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ORIGINAL RESEARCH

Assessment of CD20 Marker as a Prognostic Predictor for Patients with Classical Hodgkin Lymphoma

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Purpose: Classical Hodgkin Lymphoma (CHL) is a highly curable malignant disease of the lymphoid system. However, some patients may experience a clinical relapse. Biological marker expression may help to predict disease outcomes and guide salvage treatment options. CD20 expression occurs in approximately 30% of CHL cases. The clinical outcomes of patients with CHL and CD20 positivity remain controversial. Therefore, this study aimed to determine the prognostic value of CD20 expression in CHL patients.

Patients and Methods: This retrospective study included 52 patients with CHL between 2017–2023 with a median follow-up of 60 months (range: 24–72 months). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue biopsies to assess CD20 expression. Chi-square and Fisher's exact tests were used to analyze categorical data and determine significant differences between the CD20 expression status groups. Overall survival (OS) and Progression-Free Survival (PFS) were assessed using Log rank test. Statistical significance was set at $p < 0.05$.

Results: Of 52 CHL patients, 11 (21.2%) showed CD20-positive Hodgkin Reed-Sternberg (HRS) cells. Most parameters showed no significant differences between the CD20-positive and CD20-negative groups, except for serum albumin level ($p = 0.042$). Log-rank analysis for OS and PFS revealed no significant differences between the groups.

Conclusion: CD20 expression in the HRS cells of CHL patients was not significantly associated with clinical outcomes. Further studies with larger patient populations and extended follow-up periods are required to validate these findings.

Keywords: CD20, classical Hodgkin lymphoma, Hodgkin Reed-Sternberg cells, immunophenotype

Introduction

Hodgkin Lymphoma (HL) is a malignant neoplasm of the lymphoid tissue that primarily affecting B lymphocytes.[1–3] The therapeutics options for HL show remarkable outcomes, with overall survival rates exceeding 90% at 5 years interval duration making it as one of the most curable lymphoid neoplasms.[4–6] According to the World Health Organization (WHO) classification, HL is divided into two main groups based on clinical presentation, diagnostic morphological features, immunophenotypic profiles, and molecular characteristics. These include Classical Hodgkin Lymphoma (CHL), which accounts for approximately 95% of all HL cases, and nodular lymphocytic predominant Hodgkin lymphoma, which accounts 5% of the remaining cases.[7,8] CHL is a malignant disease of germinal-center B cells and is characterized by the appearance of Hodgkin and Reed-Sternberg (HRS) cells.[8–10] It is subdivided into four subtypes according to the cellular background of the HRS cell[11] and occurs most commonly in young adults.[1,12,13] HRS cells show a distinctive immunophenotyping profile, characterized by the expression of CD30 and variable expression of CD15. However, these HRS cells typically lack pan-B-cell antigens, including CD19, CD20, and CD22, except in 20–30% of the cases in which CHL shows expression of CD20, suggesting biological heterogeneity within this disease.[9,14] CD20 is encoded by a gene called MS4A1 (membrane-spanning 4 domains, subfamily A, member 1). This gene encodes a molecule on the B-lymphocyte surface that develops into B-cells and

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differentiates into plasma cells. The loss of this gene can lead to a negative expression of CD20 or a heterogeneous positive expression in <20% of HRS cell.[15] The conflict presence of CD20 in HRS cells makes its expression in CHL of great biological interest. Only about 11–35% of CHL cases actually express CD20, despite the fact that HRS cells are unquestionably derived from mature germinal center B cells, which normally express CD20. Despite the lineage origin, this disparity calls into question the molecular changes that typically result in the loss of this B-cell marker. Additionally, CD20 is a membrane-embedded protein that functions similarly to a Ca^{2+} ion channel and is involved in B-cell differentiation, proliferation, and signal transduction. Its existence in certain HRS cells raises the possibility of functional consequences, including modifying the effects of growth factors like interleukin-4, influencing intracellular calcium levels, or possibly affecting apoptotic resistance. On the other hand, its expression may only act as a marker for a specific gene expression linked to a specific clinical outcome. Gaining knowledge of these processes may help identify possible treatment targets and shed light on the pathophysiology of CHL as well as patient prognosis.[16–18] Some studies have shown no association between CD20 expression and patient prognosis,[19,20] while the study of Portlock et al showed that the expression of CD20 was associated with poor prognosis.[21] In comparison, Tzankov et al concluded that CD20 positivity is associated with a good clinical outcome.[18] CHL is a highly curable disease with frontline treatment consisting of chemotherapy with or without radiotherapy. However, some patients experience relapse or refractory disease.[16,22,23] Therefore, the identification of diagnostic biological markers can be used as a helpful tool by clinicians to predict the response to treatment and suggest targeted therapy for refractory patients. This study aimed to demonstrate the prognostic value of CD20 expression in CHL patients.

Materials and Methods

Population Characteristics

A sample cohort of 59 patients with CHL was identified through a retrospective review at King Abdulaziz University Hospital, Jeddah, Saudi Arabia between 2017 and 2023. Among these, 52 patients were included in the subsequent analysis, while seven patients were excluded due to unavailability of the required parameters. The obtained data included demographic information, hematological and biochemical parameters, and patient outcomes retrieved through the electronic medical record system. Of the 52 patients, 39 patients (75%) had complete Ann Arbor staging data, and 49 patients (94.2%) had treatment response data. Following their initial diagnosis at our center, the 18 untreated patients either (1) were referred to other institutions for treatment or (2) made the decision to seek treatment elsewhere. These restrictions result from our study's retrospective design as well as the referral trends in our local healthcare system. We believe our cohort is still useful for investigating the prevalence of CD20 expression and its relationship to baseline characteristics in our population. Patients were followed from the time of diagnosis through clinical visits, and laboratory assessments according to management protocol. The median follow-up time for the study cohort was 60 months (range: 24–72 months), providing sufficient duration to capture both early and intermediate-term clinical outcomes. Follow-up data were collected through December 2023, with no patients lost to follow-up during the study period. Consent from patients was not obtained for this study as it involved retrospective analysis of fully anonymized data where patients' identification was not possible, thus presenting minimal risk to participants. The study protocol was reviewed and approved by the Unit of Biomedical Ethics at King Abdulaziz University Hospital in accordance with guidelines for research using de-identified patient data with National Committee of Bioethics registration NO: (HA-02-J-008) as well as in accordance with the Helsinki Declaration.

Histopathology Processing

Histopathological processing of all biopsy samples was performed using a standardized protocol to ensure optimal diagnostic quality. This included sample fixation in 10% formaldehyde for 12–24 hours followed by sample processing using automated tissue processor (Tissue-Tek VIP). Paraffin blocks of the samples were prepared using HistoCore Arcadia. Tissue sections (3μm) were prepared using a Leica RM2235 microtome, mounted on glass slides, and stained with hematoxylin and eosin using the Tissue-Tek Prisma automated stainer. At this stage, all prepared H&E slides were assessed and reviewed by an experienced hematopathologist to verify the final report.

Immunohistochemistry Staining

Confirmation of the CHL diagnosis requires comprehensive immunophenotyping using a panel of antibodies for lymphoma detection. This panel included CD3, CD15, CD20, CD21, CD45, CD30, Epstein–Barr virus (EBV), fascin, and Paired Box-5 (Pax-5). Immunohistochemical staining was performed using Ventana Bench-Mark Ultra based on an antigen-antibody reaction to detect and localize the target antigens within the tissue.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, Ill., USA, version 28). Descriptive statistics are presented as percentages and frequencies. Comparisons between CD20-positive and CD20-negative groups were performed using Chi-square ($\chi 2$) test or Fischer Exact test (in case of small frequencies) to assess the significance of differences. Survival rate was evaluated in terms of Overall Survival (OS) and Progression-Free Survival (PFS). The OS was measured from diagnosis until either death or the last follow-up date, whereas PFS was measured from the diagnosis until death, relapse, or the last follow-up date. The Log rank test was used to assess the significant differences in OS and PFS between the two groups. Differences between the two groups were considered statistically significant when the p-value was <0.05.

Results

Patient Characteristics

Fifty-two patients with CHL were included in the study. Patients were divided into two groups based on their CD20 biomarker status. The first group was CD20-positive and comprised of 11 patients (21.2%), whereas the second group was CD20-negative and comprised of 41 patients (78.8%). The age distribution analysis showed distinct patterns between the groups. The CD20-negative group had the highest population in the 11–25 years age (39.0%), followed by the 26–40 years category (36.6%). In contrast, the CD20-positive group had the highest representation in the 26–40 years category (45.5%), with lower representation in other age groups. However, these age distribution differences were not statistically significant ($p = 0.498$). The most common histopathological subtypes among the patients in the CD20-negative and CD20-positive groups were nodular sclerosis in 23 (71.9%) and 7 (70.0%), respectively. The only statistically significant difference between the groups was found in the serum albumin levels ($p = 0.042$). A higher proportion of CD20-negative patients (70.7%) had lower albumin levels (<40g/L) compared to CD20-positive patients (36.4%). Other laboratory parameters, including white blood cell count, hemoglobin levels, and lymphocyte count, showed no significant differences between the groups (all $p > 0.05$). The parameters are listed in Table 1.

Table 1 The Patient's Characteristics and Clinical Outcome of CD20 Expression Status

Parameters	CD20 Negative (N = 41) N (%)	CD20 Positive (N = 11) N (%)	*p*-value
Gender			
Male (n = 30)	24 (58.5)	6 (54.5)	0.812
Female (n = 22)	17 (41.5)	5 (45.5)	
Age at diagnosis (years)			
≤10 (n = 4)	3 (7.3)	1 (9.1)	
11-25 (n = 18)	16 (39.0)	2 (18.2)	
26-40 (n = 20)	15 (36.6)	5 (45.5)	0.498
41-55 (n = 4)	2 (4.9)	2 (18.2)	
>55 (n = 6)	5 (12.2)	1 (9.1)	

(*Continued*)

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Table 1 (Continued).

Parameters	CD20 Negative (N = 41) N (%)	CD20 Positive (N = 11) N (%)	*p*-value
Histopathological classification (n = 42)*			
Nodular sclerosis (n = 30)	23 (71.9)	7 (70.0)	
Mixed cellularity (n = 10)	8 (25.0)	2 (20.0)	0.657
Lymphocyte-rich (n = 2)	1 (3.1)	1 (10.0)	
Albumin < 40g/L**			
Yes (n = 33)	29 (70.7)	4 (36.4)	0.042
No (n = 19)	12 (29.3)	7 (63.6)	
White Blood Cell Count > 15×10^9/L**			
Yes (n = 12)	9 (22.0)	3 (27.3)	0.495
No (n = 40)	32 (78.0)	8 (72.7)	
Hemoglobin < 10.5g/dl**			
Yes (n = 24)	19 (46.3)	5 (45.5)	0.958
No (n = 28)	22 (53.7)	6 (54.5)	
Lymphocyte count < 0.6×10^9/L**			
Yes (n = 5)	4 (9.8)	1 (9.1)	0.717
No (n = 47)	37 (90.2)	10 (90.9)	
Urea (n = 48)**			
Low (n = 23)	19 (46.3)	4 (36.4)	
Normal (n = 25)	19 (46.3)	6 (54.5)	0.839
High (n = 4)	3 (7.4)	1 (9.1)	
C-reactive protein (n = 39)*			
Normal (n = 4)	3 (10.0)	1 (11.1)	0.667
High (n = 35)	27 (90.0)	8 (88.9)	
Disease stage (n = 40)*			
Favorable early stage (n = 6)	4 (13.3)	2 (20.0)	0.861
Unfavorable early stage (n = 5)	4 (13.3)	1 (10.0)	
Advanced stage (n = 29)	22 (73.4)	7 (70.0)	
Ann-Arbor stage system (n = 39)*			
Stage I (n = 2)	1 (3.3)	1 (11.1)	
Stage II (n = 8)	7 (23.3)	1 (11.1)	0.716
Stage III (n = 13)	10 (33.3)	3 (33.3)	
Stage IV (n = 16)	12 (40.0)	4 (44.4)	

(*Continued*)

Table 1 (Continued).

Parameters	CD20 Negative (N = 41) N (%)	CD20 Positive (N = 11) N (%)	*p*-value
Chemotherapy protocol (n = 49)*			
No treatment received (n = 18)	16 (41.0)	2 (20.0)	
ABVD (n = 28)	22 (56.4)	6 (60.0)	0.085
Other than ABVD (n = 3)	1 (2.6)	2 (20.0)	
Response to chemotherapy (n = 25)*			
Complete remission (n = 18)	14 (70.0)	4 (80.0)	
Partial remission (n = 1)	1 (5.0)	0 (0.0)	0.841
Relapse (n = 6)	5 (25.0)	1 (20.0)	
Bulky disease* (n = 42)***			
Yes (n = 2)	1 (3.2)	1 (9.1)	0.460
No (n = 40)	30 (96.8)	10 (90.9)	
B-symptoms (n = 45)*			
Yes (n = 31)	23 (65.7)	8 (80.0)	0.327
No (n = 14)	12 (34.3)	2 (20.0)	

Notes: *Including some study participants because of missing data for others. **All laboratory parameters were measured at baseline prior to the initiation of any treatment. ***"bulky disease" refers to large tumor masses defined as either a lymph node/mass ≥ 10 cm or a mediastinal mass exceeding 1/3 of the thoracic diameter at T5-T6 level.

Patient Clinical Outcomes

Survival analysis revealed no significant differences in either PFS or OS between the CD20-positive and CD20-negative groups. The median PFS for the CD20-positive group was 19 months (95% CI: 2.6–35.4 months) compared to 24 months (95% CI:14.8–33.2 months) for CD20-negative group, with a *p*-value of 0.482 (Figure 1). Similarly, the median of OS for CD20-positive group was 10 months (95% CI: 5.1–14.9 months), compared to 8 months in the CD20-negative group (95% CI: 5.4–10.6 months), with a *p*-value of 0.947 (Figure 2).

Discussion

This study included 52 patients with CHL divided into two groups based on the CD20 expression status. The CD20-positive group was compared with the CD20-negative group in terms of demographic, hematological, and biochemical parameters. In addition, overall survival and progression-free survival data were analyzed to determine the potential association between CD20 expression and patient prognosis. CHL was more prevalent in males than females in both groups, with no significant difference observed ($p = 0.812$), which is consistent with previous studies.[19,21,24]

The gender is considered one of the prognostic factors, possibly due to differences in the pharmacokinetic mechanisms. Female patients tend to experience greater hematological toxicity, particularly severe leukopenia, probably due to differences in the cytotoxic drug metabolism of adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine (ABVD) regimen. While hematological toxicity is associated with a good prognosis, male patients with Hodgkin Lymphoma showed less favorable prognosis compared to female patients.[25]

In this study, we found that 71.9% of CD20-negative and 70% of CD20-positive patients showed nodular sclerosis subtype, which is also consistent with findings of previous studies.[19–21] The prevalence of nodular sclerosis was 70% among CHL patients. Fortunately, nodular sclerosis subtype is associated with a favorable prognosis.[7] However, other studies have reported contrasting results. Tzankov et al study demonstrates that CD20 positive patients with a nodular

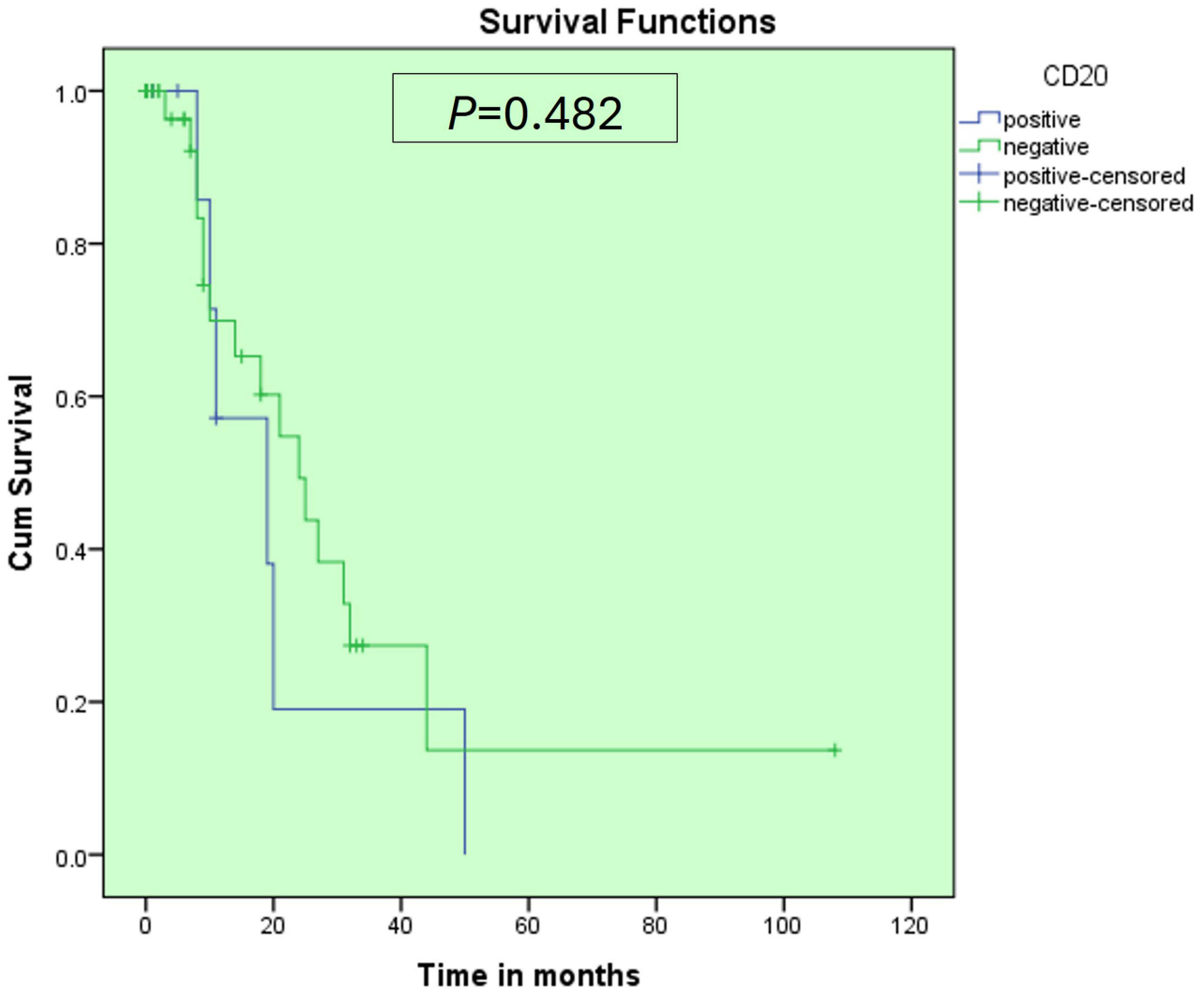

Figure 1 Comparison of progression-free survival of patients with Classical Hodgkin Lymphoma according to the CD20 biomarker status.

sclerosis subtype accounted for 16%.[18] Moreover, the Elsayed et al study was conducted in Japan and showed the most common subtype in the CD20-positive group was mixed cellularity subtype (61%), whereas in the CD20-negative group, mixed cellularity and nodular sclerosis had the same prevalence (46%).[24] The diversity in the distribution of CHL subtypes between these studies may be attributed to several factors, including patient's gender, age, socioeconomic status, and geographical location. However, the reason behind the high frequency of mixed cellularity and lymphocyte-depleted subtypes in developing countries may be due to other risk factors, including human immunodeficiency virus and Epstein–Barr virus infection.[26] In our study, 21.2% of fifty-two patients with CHL patients (n = 52) were CD20-positive and 78.8% were CD20-negative, consistent with previous studies reporting the prevalence of CD20-positive among the CHL patients ranging from 11–35%.[15,18,19]

The prognostic significance of CD20 expression in CHL has been debated in recent years with contradictory findings across studies. Tzankov et al assessed patient prognosis and showed that patients had a better prognosis with CD20 expression,[18] whereas the study of Portlock et al found that the expression of CD20 in CHL is considered a poor prognostic marker for overall survival and time to treatment failure.[21] However, the study of Abuelgasim et al performed in Riyadh, Saudi Arabia found no differences in progression-free survival and overall survival among patients with CD20-positive.[19] Furthermore, the study of Rassidakis et al concluded that CD20 expression was not associated with

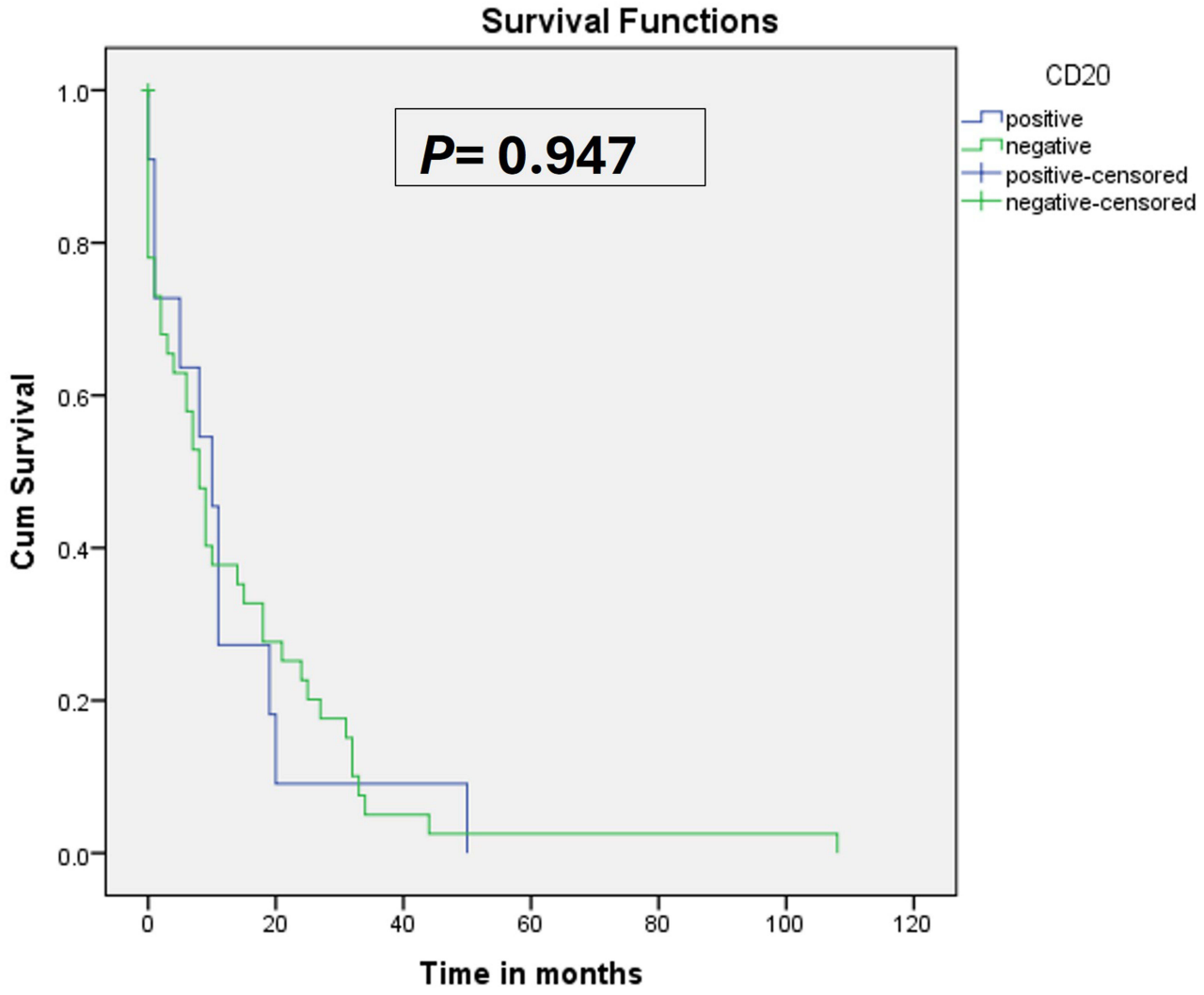

Figure 2 Comparison of the overall survival of patients with Classical Hodgkin Lymphoma according to the CD20 biomarker status.

differences in failure-free survival (FFS) treatment with equivalent regimens.[20] Our study showed no significant difference between the CD20-positive and CD20-negative groups in the survival rate described in terms of overall survival and progression-free survival, OS (p = 0.947), and PFS (p = 0.482). Interestingly, our findings matched those of a national study conducted in Riyadh, Saudi Arabia.[19] To date, the effect of the expression of CD20 on patient outcomes remains controversial.[16] In addition, our results agree with other previous studies that showed that CD20 expression has no prognostic value in CHL. However, it is a useful new information from the Western region of Saudi Arabia, specifically from King Abdulaziz University Hospital as one of the reference tertiary hospitals in the region. Our study cohort treated between 2017 and 2023 is an important addition to the global literature in the context of CHL from a region that has not had much representation in the past. The application of standardized IHC technique across all samples enhances the reliability of our observation in the real clinical setting, potentially addressing knowledge gap regarding treatment outcomes and prognostic factors in CHL patients. This regional perspective is particularly valuable for understanding potential geographic variations in CHL presentation and response pattern. Furthermore, the B-cell origin of HRS cells is probably the reason for the biological significance of CD20 expression in classical Hodgkin lymphoma. In a small portion of cases, CD20 expression may indicate an incomplete reprogramming of the B-cell phenotype, even though HRS cells normally lose the majority of B-cell markers during their pathological transformation.

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This partial loss of B-cell identity may be due to different pathways of cellular transformation or differences in the epigenetic silencing of B-cell transcription factors such as OCT-2 and PAX5. On the other hand, CD20-positive CHL may indicate a biological spectrum that overlaps with other B-cell lymphomas, such as primary mediastinal B-cell lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma, and classical Hodgkin lymphoma. Although CD20 expression itself does not have prognostic significance, knowledge of these biological foundations may help explain the variability of CHL.[15,20]

Hematological parameters, including hemoglobin concentration, white blood cell (WBC) count, and lymphocyte count, were compared between the two groups and showed no significant differences. These parameters were used to calculate the International Prognostic Index (IPI) score to predict the overall survival and progression-free survival. In our study, we showed the percentage of hemoglobin concentration <10.5g/dl and >10.5g/dl among the CD20-positive group was 45.5% and 54.5%, respectively. This means that almost half of the patients with CD20 positivity had anemia. In CD20 negative group, 46.3% of CD20 negative patients had anemia, whereas 53.7% did not suffer from anemia. In contrast to our findings, the study of Elsayed et al found that 14% of the patients suffered from anemia with CD20 positive and 24% of CD20 negative patients had anemia, which represents less than a quarter of patients with CD20 positive and CD20 negative.[24] However, the study of Rassidakis et al agreed with our findings and showed 42% of the CD20 positive group and 48% of patients the CD20 negative had anemia meaning that approximately half of the patients suffered from anemia of inflammation.[20] In addition, WBC count is considered one of the parameters used in the IPI score calculation, with a cut-off point of $15*10^9$/L. In our study, 22% of CD20-negative patients had WBC > $15*10^9$/L whereas 27.3% of CD20-positive had >$15*10^9$/L. On the other hand, the patients with CD20-negative and CD20-positive patients had <$15*10^9$/L represented 78% and 72.7%, respectively, indicating that almost a third quarter of the patients in each group had WBC < $15*10^9$/L and this finding agrees with previous work.[24] Furthermore, the albumin level was demonstrated and used in the IPI score calculation with a 40 g/L cut-point level. Interestingly, the albumin level in our study showed a significant difference between the two groups $p = 0.042$, where 70.7% of the CD20 negative group showed a level of albumin <40 g/L compared to the 36.4% CD20-positive group. About 29.3% of CD20-negative had albumin ≥40 g/L compared to 63.6% of CD20-positive group. Our findings were consistent with those reported with the study of Rassidakis et al.[20] Albumin is used among a number of prognostic scoring systems for CHL by the International Prognostic Score when measured below 40 g/L.[26] It has been reported with poor patients' outcomes, including reduced OS and PFS. This association is thought to reflect the patient's nutritional status, inflammation, and tumor burden.[27] In CHL, CD20 positivity and low albumin levels are important prognostic factors. The significance of including these factors in prognostic models and treatment planning is highlighted by their combined impact on survival rates and treatment outcomes. With regard to our findings, the low levels of albumin are probably due to the production of acute-phase proteins that are stimulated by IL-6. An inverse correlation was observed between albumin level and IL-6, tumor necrosis factor (TNF), and Interleukin-1 receptor antagonist (IL-1 RA), as well as the low level of albumin associated with malnutrition. Our CD20-positive cohort's lack of survival differences in spite of lower albumin levels. This raises a number of potential explanations: It might indicate a biological confounder that obscures possible prognostic effects of CD20 expression, or it might reveal a unique biological subgroup of CD20-positive CHL with particular inflammatory traits. In order to improve outcomes for high-risk patients, more research is required to investigate the mechanisms underlying the relationship between albumin levels and CD20 expression in CHL and to develop targeted therapies.

Regarding the response to chemotherapy, most of the CD20-negative and CD20-positive groups achieved complete remissions accounting for 70% and 80%, respectively, which is consistent with the study of Elsayed et al.[24] This finding supports the fact that the CHL is highly curable.[23] However, 25% of CD20-negative patients experienced a relapse phase after the first-line treatment, whereas 20% of CD20-positive of CHL, which agrees with prevalence of the relapse among CHL patients with approximately 20%.[28] This can provide clinicians and patients with a good indication of disease progression and help in patient management.

Conclusion and Future Directions

The present study is considered as the first study conducted in the western region of Saudi Arabia, where 21.2% of Classical Hodgkin Lymphoma were found to be CD20-positive, characterized by no difference in OS and PFS as compared with the CD20-negative group. The significant association between CD20 positivity and low serum albumin

levels represents an interesting finding that warrants further exploration. The small cohort size (n = 52) and the comparatively small CD20-positive subgroup (n = 11) are affecting our conclusion and considered as a limitation. Our statistical ability to identify significant survival differences between CD20-positive and CD20-negative CHL patients is significantly diminished by this sample size restriction. Potential prognostic of CD20 expression relevance that might have shown in a larger cohort may have been masked by the small number of CD20-positive cases. Therefore, our results should be interpreted carefully, and larger multi-institutional research or meta-analyses works warrants the prognostic significance of CD20 expression. Another limitation was that some patients lacked laboratory results or follow-up information from the profiles in the electronic medical record system due to their movement to other hospitals to complete their treatment management. Therefore, a larger sample size with longer follow-up periods is highly recommended. However, future works should investigate integrative biomarker analysis approach, looking at CD20 alongside other biological related markers like PD-L1, CD30, and EBV status. Complex interactions between these markers may be revealed by such combinatorial analyses, which could improve patient prognostic categorization and pinpoint subgroups where CD20 expression has clinical significance. Further understanding of the biological heterogeneity of CHL and the possibility of discovering new therapeutic targets may also be gained by linking CD20 expression to genetic signatures. To advance precision medicine approaches in CHL management, prospective studies that combine these various biomarkers with standardized treatment protocols would be especially beneficial.

Disclosure

The author(s) report no conflicts of interest in this work.

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