

The changing trends of adult Hodgkin's disease in Saudi Arabia

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ABSTRACT

Objective. Hodgkin's disease is one of the most common malignant lymphomas affecting the younger population. This disease has diversified pathologies and clinical stages that necessitate a well optimized clinical management. Regular updating of epidemiological behavior of Hodgkin's disease is obvious from various parts of the world; however, studies from the Kingdom of Saudi Arabia (KSA) in this field are scanty and more than a decade old. The aim of this study was to investigate the current trends in presentation and distribution of Hodgkin's disease with special reference to gender, age, histopathological subtypes, and clinical stages of this disease in Saudi patients.

Methods: A total of 142 Hodgkin's disease patients attending 2 referral hospitals (King Khalid University Hospital and Security Forces Hospital) in Riyadh, KSA, were included in this study. The records from the questionnaires were analyzed retrospectively for determining the trends of Hodgkin's disease in Saudi adults, over a period of 15 years (1985-2000).

Results: There were 86 males and 56 females, with a male to female ratio of 1.53:1. The mean age of the patients was 28.63 years, while most of the patients were <40 years (80.3%). Nodular sclerosis was the most frequent pathology. Presence of B symptoms had a significant correlation with histology type as well as clinical stage of Hodgkin's disease. Time course analysis showed the increasing trend of Hodgkin's disease frequency, especially in younger adults. The rate of nodular sclerosis continued to increase during the entire course of study whereas the frequency of other histology types showed a decreasing trend during 1992-2000.

Conclusion: To the author's knowledge, this is the largest case series of adult Hodgkin's disease from KSA. The results of this study revealed a different pattern of Hodgkin's disease as compared to earlier studies reported from this region. These findings provide valuable insights in the understanding of current epidemiological features of Hodgkin's disease in KSA.

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Thomas Hodgkin was the first who described malignant lymphomas as a clinical entity in 1832. The so-called Hodgkin's disease is one of the most common forms of malignancies in young adults, although a bimodal age distribution is generally accepted. The characteristic morphological feature of Hodgkin's disease is the cellular composition of the tumor tissue containing a small number of neoplastic Reed Sternberg cells and a major population of non-neoplastic lymphocytes, histiocytes, neutrophils, fibroblasts, eosinophilis and plasma cells. Hodgkin's disease has been classified into 4 pathological subtypes

(nodular sclerosis, mixed cellularity, lymphocyte predominance, and lymphocyte depleted) and 4 disease stages (stages I, II, III and IV) for analyzing the clinical and epidemiological behavior of disease.^{1,2} The specifically known B symptoms including fever, night sweats and weight loss may also accompany the diagnosis of Hodgkin's disease. Consequently, the mode of presentation of Hodgkin's disease appears to be quite heterogeneous and vary considerably with respect to prognosis and disease management.³⁻⁶

In the recent years, several studies have reported the time course trends of Hodgkin's disease in various

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populations.^{1,7-10} Whereas, fewer attempts have been made to describe the features of Hodgkin's disease in KSA.¹¹⁻¹⁴ These studies being more than a decade older may not reflect the current pattern of Hodgkin's disease in this region. The epidemiological data regarding cancer in KSA is less documented, apparently due to the fact that the National Cancer Registry (NCR) could be established only in 1992, which started collecting data in 1994. According to the NCR, Hodgkin's disease is ranked 10th among the most common cancers in males with a crude relative frequency of 3.9% in a total of 8791 cancer patients registered.¹⁵ The aim of this study was to determine the current clinico epidemiological and pathological patterns of Hodgkin's disease in KSA.

Methods. The Hodgkin's disease patients over 12 years of age (adult category), attended in King Khalid University Hospital (KKUH), and Security Forces Hospital (SFH), Riyadh, KSA, during 1985-2000 were included in this study. Out of 159 cases of Hodgkin's disease, 17 patients were excluded from the analysis due to undocumented histopathology (3 patients), incomplete data entry (3 patients) and <12 years of age (11 patients). The remaining 142 cases fulfilled the eligibility criteria for this study. Hospital files of all patients were reviewed and information on age, gender, histological features, and detailed clinical presentation were recorded in a structured questionnaire. The Ann Arbor staging classification for Hodgkin's disease was used for disease diagnosis.¹⁶ This included the main presenting complaints, detailed physical examination, complete hemogram, liver and renal function tests, chest radiograph and bone marrow aspiration and biopsy findings. Out of 142 patients, computed tomography of the abdomen and thorax was carried out for 126 patients and 99 patients underwent gallium scanning. Lymph node or tissue biopsy specimens from all patients were processed, embedded in paraffin blocks and ultra thin sections were stained with hematoxylin and eosin and reticulin for light microscopy observation. Immuno histochemical staining was performed using a panel of monoclonal antibodies against CD20, CD15, CD30, CD3 and CD45 RO for 115 patients.

Statistical analysis. The records were fed in the statistical software SPSS for Windows (Version 10.0) for analyzing frequency distribution and cross tabulation. The non-parametric comparisons were carried out using χ^2 test. Spearman's test was adopted for correlation studies on the categorical data. A P value of <0.05 was considered as statistically significant.

Results. Among the 142 Hodgkin's disease patients, 86 (60.6%) were males and 56 (39.4%) were females with a male to female ratio of 1.53:1. The mean age of the patients was 28.63 years, ranging from 12-78 years, with a SD of 14.90 years. The categorical distribution of patients from various age groups is given in **Table 1**. The frequency of patients in the age groups of 12-20 years

(38.7%) and 21-30 years (27.5%) was comparatively higher than the patients in the age groups of 31-40 years (14.1%), 41-50 years (8.5%), 51-60 years (6.3%), and >60 years (4.9%). Eighty-four patients (59.2%) had histologic features of nodular sclerosis (**Table 2**). The next most frequent histologic type was mixed cellularity (22.5%) followed by lymphocyte predominant (14.8%), while only 4 (2.8%) patients belonged to the histology of lymphocyte depleted (**Table 2**). The male to female ratios in relation to histopathology were: lymphocyte predominant (4.25:1), lymphocyte depleted (3:1) and mixed cellularity (2.2:1). On the other hand, the frequency of nodular sclerosis was comparatively higher in females (67.9%) as compared to males (50%). The histology of one patient was not specified. **Table 3** shows the distribution of patients according to various clinical stages of Hodgkin's disease. Twenty patients (14.1%) had stage I disease; 48 (33.8%) had stage II; 32 (22.5%) had stage III and 41 (28.9%) had stage IV. The disease stage was not specified in one patient. The relationship between clinical stage of disease and histologic subtypes is given in **Table 4**. The findings on the relationship between nodular sclerosis or mixed cellularity and the disease stage remained inconclusive, whereas a significant association was observed between the clinical stage and the histologic subtype of lymphocyte predominance or lymphocyte depleted ($\chi^2 = 20.47$, $p < 0.05$). The frequency of lymphocyte predominance was higher in the patients with disease stages I/II as compared to stages III/IV, whereas approximately the reverse was true with lymphocyte depleted histology (**Table 4**).

Seventy patients (49.3%) were reported with B symptoms (fever, night sweats, weight loss), without any association with the gender of patients ($\chi^2 = 0.183$, $p = 0.669$, **Figure 1a**). Patient's age also had no correlation with the frequency of B symptoms ($r = 0.053$, $p = 0.53$, **Figure 1b**). The frequency of B symptoms was highest (100%) in the patients with lymphocyte depleted histology, and the least (23.81%) in patients with lymphocyte predominant histology ($\chi^2 = 13.92$, $p < 0.01$). In patients with morphology of nodular sclerosis or mixed cellularity, B symptoms were found in 63% and 50% (**Figure 1c**). A significant correlation ($r = 0.358$, $p < 0.001$) was observed between the frequency of B symptoms and the disease stages; stage I (10%), stage II (54.2%), stage III (56.25%) and stage IV (75.6%) (**Figure 1d**).

The time course analysis of data on the basis of diagnosis date revealed an increasing trend of Hodgkin's disease (**Figure 2a**), especially in the age group of 12-40 years (**Figure 2b**). The incidence of nodular sclerosis continuously increased since 1984 and peaked during 1999-2000, while the frequencies of the other 3 histology types showed slight variations and a decreasing trend following the year 1992-2000 (**Figure 2c**). There was no stable time course trend in the frequency of Hodgkin's disease patients with different clinical stages of disease (**Figure 2d**).

Discussion. We observed an excess of male patients in our series. However, the male to female ratio of 1.53:1 is comparatively less than on what has been reported earlier from KSA (2.2:1)¹⁴ and many other developing countries¹⁷⁻²¹ but is closer to the ratio 1.45:1, reported from the United Kingdom and other Western European states.²² On further analysis of the relationship of gender to histopathologic classification in our patients, there was a comparatively higher number of females with nodular sclerosis pathology, a finding which is similar to that observed in studies from other parts of the globe.^{17,23} In our study, advanced stage (stage III or IV) disease was seen in 52.3% patients. This presentation is comparatively less than a frequency range of 65-95% reported earlier from KSA and other developing countries.^{12,13,17,18,24} Our results showed an increasing trend of Hodgkin's disease in young adults. Several studies have reported a bimodal age distribution of Hodgkin's disease; an early peak appears in young adulthood and the another peak in advanced age.^{1,25} Most of the patients in our series were in the second and third age decade, whereas their frequency decreased with advancing age. The absence of age related bimodality might be linked with the possibilities that most of the cases of Hodgkin's disease are either diagnosed at an early stage or the older patients are being diagnosed as non-Hodgkin's lymphoma, due to availability of improved diagnostic tools.²⁶ We observed the prevalence of B symptoms in Hodgkin's disease patients to be 49.3%, which is comparatively less than a recently published report.²⁷ The presence of B symptoms showed a significant association with the histopathology and the clinical stage of Hodgkin's disease. A multivariate analysis of adverse prognostic factors has concluded that absence of B symptoms plays a significant role in progression free survival of Hodgkin's disease patients.⁶

One of the most important findings of this study is the steep rise in the incidence of nodular sclerosis histopathology, suggesting that a new pattern of Hodgkin's disease is emerging in KSA, which is in sharp contrast to the morphological pattern reported in the past.¹¹⁻¹⁴ In 1985, Mughal et al¹² in a retrospective review of hospital case series, reported an excess of mixed cellularity morphology with male to female ratio of 2.38:1. In a prospective study of adult Hodgkin's disease, Al-Idrisi et al¹³ observed an excess of mixed cellularity morphology and advanced stage presentation in 70% of patients with this disease. Later on, Koriech and Al-Kuhaymi¹⁴ reported the histologic features of Hodgkin's disease to be: mixed cellularity (55%), nodular sclerosis (29%), lymphocyte predominance (4%) and lymphocyte depleted (4%). Kingdom of Saudi Arabia has seen unprecedented urbanization and economic growth in the last 2 decades. There have been remarkable improvements in its health services and the standard of living. It is possible that this rapid development has influenced the character of Hodgkin's disease, which is related to both environmental and host factors. Interestingly, studies from Kuwait and United

Table 1 - Age distribution of Hodgkin's disease patients.

Age category (years)	n (%)	Male to female ratio
12-20	55 (38.7)	1.03:1
21-30	39 (27.5)	1.60:1
31-40	20 (14.1)	4.00:1
41-50	12 (8.5)	2.00:1
51-60	9 (6.3)	0.80:1
>60	7 (4.9)	6.00:1
Total	142 (100)	1.53:1

Table 2 - Histologic distribution of Hodgkin's disease patients.

Histology	n (%)	Male to female ratio
Nodular sclerosis	84 (59.2)	1.13:1
Mixed cellularity	32 (22.5)	2.20:1
Lymphocyte predominant	21 (14.8)	4.25:1
Lymphocyte depleted	4 (2.8)	3.00:1
Other	1 (0.7)	
Total	142 (100)	1.53:1

Table 3 - Distribution of clinical stages in Hodgkin's disease patients.

Clinical stage	n (%)	Male to female ratio
Stage I	20 (14.1)	2.33:1
Stage II	48 (33.8)	1.00:1
Stage III	32 (22.5)	1.91:1
Stage IV	41 (28.9)	1.73:1
Unspecified	1 (0.7)	1.00:0
Total	(142) (100)	1.53:1

Table 4 - Clinical stages of various histological types of Hodgkin's disease.

Histology	Clinical stages				Total
	I	II	III	IV	
Nodular sclerosis	8	27	21	25	81
Mixed cellularity	4	10	7	10	31
Lymphocyte predominant	8	9	2	2	21
Lymphocyte depleted	0	0	1	3	4
Other	0	2	1	1	4
Total	20	48	32	41	141

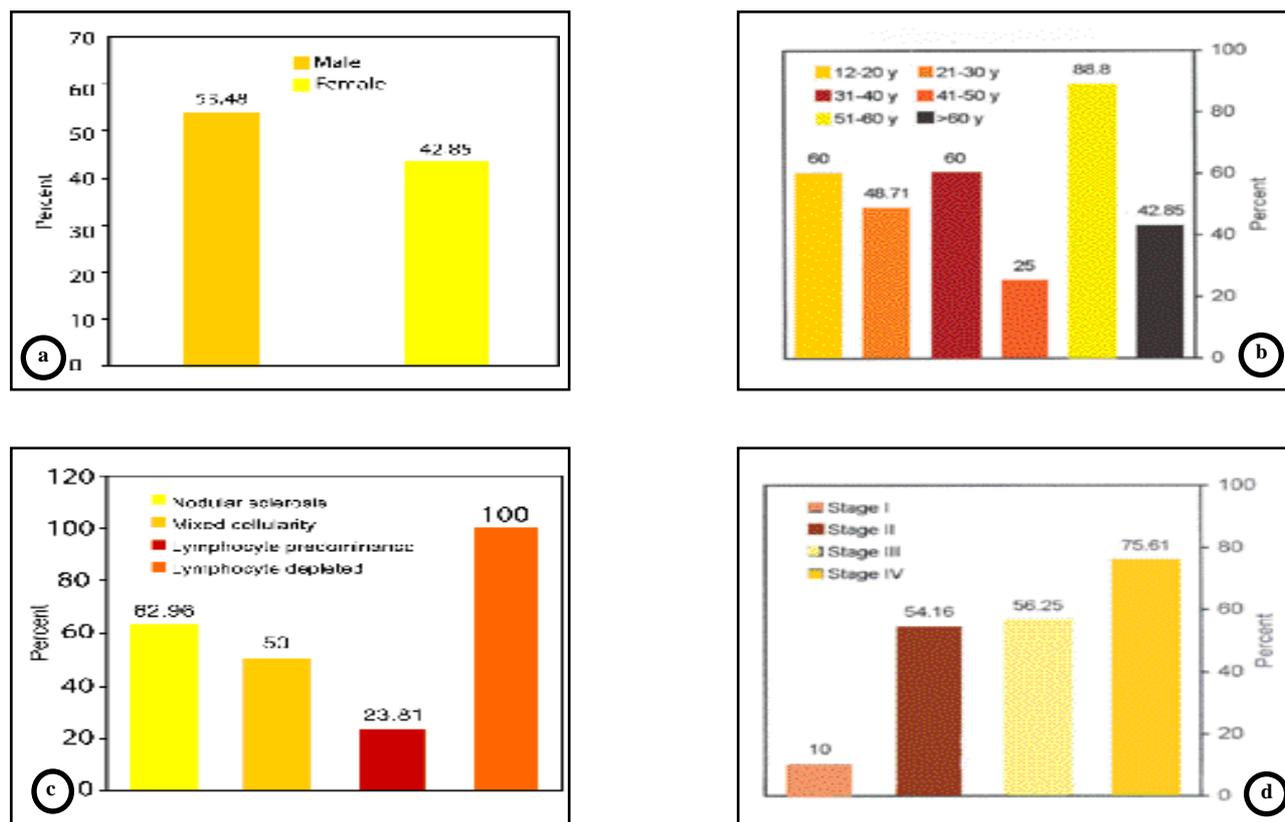


Figure 1 - Effect of a) gender, b) age, c) histology type and d) clinical stage of disease on the frequency of "B" symptoms (fever, night sweats, or weight loss) in Hodgkin's disease patients.

Arab Emirates, where a similar upsurge in the advancements of economic and healthcare facilities has occurred, also reveal a changing trend towards nodular sclerosis morphology of Hodgkin's disease.^{28,29} However, recent studies on various populations have reported increasing rate of both nodular sclerosis^{5,7,8} or mixed cellularity^{16,30,31} type of histopathologies.

The role of Epstein-Barr virus (EBV) infection in the etiology of Hodgkin's disease has received considerable attention. Numerous reports have suggested a strong association between EBV infection and the development of Hodgkin's disease.³²⁻³⁴ However, the increasing trends of nodular sclerosis histology in this study may not be explained solely on the basis of EBV risk factor due to following reasons. The presence of EBV genome is primarily associated with the mixed cellularity type,³⁵ which shows a persistently decreasing pattern in our study (Figure 2c). A significantly high prevalence of EBV has been reported in mixed cellularity as compared to nodular sclerosis in various studies from KSA (88% versus 46%)³⁶ and other places (58-68% versus 18-24%).^{37,38} Takeuchi et al³⁹ have recorded a decreasing trend of EBV positive nodular sclerosis Hodgkin's

disease during the last 4 decades, whereas Clarke et al⁴⁰ have observed that EBV positive Hodgkin's disease patients are less likely to have nodular sclerosis histology. Furthermore, recent studies have shown that EBV positive Hodgkin's disease patients belong to the 2 extreme age groups, either pediatric or old age.^{34,40-43} Recently, Flavell et al⁴⁴ have suggested that Hodgkin's disease of childhood and elderly is commonly EBV associated, whereas the adult Hodgkin's disease is not significantly associated with EBV infection. In this study, the majority of patients were in the age range of 12-40 years, while the participation of patients with extreme ages was minimal (<12 years = 0; >60 years = 4.9%). A possible role of delayed exposure to EBV in the pathogenesis of adult Hodgkin's disease may not be fully ruled out⁴⁵ and should be intensively investigated by detecting various sub types of EBV in adult Hodgkin's disease patients from KSA.

The data presented here reflect the current epidemiological features of Hodgkin's disease in KSA. Although our findings clearly demonstrate changing trends of Hodgkin's disease in Saudi patients, it may be

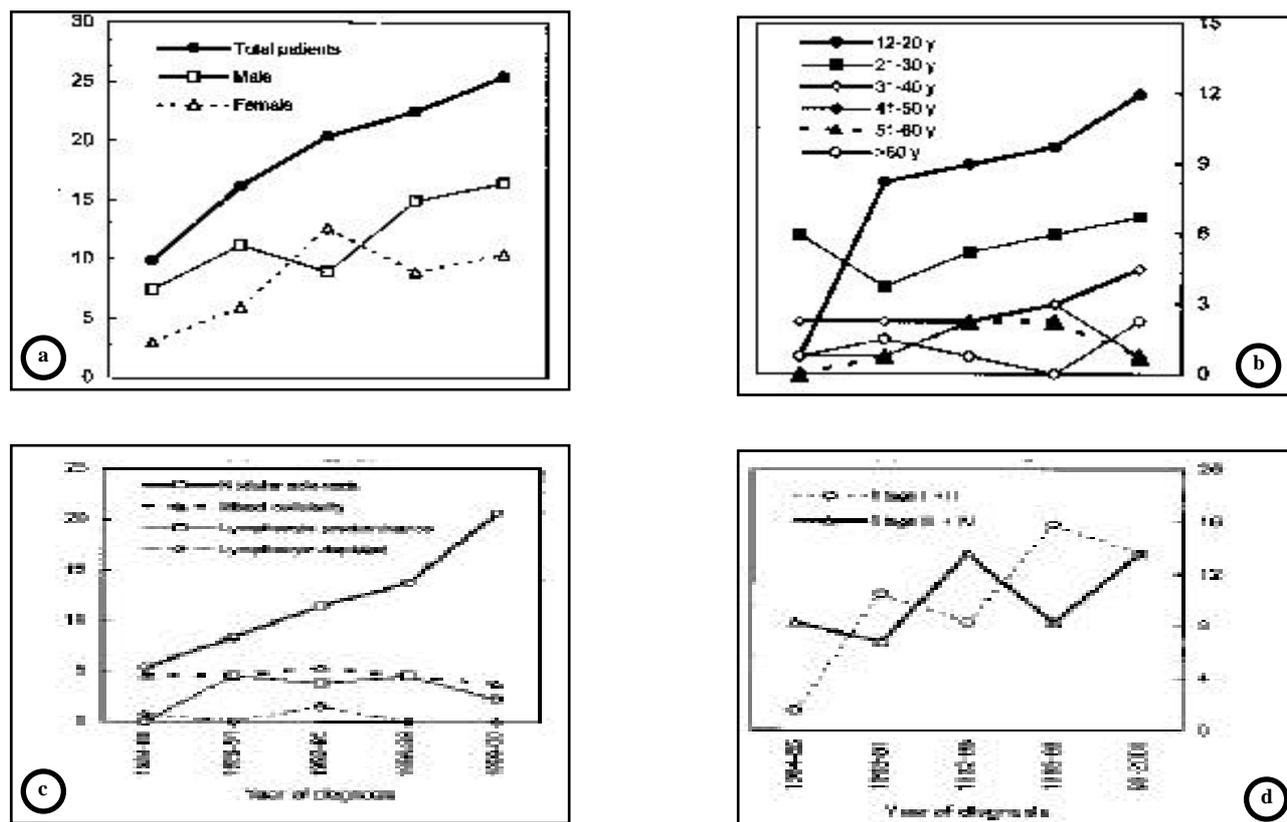


Figure 2 - Year-wise trends showing the frequencies of Hodgkin's disease patients according to a) gender, b) age category, c) histology type and d) clinical stage of disease.

too premature to draw any firm conclusion from these results. The authors however feel that there is a dire need for population-based large collaborative studies, to investigate the time trends and true epidemiology of Hodgkin's disease.

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