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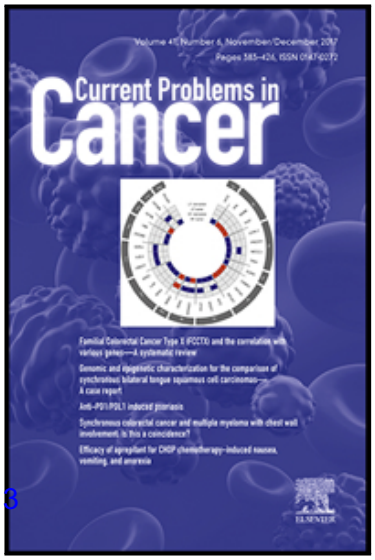

Diagnosis and management of classical Hodgkin lymphomaduring the COVID-19 pandemic

Selin Küçükyurt , Kübra Şahin , Umut Yılmaz , Abdülkadir Erçalışkan , Tuba Özkan Tekin , Damla Ortaboz , Tuğrul Elverdi , Ayşe Salihoğlu , Muhlis Cem Ar , Şeniz Öngören , Zafer Başlar , Ahmet Emre Eşkazan

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Hematologic Malignancy

Diagnosis and management of classical Hodgkin lymphomaduring the COVID-19 pandemic

Running Title: cHL management in COVID-19 pandemic

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has brought life to a standstill globally. Intermittent quarantines were applied to control the pandemic and reduce contamination. During the pandemic, patients with hematological malignancies were among the most vulnerable population. Our aim was to compare in terms of demographic data, disease related factors, symptom-to-diagnosis interval (SDI), diagnosis-to-treatment interval (DTI), and interim and end-of-treatment (EOT) response in classical Hodgkin lymphoma (cHL) patients diagnosed during the

pandemic and in the pre-pandemic periods. A total of 90 patients were included, of which 65 and 25 were diagnosed in the 2 years before the pandemic and the 12-month period during the pandemic, respectively. Demographic features were comparable in both groups. Although the percentage of patients with advanced-stage disease was higher during the pandemic (64% vs. 53.8%), this difference did not reach statistical significance (p=0.384). The median SDI was significantly longer during the pandemic than was observed within the pre-pandemic era (16 weeks vs. 8 weeks, p=0.042). The median DTIs were similar in both groups (13 days vs. 15 days, p=0.253). In the pre-pandemic and pandemic periods, 85.2% and 72.7% of the patients had complete response at EOT evaluation, respectively (p=0.208). We found that SDI was significantly prolonged during the pandemic. Higher percentage of patients with advanced-stage disease during the pandemic might also be due to this delay, nevertheless, this difference did not reach to a significant difference regarding treatment response in both groups.

Keywords

COVID-19; diagnosis-to-treatment interval; diagnostic delay; Hodgkin lymphoma; management; SARS-CoV-2; symptom-to-diagnosis interval

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has disrupted daily life, especially in the field of health, in Turkey as well as all over the world [1]. The susceptibility of COVID-19 is especially higher in patients with hematological cancer. COVID-19-related severe disease, serious complications, and the risk of death is higher in adult patients with hematological malignancies due to their inadequate and varying immune responses to the virus [2]. Considering higher risk of fatal COVID-19 infection in immunocompromised hosts, as well as the risk of cancer-related morbidity and mortality, the management of such patients have become difficult during the pandemic [1, 2].

Especially in Istanbul, the most populated city in Turkey, many hospitals served as pandemic hospitals and lockdown was also applied during this period, and as a result, the evaluation of patients who were not infected with COVID-19 generally needed to be postponed. Under such extraordinary conditions, hospital admissions of patients having complaints have decreased both due to the fear of contamination and quarantine practices [3, 4]. On the other hand, it is known that the delay in diagnosis and treatment of cancer patients can sometimes be fatal [5].

Martin-Moro et al. [6] compared the clinical and laboratory presentations of the patients diagnosed with acute myeloid leukemia (AML) in the first three months of the pandemic and in the same months before the pandemic, in order to investigate the effects of a 3-month country-wide lockdown in Spain. They reported that the patients diagnosed during the pandemic admitted the hospital with worse performance status, higher bleeding rate, higher leukocyte count and lactate dehydrogenase (LDH) level, and lower hemoglobin level at the time of diagnosis.

However, none of the variables reached a statistically significant difference between the groups [6].

Our aim was to compare the time from symptom onset to diagnosis and period between diagnosis and treatment initiation, as well as the distribution of stages and treatment responses in classical Hodgkin lymphoma (cHL) patients diagnosed and treated during the COVID-19 pandemic and in the pre-pandemic period.

2. Material and Methods

2.1. Study Population

This is a retrospective, single-center, chart review study carried out at the Cerrahpaşa Faculty of Medicine in Istanbul. Patients with cHL who were diagnosed and treated at our tertiary center within a 3-year frame were enrolled. Demographic, clinical, radiologic, pathologic, and therapeutic data were extracted from patients' paper charts by two investigators (SK and KŞ). We divided this patient cohort into two groups as cases who were diagnosed and treated within the 2 years before the pandemic (between March 2018 and March 2020) and those managed in a 12-month period during the pandemic (between March 2020 and March 2021). These patients were retrospectively analyzed, and two groups were compared in terms of demographics, disease characteristics including histopathological subtypes, Epstein-Barr virus (EBV) status, disease stage at diagnosis, disease risk scores, time interval between symptom to diagnosis and diagnosis to initiation of chemotherapy, the distribution of first-line treatments, interim and end-of-treatment (EOT) responses.

Symptom-to-diagnosis interval (SDI) was defined as time from first symptoms to pathologic diagnosis. The patients were grouped as favorable early stage, unfavourable early-stage and

advanced-stage according to the German Hodgkin Study Group criteria [7, 8]. Also, the International Prognostic Score (IPS-7) as well as its simplified form (IPS-3), were used for prognostic stratification in advanced-stage disease [9]. Diagnosis-to-treatment interval (DTI) was defined as number of days from the histopathological diagnosis to the initiation of chemotherapy.

2.2. Treatment

In our center, we generally prefer ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2) intravenous combination chemotherapy on days 1 and 15 of each 28-day cycle, as it is one of the most commonly used regimens in the first-line treatment of cHL worldwide and it is easy-to-manage [10]. Thus, all patients were planned to receive ABVD +/− involved-field radiotherapy (IFRT). However, if drug intolerance or unacceptable toxicity existed initially or subsequently developed, the causative chemotherapeutic agent was excluded from the protocol.

All patients received at least one dose of chemotherapy. We evaluated pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide (DLCO), at baseline and at intermittently every 2 courses during treatment, based on our planning to administer bleomycin in all patients. While the DLCO value was appropriate for treatment at the beginning, if there was a 25-50% decrease in DLCO in the following courses, bleomycin was omitted from the remaining cycles. In Turkey, we may prescribe off-label drugs including brentuximab vedotin (BV) under the control of Turkish Medicines and Medical Devices Agency (TITCK). We applied to TITCK for the off-label use of BV 1.2 mg/kg for those who could not receive bleomycin. If approved, we added BV to the treatment, if not, patients received the treatment as AVD. We removed bleomycin from the protocol in some patients over 60 years, and patients with ECOG 3-4 and

added off-label BV in these patients. In some patients with interim positron emission tomography combined with computed tomography (PET-CT) scan negative, bleomycin was interrupted in subsequent courses based on physician preference. Patients with normal left ventricular ejection fraction (≥50%) on echocardiography received anthracycline.

2.3 Evaluation of Response

PET-CT scans were performed at baseline, after two cycles of chemotherapy, and EOT. Interim and EOT PET-CT scans were performed within 10 – 14 days following the first 2 ABVD cycles and after 6 weeks following completion of the last scheduled treatment dose, respectively. Similarly, response assessment by PET-CT scans were performed 12 weeks following the completion of RT.

The Deauville five-point scale (5-PS) was used in the initial staging and assessment of treatment response. Based on interim PET-CT assessment according to Deauville 5-PS; a score of 1, 2, or 3 was considered as negative. The 5-PS score 4 or 5 was positive [11]. If PET-CT scan was "negative" within 3 months following the completion of treatment, it was accepted as complete response (CR) [10, 11].

3. Statistical Analysis

All data were analyzed by using IBM SPSS Statistics 20.0. Nominal variables were presented as frequency and percentages. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test, as appropriate. For variables not normally distributed, median with variables range (minimum to maximum) were used. Mann–Whitney U test was used for continuous variables that did show non-normal distribution (e.g., median age at diagnosis and

time intervals including SDI and DTI) to test whether there were any differences between the two groups. All tests were two sided, and $p<0.05$ was considered statistically significant.

4. Results

The study included 90 newly diagnosed cHL patients, with a median age of 33.5 years (range, 17 – 70 years) and a male predominance (53.3%, male/female = 1.14) (Table 1). For the entire patient cohort (n=90), the most common presenting symptom was a mass in the neck (41.1%), and 61.1% of the cases had at least one B symptom. EBV positivity in the entire cohort was 34.4%. The presence of bulky disease at presentation was 4.4% (Table 1). Nodular sclerosis cHL was the most common histopathological subtype (47.8%) followed by mixed cellularity cHL (36.7%). Thirty-nine patients (43.3%) had early-stage disease, whereas 51 (56.7%) had advanced-stage disease (Table 1). The extranodal involvement was detected in 44 cases (48.9%), and the most commonly involved extranodal sites were spleen (38.9%), lungs (11.1%), liver (10%) and bone (7.8%). Histopathologically confirmed bone marrow involvement was present in 4.4% of the cases.

Of these 90 cases, 65 (72.2%) were diagnosed in the pre-pandemic period and 25 cases (27.8%) were diagnosed during the COVID-19 pandemic. Demographic features and patient characteristics of the entire cohort, and 2 groups were displayed in Table 1.

Age and sex distributions were similar in both groups. Also, the percentage of patients >60 years was comparable (p=0.868). The most common histopathological subtype in both groups was nodular sclerosis (47.7% vs. 48%). The EBV status (p=0.744), presence of bulky disease (p=0.308), accompanying any B symptom (p=0.537) and extranodal disease (p=0.075) were also comparable between groups (Table 1).

In the pre-pandemic period and during the pandemic, among the early-stage patients, the percentages of cases with early unfavorable disease were 66.7% and 77.8%, respectively (p=0.526). Although the percentage of patients with advanced-stage disease was higher during the pandemic than that observed in the pre-pandemic period (64% vs. 53.8%), this difference did not reach statistical significance (p=0.384). There was no difference between the patients in both groups in terms of risk status in early-stage disease (p=0.693), and IPS-3 (p=0.155) and IPS-7 (p=0.079) scores in advanced-stage disease (Table 1).

The median SDI was significantly longer during the pandemic than was observed within the pre-pandemic era (16 weeks vs. 8 weeks, p=0.042). The median DTIs were similar in both groups (13 days vs. 15 days, p=0.471) (Table 1).

First-line treatment distributions of the entire cohort and the 2 groups were shown in Figure 1. A total of 476 courses of chemotherapy were administered. The majority of patients in both groups received first-line ABVD as initially planned (67.7% vs. 60%, p=0.416). In most of the remaining patients, treatment was started as ABVD, however, among some cases, bleomycin was omitted [the rate of bleomycin-induced pulmonary toxicity in the entire cohort was 13.3% (n=12)], while the rest of the drugs were continued, and the percentages of these patients were similar for both groups (15.4% vs. 16%). Vinblastine was withheld for grade 3 neurotoxicity in 2 patients. No other adverse events requiring dose reduction or discontinuation occurred. Other protocol modifications due to intolerance or toxicity (e.g., adding BV instead of bleomycin) were presented in Figure 1 and there was no significant difference between the 2 groups. Also, the percentages of cases who received IFRT were also comparable (6.2% vs. 4%) (Figure 1).

In our cohort, 87.5% of the cases had negative interim PET-CT scan results, and this percentage was similar for both patient groups (87.3% vs. 88%, p=0.929) (Figure 2). Interim treatment response of 2 patients diagnosed in the pre-pandemic period could not be evaluated, because they died due to neutropenic fever and septic shock following first chemotherapy.

In addition, EOT PET-CT of 4 patients in the pre-pandemic period could not be evaluated (3 patients died while on treatment (in addition to the above-mentioned 2 patients, the 3rd patient died due to pneumonia and respiratory failure during the 4th cycle of chemotherapy), and one was lost to follow-up). Also, we did not include 3 patients diagnosed during the pandemic period for response evaluation at EOT. One of them was a 63-year-old female and her treatment was continued with combination of 2 drugs (dacarbazine and BV) uniquely due to intolerance to BV-AVD (BV, doxorubicin, vinblastine, dacarbazine) treatment, then there was a residual mass in EOT PET-CT. Also, the other 2 patients were lost to follow-up, so EOT PET-CT results couldn't be evaluated for those cases. In the pre-pandemic and pandemic periods, 85.2% and 72.7% of the patients had CR at EOT, respectively (Figure 2). There was no statistically significant difference between these two groups (p=0.208).

The median DTI in the entire cohort was 14 days. Those who lasted 14 days or less and those who lasted longer than 14 days did not have a significant effect on the treatment response (p=0.771).

Since the follow-up period after EOT was relatively short, progression-free survival (PFS) and overall survival (OS) were not calculated. A total of 5 patients died (including the 3 patients above), all of whom were in the pre-pandemic group. Of the 2 cases not detailed above, one died

due to pneumonia and respiratory failure and the other because of multi-organ dysfunction syndrome.

5. Discussion

The pandemic negatively affected the delivery of healthcare services globally [12]. Intermittent quarantine practices and its psychological effects on patients reduced hospital admissions [3, 4]. On the other hand, getting an appointment was generally not so easy due to the lack of non-COVID19 patient care centers. In addition, decision making in the management of patients with malignancies was difficult [12].

During the pandemic, patients with hematological malignancies form one of the most frail patient groups [2], and as diagnosis could be challenging, treatment initiation and persistence among were other important issues [4, 13]. Based on this, we performed a study investigating the impact of COVID-19 pandemic on the diagnosis and management of patients with newly diagnosed cHL.

In our patient cohort, there was a male predominance (male/female = 1.14), and the median age at diagnosis was 33.5 years (Table 1). Similarly, this ratio was 1.3 in one study, whereas the median age was slightly higher (39 years) than ours [14]. Nodular sclerosis cHL was the most common histopathological subtype (47.8%) followed by mixed cellularity cHL (36.7%) (Table 1), and supporting this, in the study of El-Galaly et al. [14], 57% of the cases had nodular sclerosis cHL and 20% with mixed cellularity cHL. In the same study, the percentages of cases with B symptoms, extranodal disease, and advanced stage disease (Ann Arbor stage III-IV) were 46%, 26%, and 41.6%, respectively. All of these were higher in our cohort (Table 1), and most probably, this was because of the diagnostic delays resulting in patients presenting with advanced

stage disease (56.7% of our cases were with advanced stage) and/or maybe due to more aggressive biology of their diseases. On the other hand, compatible with our findings, in another series of 955 cHL patients, 62% of the patients had Ann Arbor stage III-IV disease [15]. Bone marrow involvement was detected in 5.2% of the cases by trephine biopsy [15], and similarly, this was 4.4% among our patient cohort.

Especially in the first wave of the COVID-19 pandemic, public health measures such as quarantine caused mental effects in cancer patients [16]. In a survey conducted by Gebbia and colleagues [4] by evaluating 446 cancer patients online, a significant portion of cancer patients demanded to postpone their visits and even adjuvant treatments due to fear of contagion, that was, possible COVID-19 transmission was more frightening than progressive cancer. Similarly, in our study, the SDI was significantly prolonged in the COVID-19 era. Most probably this finding was because of, patients being afraid to admit to the hospital because of the fear of contagion, and/or experiencing difficulties in applying to the health facilities. Lastly, maybe patients had tolerable symptoms, which might all had played a role in the diagnostic delays experienced during the pandemic.

Cancer screening, diagnostic tests, and interventions have been delayed due to the quarantine and other physical measures implemented in the UK due to the pandemic, which will lead to a delay in diagnosis [13]. In our cohort, we found a significant delay in diagnosis due to pandemic conditions during the pandemic compared to the pre-pandemic era. Except for the pandemic, there was no other condition (relocation of the clinic, change in appointment system, etc.) that could have an impact on this delay. In general, delay in diagnosis may occur depending on patient-related factors and/or the healthcare system [17]. Since we did not make a detailed assessment of the possible causes of this delay, this was one limitation of our study. With

knowing the fact that reasons outlined above could also lead to DTI prolongation, among our patient cohort, we did not observe a difference between the DTIs in the pandemic and pre-pandemic conditions.

There were studies evaluating the effect of DTI on clinical outcome and survival in patients with newly diagnosed diffuse large B cell lymphoma (DLBCL) [18-20]. Yoshida et al. [18] reported that DLBCL patients with a shorter DTI (i.e. <22 days) had inferior overall survival (OS) and PFS at 2-years. Phipps and colleagues [19] analyzed the effect of DTI on clinical factors and outcomes in 581 patients with DLBCL. The median DTI was 14 days, and longer DTI was associated with worse OS and PFS in advanced-stage patients presenting with elevated LDH. Similarly, Brooks et al. [20] examined the impact of DTI on survival in 810 patients with cHL in the pre-pandemic era. Although a DTI of >8 weeks was found to be associated with poor OS in univariate analysis, this was not shown in multivariate analysis. The follow-up period of our cohort was relatively short, so we did not evaluate the impact of the pandemic on PFS and OS rates. The impact of COVID-19 pandemic on DTI in DLBCL was evaluated in another study [21]. The DTIs in patients diagnosed in the pre-pandemic era and during the pandemic were found to be comparable (28 days and 19 days, respectively). Median DTI in our entire cohort was 14 days, which were similar in both groups. Also, in our entire cohort, the length of DTI did not have an impact on response rates.

The factors that determine the choice of first-line treatment in cHL are the anatomical stage of the disease (limited or advanced disease) and the presence or absence of poor prognostic factors. The patients with favourable early-stage disease are generally treated with 2 cycles of combination chemotherapy followed by IFRT. On the other hand, patients with unfavorable early-stage and advanced stage diseases usually receive more cycles of chemotherapy. Advanced stage disease

has prognostic significance according to IPS-3 and IPS-7 and it also alters treatment approach [7].

Caldarella et al. [22] compared the FDG-PET/CT staging of cancer patients with different tumor types in a 5-month period of the pandemic and in the same months 1 year before the pandemic. The study included 611 patients, 39.3% and 60.7% of the patients were diagnosed prior to and during the pandemic, respectively. Lymphoma patients (subtype not specified) formed 14.7% (n=99) of all cases, and of these 99 lymphoma patients, 32.3% and 67.7% were diagnosed in the pre-pandemic period and during the pandemic, respectively. Rates of lymphoma patients diagnosed with an advanced stage disease increased significantly [21]. Similarly, in our study, although the difference was not significant, percentage of patients with advanced stage cHL was higher during the pandemic than that of patients diagnosed before the pandemic.

cHL is a curable disease and ABVD is currently the recommended first-line therapy among other [10]. Most of our patients received ABVD and we planned to continue this treatment in the pandemic conditions, as it was also recommended in the most recent European Hematology Association/European Society of Medical Oncology (EHA/ESMO) guidelines, since ABVD is an effective regimen with minimal myelotoxicity [23].

With ABVD chemotherapy, approximately 80% of patients with advanced stage cHL will achieve a CR [24], but eventually, up to one-quarter of the cases will develop disease progression [7]. Although CR rates at the EOT evaluation were comparable between the time periods analyzed, this was lower in cases diagnosed during the pandemic (72.7% vs. 85.2%). Since the percentage of cHL patients with advanced stages diagnosed during the pandemic was higher

(although not statistically significant) than that observed in the pre-pandemic era, the reason of this difference was most probably due to this.

6. Conclusion

In our study, SDI was significantly prolonged in the pandemic compared to the pre-pandemic period, but DTIs and treatment response rates were comparable between two time periods. Delay in the diagnosis may lead patients to be diagnosed at advanced stages, and as a result, this may be associated with inferior treatment outcomes. The pandemic we are experiencing has made the profession of medicine even more difficult, complicated and added a new dimension. Our study is important since it is one of the few studies evaluating the short-term effects of the pandemic on diagnosis and management of cHL. In the future, multicenter studies using similar interval timepoint in cHL patients should be conducted, especially focusing on the impact of the pandemic on long-term outcomes including PFS and OS.

CRediT author statement

Selin Küçükyurt: Conceptualization, Methodology, Data curation, Formal analysis, Writing **Kübra Şahin:** Data curation, Writing **Umut Yılmaz:** Conceptualization, Methodology **Abdülkadir Erçalışkan:** Conceptualization, Methodology **Tuba Özkan Tekin:** Conceptualization, Methodology **Damla Ortaboz:** Conceptualization, Methodology **Tuğrul Elverdi:** Conceptualization, Methodology **Ayşe Salihoğlu:** Conceptualization, Methodology **Muhlis Cem Ar:** Conceptualization, Methodology **Şeniz Öngören:** Conceptualization, Methodology **Zafer Başlar:** Conceptualization, Methodology **Ahmet Emre Eşkazan:** Conceptualization, Methodology, Supervision, Writing, Reviewing and Editing. All authors approved the final draft.

Conflict of interest

All authors have no conflicts of interest to declare.

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Ethics approval

This study was approved by Ethics Committee on Non-Interventional Studies (20.09.2021, E-83088843.604.01.01-189181).

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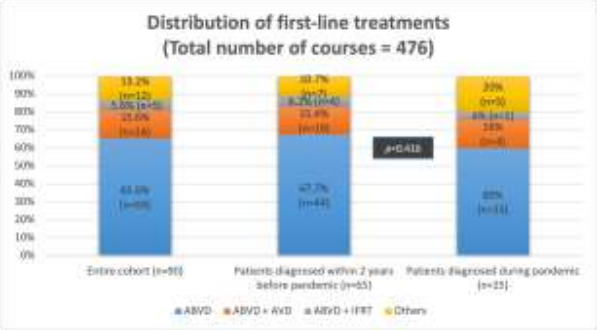

Figure 1. The distribution of first-line treatments (A, doxorubicin; B, bleomycin; BV, brentuximab vedotin; V, vinblastine; D, dacarbazine; IFRT, involved-field radiotherapy. Others; BV-AVD, BV-AVD+BV-D, ABVD+ABD, ABVD+AVD+BV-AVD, AVD+BV-AVD, AVD, ABVD+BV-AVD).

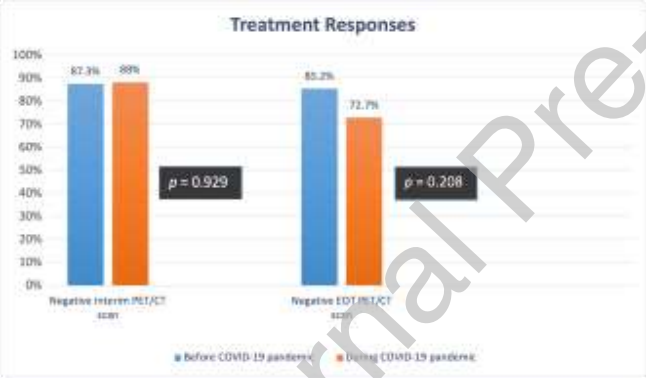

Figure 2. Comparison of treatment response rates before and during COVID-19 pandemic (EOT, end-of-treatment; PET/CT, Positron emission tomography-computed tomography).

Table 1. Demographic features and baseline characteristics of the patients (EBV, Epstein-Barr virus; IPS, International prognostic score).

Characteristics	**Total (n: 90)**	**01.03.18 – 01.03.20 (Before Covid-19 pandemic) (n: 65)**	**01.03.20 – 01.03.21 (During Covid-19 pandemic) (n: 25)**	***p* value**
Sex, n (%)				
Male	48 (53.3)	31 (47.7)	17 (68)	0.084
Female	42 (46.7)	34 (52.3)	8 (32)	
‡Age at diagnosis, years				
Median (Range)	33.5 (17 – 70)	31 (17 – 68)	40 (17 – 70)	0.215
Age categories, n (%)				
< 45 years	69 (76.7)	51 (78.5)	18 (72)	0.516
≥ 45 years	21 (23.3)	14 (21.5)	7 (28)	
> 60 years	10 (11.1)	7 (10.8)	3 (12)	0.868
Histological subtype, n (%)				0.893
Nodular sclerosis	43 (47.8)	31 (47.7)	12 (48)	
Mixed cellularity	33 (36.7)	24 (36.9)	9 (36)	
Lymphocyte rich	9 (10)	7 (10.8)	2 (8)	
Lymphocyte depletion	1 (1.1)	1 (1.5)	0	
Unclassified	4 (4.4)	2 (3.1)	2 (8)	
EBV positivity, n (%)	31 (34.4)	23 (35.4)	8 (32)	0.744
Stage, n (%)				0.384
Early (Stages I-II)	39 (43.3)	30 (46.2)	9 (36)	
Advanced (Stages III-IV)	51 (56.7)	35 (53.8)	16 (64)	
Early Stage (n: 39), n (%)				
Favorable	12 (30.8)	10 (33.3)	2 (22.2)	0.693
Unfavorable	27 (69.2)	20 (66.7)	7 (77.8)	
Advanced Stage (n: 53), n (%)				
IPS-3				
0 point	18 (34)	13 (35.1)	5 (31.2)	0.155
1-2 points	31 (58.5)	23 (62.2)	8 (50)	
3 points	4 (7.5)	1 (2.7)	3 (18.8)	
IPS-7				
0-2 points	24 (47.1)	15 (42.9)	9 (56.3)	0.079
3-4 points	17 (33.3)	15 (42.9)	2 (12.5)	
5-7 points	10 (19.6)	5 (14.3)	5 (31.3)	
Patients with B symptoms, n (%)	55 (61.1)	41 (63.1)	14 (56)	0.537
Bulky disease, n (%)	4 (4.4)	2 (3)	2 (8)	0.308
Extranodal involvement, n (%)	44 (48.9)	28 (43)	16 (64)	0.075

Time interval between symptoms onset and diagnosis, weeks Median (Range)	10 (4 – 48)	8 (4 – 48)	16 (4 – 36)	**0.042**
Time interval between diagnosis and initiation of chemotherapy, days Median (Range)	14 (1 – 64)	15 (1 – 64)	13 (1 – 35)	0.471
Time interval between diagnosis and initiation of chemotherapy, n (%) ≤14 days >14 days	48 (53.3) 42 (46.7)	32 (49.2) 33 (50.8)	16 (64) 9 (36)	0.208