine and Prednisolone and switched to Cyclophosphamide, Hydroxodaunorubicin and Oncovin.

Figure 4. Bar chart showing duration of follow up, absolute neutrophil count and Hb at 3 months in people who received the various drug regimens



ABVD= Adriamycin, Bleomycin. Vinblastine and Dacarbazine; ABVD/COPP = Adriamycin, Bleomycin. Vinblastine and Dacarbazine then switched to COPP; BEACOPP = Bleomycin/Etoposide/Adriamycin/Cytosine Arabinoside/Oncovin/Procarbazine/Prednisolone; COPP = Cyclophosphamide, Oncovin, Procarbazine and Prednisolone; CVP/CHO= Cyclophosphamide, Vincristine and Prednisolone and switched to Cyclophosphamide, Hydroxodaunorubicin and Oncovin; Lost to = lost to follow up.

Figure 5. Mean duration of follow up observed in patients placed on the various drug combinations used in Hodgkin Lymphoma

Advanced disease (later than Stage II disease) was found in 57.1% (20/35), while 42.8% (15/35) had earlier stages of the disease. The clinical stage at presentation was not recorded for 5 cases. Figure 2 shows the distribution of the patients with respect with their Ann-Arbor Stage at presentation. The nodular sclerosis subtype was the most prevalent 50% (16/32), followed by the lymphocyte depletion 25% (8/32), mixed cellularity 7.5% (3/32) and lymphocyte rich 5% (2/32). Figure 3 shows the distribution of the various subtypes of HL in the cohort. The

lymphoma subtype was not recorded for 8 cases. The Chi-square analysis of the relationship between tumor subtype and mortality showed a significant relationship (p=0.001). Constitutional B symptoms were observed in 14.2% (5/35) of the patients and 80% (4/5) of those that had the NS subtype. Thirty of the patients had no B symptoms at presentation. The duration of follow-up ranged from 2 to 58 months, with a median of 12 months. As at the time of this write up, 27.3% (9/33) were either dead (4/33) or lost to follow up (5/33), while 72.7% (24/33) were still alive. Of all the patients enrolled in this study 17.5% (7/40) had relapsed. The correlation coefficient showed a positive relationship between survival and absolute neutrophil at 6 months (r=0.806; p= 0.016) as well as serum urea (r= -0.425; p = 0.034).

Twenty nine patients received the Adriamycin/Bleomycin/Vinblastine/Dacarb azine (ABVD) at some point in their treatment. In 20.7% (5/29) cases ABVD was later switched to other drug combinations due to relapse or sub-optimal response. In 8.1% (3/37) of cases other combinations were given before switching to ABVD. Figure 4 shows the absolute neutrophil count and Hb after 3 months of chemotherapy as well as the duration of follow-up in patients who were given ABVD compared with Cyclophosphamide/Oncovin/Procarbazine/ Prednisolone (COPP) who were later switched to other combinations. While Figure 5 shows the median duration of follow up/survival with the various chemotherapy regimen. There was a significant relationship between the number of cycles given and the patients age (r= -0.414; p=0.026), Hb (r=0.651; p=0.03) and serum creatinine (r= -0.456; p=0.025), serum acid (r= -0.737; p=0.01), both at 6 months of treatment.

The duration of follow-up was found to have a direct and significant relationship with the Hb at diagnosis (r = 0.637; p = 0.011) and number of cycles of chemotherapy given (r = 0.619; p = 0.018). This was also observed to have an inverse relationship with the serum conjugated bilirubin (r = -0,753; p = 0.019) and serum alkaline phosphatase (r = -0.597; p = 0.04). Age was not found to have any relationship with survival (r = -0.147, p = 0.474) though older patients were noted to have received fewer cycles of chemotherapy (r = -0.302, p = 0.031). The disease subtype and spleen size were not found to have a significant relationship with the duration of follow up (r = 0.389; p = 0.189; and r = 0.012; p=0.967 respectively).

DISCUSSION

The age incidence of patients in this study was found to be in the third decade. This is similar to the findings of other studies [15,16] though the plot of the age prevalence also shows a bi-modal peak. These findings are similar also to the bimodal age prevalence previously found in the second and sixth decades of life by other investigators.[17-19] There is no ready explanation of this age distribution though this may indicate periods of extensive immunological activity in those moving to adulthood from adolescence and the second group transiting from middle to old age. The HIV prevalence in the HL cohort was found to be 5.4% and this is higher than the current prevalence rate of 1.5% in the general Nigerian population.[20] This implies that HIV is associated with occurrence of HL and a reduction in the prevalence of HIV may lead to reduction in HL rates.

Less than a third of the patients were noted to have a palpable splenomegaly and this was not found to correlate with survival or tumour stage. This implies that splenomegaly in HL may also have some reactive basis, just like the reactive component of the lymphoid mass found in lymph nodes of diagnosed cases. This may also be a likely cause of the waxing and waning of the size of affected nodes as previously described in HL. The leucocyte and absolute neutrophil counts were both found to depreciate with time and this is probably due to the myelosuppressive nature of the anti-cancer agents used in treatment of HL. Both parameters when considered in each subtype of HL were found to be significant predictors of mortality. This is not completely surprising as neutropaenia will preclude the capacity

to receive chemotherapy as well as limit its frequency. It has also been shown by previous studies that severe neutropaenia is associated with death within 30 days.[21,22] Absolute neutrophil count at diagnosis may be considered as a necessary determinant of survival as it both indicates tumor invasion as well as capacity to tolerate optimal treatment.
More than half of the patients were seen with later than stage II disease and interestingly, the Ann-Arbor staging was found not to correlate with survival. This may indicate that this staging system may be of more importance in Non-Hodgkin lymphoma than in HL and it has also been proposed by some investigators.[23] The tumour subtype, on the other hand, was found to influence mortality and this implies that the various types of HL have varying expected outcomes as had been previously thought.[24] The nodular sclerosis HL was found to be most common followed by the lymphocyte depletion subtype. The lymphocyte depletion type is known to run an aggressive course and may be responsible for the overall poor treatment outcome in this group. About a tenth of the patients had B symptoms at presentation and these were mainly patients who had the NS subtype of the disease. This may connote a poor prognosis for individuals with this disease subtype, this has been proposed in previous studies.[24]

In this study, about a quarter of the patients had relapsed and a further 15% had been lost to follow up, thus demonstrating the sub-optimal response in this particular cohort as opposed to the records of 80 to 90% cure rate reported in most other recent studies. This may be due to late presentation as well the predominance of the NS subtype of HL which is known to confer poor prognosis.[2,25] The high number of patients lost to follow up indicates poor patient documentation and lack of a tracking systems to ensure retention in care.

Majority of the patients received ABVD and a small fraction of these were switched to other drug combinations either due to relapse or sub-optimal response. This is representative of the current standard of care for treatment of HL in other climes. However, a failure rate of close to 75% in these patients indicates that there may be need to further investigate their higher rate of relapse or failure. The age of the patient was not found to be associated with survival in this study in spite of the fact that older patients were noted to have received fewer cycles of therapy. This does not agree with previous studies, which have actually proposed age as an independent indicator of survival.[26-28] However, in the study by Josting *et al*, Hb at presentation was noted to be a good indicator and this is supported by the findings of our study. This is to be expected as this is one of the criteria for suitability for chemotherapy as well as an indirect indicator of marrow invasion or immune haemolysis, all of which confer poor prognosis. Elevated serum bilirubin and alkaline phosphatase were also noted to confer poorer outcome. These may be signs of co-morbidities or autoimmune affectation of other organ systems, which has been noted to have some relationship with HL.

The variations in the distribution of the various subtypes of HL across different populations has been noted in previous studies [29,30] and is worth exploring. The need to develop a newer and simpler method of assessing prognosis and disease outcome is becoming more apparent in the face of newer studies, which indicate that the current staging system may not be all encompassing.

CONCLUSION

In this cohort of patients, the nodular sclerosis subtype of HL was found to be the most common. The prevalence of HIV in patients in this study was found to be higher than that of the normal population. Absolute neutrophil counts and nodular sclerosis subtype of HL were associated with increased risk of death, while Hb concentrations at presentation had a direct relationship with survival, but age and spleen size did not. This study supports the view that the staging of HL be reviewed, as disease subtype, Hb concentration and neutrophil count are correlates of survival that may be used for the calculation of a reliable prognostic scoring system.

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Conflict of Interest: Authors declare no conflict of interest in the writing of this paper.

Authors' Contributions:
Study Design: AM, KK, NU and HO; Literature Review: AU, AD, FM, KM and CE; Data Collection: AM, KK, NU, CE and IN; Statistical Analysis: AU, AD, KM and FM; Manuscript writing: HO, IN, KK, AM and IN.

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