RESEARCH ARTICLE

Factors Associated with Delayed Diagnosis of Lymphomas: Experience with Patients from Hematology Centers in Morocco

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Abstract

Background: Moroccan cancer patients usually have to go through several steps before they are diagnosed. It is important to assess factors associated with diagnosis delay for lymphomas, which might have significant effects on survival. The aim of this study was to determine factors leading to late diagnosis of lymphomas. **Methods:** A cross-sectional study was conducted with three hematology centers in Morocco in 2008, to analyze the impact of sociodemographic and clinical factors on delay-time from symptoms to diagnosis. **Results:** A total of 151 patients were included in the study. Late delay was significantly associated with gender, (for men compared to women: OR=2.46; 95% CI: 1.06-5.74), to marital status (not married: OR=2.50; 95% CI: 1.06-5.92) and low socioeconomic level (OR=5.82; 95% CI: 2.23-15.17). Late medical delay was significantly associated with having three or more medical visits before diagnosis (Adjusted OR=5.67; 95% CI: 2.55-12.59). Late total delay was observed for patients with three children or less (adjusted OR=4.39; 95% CI: 1.32-14.56), those who were non-married (adjusted OR=2.49; 95% CI: 1.07-5.81), had a non Hodgkin's lymphoma (Adjusted OR=2.08; 95% CI: 1.06-4.00) or featuring three or more medical visits before the diagnosis (Adjusted OR=2.13; 95% CI: 0.99-5.88). **Conclusion:** This analysis provides a basis for understanding the sources, extent, and root causes of lymphoma diagnostic delays. The findings appear crucial for system-wide interventions aimed to facilitate clinical management of patients with lymphoma and to improve prognosis and quality of life.

Keywords: Lymphomas- sociodemographic factors- patient delay- medical delay- diagnosis delay

Introduction

Moroccan cancer patients usually have to go through several steps before they are diagnosed (Lalla Salma Foundation for Prevention and Control of Cancer, 2008). These steps include onset of symptoms, medical help-seeking behavior, referral to oncology hospital, oncology hospital appointment, diagnosis and treatment. In a national study, it was observed that patients' satisfaction towards waiting time and hospital access was significantly lower in patients having a medical appointment and differed significantly according to cancer localization (Obtel et al., 2011). Reducing the lengthy duration before the diagnosis is considered to bring survival advantages (Howell, Smith and Roman, 2006). Therefore, it is important to assess the factors associated to diagnosis delay of lymphomas, in which delays might have a significant effect on survival (Summerfield, 2000). Although some forms of lymphoma can stay indolent for years (lymphocyte-predominant HL), most follow a fatal course in days, weeks or months without early treatment (Morley-Jacob and Gallop-Evans, 2008). Little is known about the pathway between onset of lymphoma symptoms and its diagnosis, or factors influencing the duration from one to the other (Howell, Smith and Roman, 2008). Around the world, only few studies have investigated the time intervals between steps on the pathway to diagnosis. They have identified the interval between onset of symptoms and help-seeking behavior as the longest (Howell, Smith and Roman, 2006; Summerfield, 2000). To our knowledge, no study exploring delayed diagnosis of lymphoma patients has ever been conducted in Morocco. The aim of this study was to analyze socio-demographic and clinical characteristics associated to delayed lymphoma diagnosis in Moroccan hematologic hospital centers.

Materials and Methods

Methods

This cross-sectional study was conducted at two

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hematology centers in Morocco (IBN Rochd of Casablanca and the National Institute of Oncology (NIO) of Rabat) over a period of 2 months starting in June 2008. Informed consent and local ethical committee approval was obtained.

Patients

Patients had to be diagnosed lymphoma, aged 16 years or older, hospitalized or attending a hospital appointment for treatment and to be mentally fit to complete a questionnaire.

Questionnaire and data collection

Data was collected through face to face questionnaires with the patients, and supplemented with their medical records. The information was collected by oncology residents of the hematologic centers (Rabat, Casablanca) selected and trained to administer the questionnaire. The socio-demographic and clinical data were collected for each patient including age, sex, educational level, marital status, residence area, type of lymphoma, lymphadenopathies, number of medical visits before the diagnosis, etc. The dates of first symptom, first consultation and first diagnosis were obtained. Patient delay was defined as the time between date of first symptom and date of first consultation; medical delay as the time between first consultation and date of diagnosis and total delay as the sum of patient delay and medical delay. We took 2 months for patient delay, 1month for medical delay, and 3 months for total delay as cut off points to dichotomize the sample in to either early or late delay period. These delay periods were chosen based on the hematologist team treating lymphoma patients on a routine basis at the two centers. They were asked to choose 'acceptable' delay, based on their medical knowledge and taking into account the socio-economic conditions of their patients.

Data Analysis

Descriptive statistics and frequencies were computed for each variable in the questionnaire. Patients were stratified into two distinct patient groups according to age (<50 years versus ≥50 years), in order to obtain an equivalent number of patients per group. We analysed the differences between patients who had less than three medical visits before diagnosis and those who had three or more. Univariate analysis was performed using parametric (Chi2 test) and nonparametric (Fisher test) tests according to the conditions. Multivariate logistic regression analysis was undertaken to assess the associations between the different delays in lymphoma diagnosis (as the dependent variables) and socio-demographic and clinical characteristics, adjusting for potential confounding factors. The list of the explanatory variables was established according to the results of the univariate analysis. Variables associated with the outcome with a p value <0.25 were included in a step-wise multiple logistic regression analysis. The age was a forced variable included in the model, since a UK study exploring the relationship between socio-demographic factors and the components of diagnostic delay showed that age was significantly

associated to total delay of non Hodgkin's lymphoma (Neal and Allgar, 2005). Adjusted ORs and 95% CIs were calculated. Statistical analysis was performed using statistical software: SPSS version 17.0 and SAS 9.2.

Results

Socio-demographical and Clinical characteristics

This study included 151 patients (96 from the IBN

Table1. Socio-Demographic and Clinical Characteristics of Patients Affected by Lymphomas (Non-Hodgkin's Lymphomas and Hodgkin's Lymphoma)

	N (%)
Age	
≤ 50 years	98 (65.3)
> 50 years	52 (34.7)
Gender (n=147)	
Male	75 (51.0)
Female	72 (49.0)
Marital status (n=148)	
Married	91 (61.5)
Unmarried/Divorced/Widowed	57 (38.5)
Number of children (n=105)	
≤ 3 Children	57 (54.3)
> 3 Children	48 (45.7)
Occupation (n=147)	
Active	48 (33.3)
Inactive	96 (66.7)
Educational level (n=144)	
Illiterate	71 (49.3)
Primary/Secondary/University school level	73 (50.7)
Socioeconomic level (n=142)	
Low	87 (61.3)
Moderate or high	55 (38.7)
Residence areas (n=130)	
Urban	45 (34.6)
Rural	85 (65.4)
Social insurance (n=149)	
No	116 (77.9)
Yes	33 (22.1)
Type of lymphoma (n=130)	
Non-Hodgkin's lymphoma	70 (53.8)
Hodgkin's lymphoma	60 (46.2)
Family histories of lymphomas (n=150)	
No	135 (90.0)
Yes	15 (10.0)
Lymphadenopathy (n=147)	
No	53 (36.1)
Yes	94 (63.9)
Number of medical visits before diagnosis (n=147)	
< 3	72 (49.0)
≥ 3	

Table 2. Association of Socio-Demographic and Clinical Factors and Patient's Delay

	Univariate	analysis		Multivariate analysis	
	<2mois (%)	≥2mois (%)	p	Adjusted OR (95% CI)	p
Age (n=139)					
≤ 50 years	65.3	70.7	0.53	Referent	0.92
> 50 years	34.7	29.3		0.95 (0.38-2.41)	
Gender (n=136)					
Male	47.9	63.4	0.1	2.46 (1.06-5.74)	0.03
Female	52.1	36.6		Referent	
Marital status (n=137)					
Married	67.7	48.8	0.04	Referent	0.03
Unmarried/Divorced/Widowed	32.3	51.2		2.50 (1,06-5,92)	
Number of children (n=99)					
≤ 3 Children	47.9	64.3	0.14		
> 3 Children	52.1	35.7			
Working (n=136)					
Active	32.0	38.5	0.47		
Inactive	68.0	61.5			
Educational level (n=136)					
Illiterate	50.0	45.0	0.59		
Primary/Secondary/University school level	50.0	55.0			
Socioeconomic level (n=134)					
Low	51.6	82.9	<10-3	5.82 (2.23-15.17)	<10-4
Moderate or high	48.4	17.1		Referent	
Residence areas (n=123)					
Urban	59.0	51.4	0.43		
Rural	41.0	48.6			
Social insurance (n=138)					
Yes	22.4	17.5	0.52		
No	77.6	82.5			
Type of lymphoma (n=121)					
Non-Hodgkin's lymphoma	61.0	38.5	0.02		
Hodgkin's lymphoma	39.0	61.5			
Family history of lymphoma (n=139)					
No	92.9	85.4	0.17		
Yes	7.1	14.6			
Lymphadenopathy (n=139)					
No	42.9	22.0	0.02		
Yes	57.1	78.0			

Rochd hematologic center of Casablanca and 55 from the National Institute of Oncology (NIO) in Rabat. No patients refused to participate in the study.

The characteristics of the 151 patients are summarized in Table 1. The mean age was 45 years with 17 years of standard deviation (Range, 17-85 years). Adults younger than 50 years comprised 65.3% of the patients. The number of female and male patients was nearly equal. Most of the patients were illiterate (49.3%), married (61.5%), from rural areas (65.4%), from low socioeconomic level (61.3%) and had no social insurance (77.9%). A third of them were active and 66.7% were unemployed. Non-Hodgkin's lymphoma was slightly more frequent, with a proportion of 53.8%. 10% of patients had family histories of lymphoma. Almost 64% of the patients had lymphadenopathies. Table 1 also shows that 51.0% of the study patients had at least 3 medical visits before diagnosis.

Patient delay and socio-demographic and clinical factors
Table 2 describes the various socio-demographic and clinical factors and their association to patient delay. 34.7% consulted late (≥2 months) and 58.0% consulted in a short delay (<2months) (7.3% unknown). In the univariate analysis, it was observed that patients were more likely to consult late if they were not married (unmarried, divorced

Table 3. Association between Medical Delay and Socio-Demographic and Clinical Factors

	Univariate analysis			Multivariate analysis	
	<1mois(%)	≥1mois(%)	p	Adjusted OR (95% CI)	p
Age (n=139)					
≤ 50 years	66.0	66.3	0.56		
> 50 years	34.0	33.7			
Gender (n=136)					
Male	55.8	49.4	0.47		
Female	44.2	50.6			
Marital status (n=137)					
Married	66.0	60.7	0.53		
Unmarried/Divorced/Widowed	34.0	39.3			
Number of children (n=99)					
≤ 3 Children	50.0	55.5	0.63		
> 3 Children	50.0	45.5			
Working (n=136)					
Active	39.2	30.6	0.3		
Inactive	23.5	34.1			
Educational level (n=136)					
Illiterate	53.8	46.4	0.4		
Primary/Secondary/University school level	46.2	53.6			
Socioeconomic level (n=134)					
Low	72.0	54.8	0.04	2.10 (0.93-4.72)	0.07
Moderate or high	28.0	45.2		Referent	
Residence areas (n=123)					
Urban	66.7	62.3	0.63		
Rural	33.3	37.7			
Social insurance (n=138)					
Yes	18.9	24.4	0.62		
No	81.1	77.6			
Type of lymphoma (n=121)					
Non-Hodgkin's lymphoma	48.9	56.6	0.41		
Hodgkin's lymphoma	51.1	43.4			
Family history of lymphoma (n=139)					
No	90.6	90.7	0.97		
Yes	9.4	9.3			
Lymphadenopathy (n=139)					
No	30.0	42.7	0.14		
Yes	70.0	57.3			
Number of medical visits before diagnosis (n=139)					
< 3	75.5	34.9	$<10^{-5}$	Referent	
≥ 3	24.5	65.1		5.67(2.55-12.59)	$<10^{-3}$

or widowed) (p=0.04), from a lower socioeconomic level (p=0.001), with Hodgkin's lymphoma (p=0.02), or with lymphadenopathies (p=0.02). After adjustment in the multivariate analysis, some factors were still significant: late patient delay for men (OR=2.46; 95% CI: 1.06-5.74), unmarried, Divorced or Widowed (OR=2.50; 95% CI: 1.06-5.92) and lower socioeconomic level (OR=5.82; 95% CI: 2.23-15.17) (Table 2).

Medical delay and socio-demographic and clinical factors

Table 3 shows the results from univariate analysis of the association between medical delay and socio-demographic and clinical characteristics.

Around 57.3% were diagnosed late (>1 month) and 35.3% were diagnosed in a short delay (<1month) (7.3% unknown). Compared to patients with moderate or high socioeconomic level, those with low socioeconomic

Table 4. Association Between Total Delay and Socio-Demographic and Clinical Factors in Lymphomas Diagnosis

	Univariate	analysis		Multivariate analysis	
	< 3mois (%)	≥ 3mois (%)	p	Adjusted OR (95% CI)	p
Age (n=139)					
≤ 50 years	61.7	70.5	0.28	Referent	0.61
> 50 years	38.3	29.5		1.29 (0.47-3.53)	
Gender (n=136)					
Male	51.7	52.6	0.92		
Female	48.3	47.4			
Marital status (n=136)					
Married	71.2	55.8	0.07	Referent	<0.01
Unmarried/Divorced/Widowed	28.8	44.2		6.27 (1.66-23.73)	
Number of children (n=99)					
≤ 3 Children	39.5	62.5	0.02	3.45 (1.21-9.81)	0.02
> 3 Children	60.5	37.5		Referent	
Working (n=135)					
Active	30.0	37.3	0.37		
Inactive	70.0	62.7			
Educational level (n=135)					
Illiterate	56.9	42.9	0.1		
Primary/ Secondary/University school level	43.1	57.1			
Socioeconomic level (n=133)					
Low	58.9	62.3	0.69		
Moderate or high	41.1	37.7			
Residence areas (n=122)					
Urban	70.6	59.2	0.19		
Rural	29.4	40.8			
Social insurance (n=137)					
Yes	16.7	24.7	0.25		
No	83.3	75.3			
Type of lymphoma (n=121)					
Non-Hodgkin's lymphoma	53.1	53.5	0.96	2.08 (1.06-4.00)	0.03
Hodgkin's lymphoma	46.9	46.5		Referent	
Family histories of lymphoma (n=138)					
No	95.0	87.2	0.12		
Yes	5.0	12.8			
Lymphadenopathy (n=138)					
No	33.3	37.2	0.64		
Yes	66.7	62.8			
Number of medical visits before diagnosis (n=138)					
< 3	60.0	41.0	0.03	2.13 (0.99-5.88)	0.05
≥ 3	40.0	59.0		Referent	

level were significantly more likely to be diagnosed late (p<0.04). Patients having three or more medical visits before the diagnosis were diagnosed late (p<10-5). There was no significant variance between the medical delay in lymphoma diagnosis and the other factors. In multivariate analysis, only patients having three or more medical visits before diagnosis showed a significant relation to late medical delay (Adjusted OR=5.67; 95% CI:

2.55-12.59). However, low socioeconomic level reached borderline statistical significance (Adjusted OR=2.10; 95% CI: 0.93-4.72) (Table 3), making it a factor deserving attention.

Total diagnosis delay and socio-demographic and clinical factors

Fifty-two percent of the population studied was

diagnosed at a late total delay (>3months) and 40.0% in a short delay (8.0% unknown). As is shown in Table 4, the univariate analysis reported that patients were more likely to be diagnosed late if they had three children or less compared to those who had more than three children (p=0.02), and if they had three or more visits before the lymphoma diagnosis (p=0.03). No other significant association between total delay and socioeconomic or clinical factors was observed. In multivariate analysis, late total delay was observed for patients not married (unmarried, widowed or divorced) (Adjusted OR=6.27; 95% CI: 1.66-23.73), with three children or less (Adjusted OR=3.45; 95% CI: 1.21-9.81), having non Hodgkin's lymphoma (Adjusted OR=2.08; 95% CI: 1.06-4.00) and having less than three medical visits before the diagnosis (Adjusted OR=2.13; 95% CI: 0.99-5.88) (Table 4).

Discussion

To evaluate lymphoma diagnosis delay in the Moroccan oncology hospitals, a questionnaire was used to determine socio-demographic and clinical factors related to late diagnosis of lymphomas in the two only hematologic centers.

Analysis showed a high proportion of a late total delay (52% diagnosed at a > 3months).

The results show significant associations between late diagnosis of lymphomas and some of the socio-demographic and clinical variables. These findings have significant implications for further research and policy development. When considering the patient delay, and looking through lenses of socio-demographical and clinical features, it was observed that men have late patient delay compared to women; this could be explained by the assumption that women worry more about cancer than men do (Sach and Whynes, 2009). Also, patients who were not married have significantly late patient delay.

The Explanation could be that, married people are generally more stable and more interested in their health status, and worry more about their disease than their not married contemporaries. Some studies have shown that not married patients are less likely to consult than those married (Coombs and Robert, 1991; Kiecolt-Glaser et al., 2001; Knox et al., 2002; Politi et al., 2008).

In addition, lower socioeconomic levels seem to influence patient delay before consultation: patients were more likely to consult later if they were from low socioeconomic level. This could be explained by the high level of illiteracy, the socioeconomic deprivation and the distance and location of health care services in low socioeconomic categories of the population (Maheswaran et al., 2006; Krieger et al., 2002). Our study showed in univariate analysis that, patients with lymphadenopathies were more likely to consult late than those without. This could be explained by the fact that diseases other than lymphomas can produce similar symptoms (for example tuberculosis), responsible for delays in consultation, since tuberculosis has a high incidence in Morocco (83.1 per 100,000 in 2015) (Santé en Chiffre 2014). Moreover, it was observed that, even after their consultation, the patients with lymphoma, particularly those in whom symptoms

were atypical or included lymphadenopathies, could be initially referred to disciplines other than haematology (Howell, Smith and Roma, 2008).

In medical delay, patients were more likely to be diagnosed later if they were from a low socioeconomic level. This could be explained by the high cost of diagnosis and treatments of cancer, including lymphomas, in the Moroccan context. In addition, two thirds of the Moroccan populations are not covered by social insurance for medical care, the majority from low socioeconomic levels (Lalla Salma Foundation for Prevention and Control of Cancer, 2008). It suggests that lymphoma patients who lack health insurance are more likely to receive less care for financial reasons (Thorpe and Howard, 2003). Moreover, we also noticed that patients having at least three medical visits before the diagnosis were significantly diagnosed later. It has been shown that hospitalized patients have faster access to diagnostics tests, making an appropriate early diagnosis (Daly and Collins, 2006). In our context, patients are more likely to see many doctors before being hospitalized and getting their diagnosis. In addition, a UK study showed that due to the characteristics of this disease, patients with lymphoma continue to be referred to disciplines other than hematology (Howell, Smith and Roman, 2008). In medical delay, the different studies showed that the variation in time to diagnosis differed by type of lymphoma and derived areas. However, in the same studies, there was a significant association between late diagnosis and age (Howell, Smith and Roman, 2006), and lack of knowledge about lymphoma and the symptoms of this disease (Howell, Smith and Roman, 2008). The health system in Morocco is not regulated as it is in developed countries. Patients can go directly to the specialist without seeing the GP. In total delay, multivariate analysis showed that patients who were not married, who had non Hodgkin's lymphoma, who had three children or less and who had less than three medical visits before the diagnosis were significantly diagnosed with a late delay. Explanations for these results could be that married patients are more stable and likely to have increased familial support (Coombs and Robert, 1991, Kiecolt-Glaser et al., 2001; Knox et al., 2002; Politi et al., 2008). Furthermore, it was observed in this study that the type of lymphoma has an impact on the diagnostic delay: patients with non Hodgkin's lymphoma were more likely to be diagnosed late compared to those with Hodgkin's lymphoma. It could be explained by the fact that many of the symptoms of non-Hodgkin lymphoma are not specific enough to say that lymphoma is present, only a biopsy may diagnose non-Hodgkin lymphoma (Martin et al., 2007). In addition, patients with three children or less were more likely to be diagnosed late. It is important to note the more important impact of children on the parents' health in large families than in smaller families. Then it can be inferred that patients are healthier when they have an important family number (Ross, Catherine et al., 1990; Cal, 2009). Finally, we observed that less medical consultations were significantly associated to late diagnosis. This result suggests that the more a patient consult, the more he has a chance to be diagnosed early. These results are coherent with those found in UK

studies aimed to evaluate illness trajectories of patients with lymphoma (Howell, Smith and Roman, 2006 and 2008). Not taking into account medical classification of the patients' tumour's limits the results of our study. This was because clinical and anatomic-pathological stages of patients' cancer figured only in a few medical files. Other factors related to diagnosis delay have been noted in the literature Howell., Smith and Roman, 2006 and Howell, Smith and Roman, 2008) but were not taken into account here: stage, advanced-stage, site and size of the disease and some features of the symptoms related to each type of lymphoma. Moreover, there is little information on patients' attitudes following doctors' advices. Our study has stressed out many observations and facts. Thus, some recommendations ought to be formulated in order to bridge the gaps in the current medical care system. First, developing workshops to provide patients with information and more education about the potential symptoms of this disease is needed among the general public. The future workshops should inform patients and general practitioners about variations in the type, site and size of the lymphoma at each step on the pathway to lymphoma diagnosis, to reduce the time taken before to diagnosis. Thus, a standard protocol should be developed on how to inform patients and general practitioners. In order to implement such a project, it is necessary to introduce referral guidelines and waiting-time targets for suspected cancers including lymphomas, as is reported in some UK studies, to ensure that general practitioners make appropriate hospital referrals (Howell, Smith and Roman, 2006, 2007 and 2008). In this regard and in parallel, an up-date of the existing procedures is highly recommended. Furthermore, for better medical and social equity, more oncology centers should be opened in the main Moroccan regions to tackle the accessibility to healthcare services. In March 2010, Morocco officially launched the National Plan of Prevention and Control of Cancer, aiming at reducing morbidity and mortality rates and improving survival and quality of life of cancer patients by promoting prevention, early detection and effective screening practice; by improving diagnosis, treatment, and palliative care services; and by supporting the development of facilities and research for cancer through- out the country (Lalla Salma Foundation for Prevention and Control of Cancer, 2010). In fact, under the main activities of this National Plan of Prevention and Control of Cancer and for better understanding of late diagnosis in lymphoma, a larger study (including other oncology centers) would be useful complementary work to ours. Longitudinal research (mainly cohorts in order to give more scientific evidence using advanced statistical analysis (survival analysis) would also be very important in detecting changes in diagnosis delay after any government's action in this domain.

This First study helped to identify populations at increased risk of late lymphoma diagnosis in Morocco. This analysis helped to understand the sources, extent, and root causes of diagnostic delays for lymphoma. These results are crucial for system-wide interventions aimed to facilitate the clinical management of patients with lymphoma and to improve prognosis and quality of life.

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