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RESEARCH ARTICLE

Haematolymphoid Tumours Karyotypes: A Moroccan Population Retrospective Study from 1992 to 2021

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Abstract

Background: Haematolymphoid tumours are a heterogeneous group of pathologies involving cells of the haematopoietic lineage. Data reported here focus on the results of a descriptive, general, exclusive epidemiological study from a Moroccan population. **Objective:** Our research aimed to study the distribution of Haematolymphoid tumours in the regional context in Casablanca. **Method:** We focused on malignancies diagnosed between January 1992 and December 2021 at the Cytogenetics Department of the Pasteur institute of Morocco. Conventional karyotype analysis was performed on bone marrow samples from patients aged between 1 and 95 years and collected data were analyzed to perform statistical analyzes using SPSS20.0 software. **Results:** Of the karyotypes investigated 69.8% (1118/1601) were positive for haematolymphoid tumours. The mean age at diagnosis was 42.68 ± 18.20 years. The most frequent pathologies were myeloid neoplasms, with chronic myeloid leukaemia (CML) in first place at 69.8% (780/1118), followed by acute leukaemias (ALL, AML and ALAL) at 21.4% and myelodysplastic neoplasm (MDS) at 5.5%. The most recurrent clonal abnormalities were translocations t (9;22) with 74.2% in CML cases. Deletions 12.5% and additions 8% were found in all diseases with mainly trisomy's 8 and 21 in AML and MDS and deletions in AML and ALAL. An association was also found in 12 cases of AML between t (8;21) translocation and sexual chromosome deletion (X and Y). The proportion of karyotype's complexity (9.9%) seems to increase with ages. **Conclusions:** Haematolymphoid tumours occur at an earlier age in this cohort. Leukaemia represents the most frequent pathologies with a preponderance of chronic diseases, mainly affecting adults.

Keywords: Haematolymphoid tumours- Cytogenetic- Epidemiology- Karyotype- Morocco

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Introduction

Haematolymphoid tumours (HLTs) are blood and lymphoid cell diseases caused by an uncontrolled clonal proliferation of haematopoietic cells, whether they are of the myeloid or lymphoid lineage or even originate from the periphery. Traditionally, HTLs were considered leukaemia, lymphoma, and myeloma until the 2008 World Health Organization (WHO) classification system recognized more than 60 different clinical and pathological disease subtypes [1-4]. However, lymphoid neoplasms and myelodysplastic/myeloproliferative neoplasms remain the three major groups of HLTs [2].

HLT is an insidious and progressive disease that progresses with varying degrees of rapidity and is fatal if left untreated. There are two types of HLTs depending on the cell stage involved in the pathogenesis. The insidious types are neoplasms that arise from premature or mature cells, while the acute types include neoplasms arising from immature precursor cells.

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Because of their heterogeneity, the exact causes of the development of HTLs remain poorly understood, and comparison of the incidences of the different subtypes is a first step in generating critical data to initiate future etiological investigations.

According the GLOBOCAN, the third most frequently diagnosed cancer in Africa, in both men and women, is cancer of "other specified sites", which encompasses breast, bone, connective tissue and eyes [5, 6]. Data on HTLs are inexistent or underrepresent, while in Europe and the United States, HTLs are the fourth most common cause of cancer. In 2008, the incidence of cancer cases in Africa was estimated to be 681,000 with a mortality of 512,000 where, approximately 10% accounted for HLTs including Classic Hodgkin lymphoma (CHL), Non-Hodgkin lymphoma (NHL), leukaemia and Plasm cell Myeloma (PCM) [7, 8]. Recently, worldwide HLT's incidence has fluctuated due to the discovery of new techniques and advances in molecular tools, rising from 30.2% in 1990 to 32.4% in 2017, with an age-standardized incidence rate of 6.2 cases/year/100,000 population [9]. In Morocco, HLTs account for 12.9% of all cancer types (non-melanoma skin cancers excluded) in males and 8.7% in females [10]. In fact, HLTs are often associated with mutations or asymmetric divisions in immature blood cell lineages and specific chromosomal abnormalities (numerical and structural) such as aneuploidy, deletions, translocations, and inversions [11]. Since 2001, HLTs have become a major focus of cytogenetic analysis, from inclusion of chromosomal abnormalities among the main diagnostic criteria by the WHO. In the era of precision medicine, abnormalities represent an essential step in the understanding of pathophysiology, diagnosis, classification, prognosis and the development of targeted therapies. Analyzes that are still not accessible to all the local population, despite the development of new molecular biology technologies. It is therefore difficult to establish a cumulative experience from the region for most HLTs [12]. Conventional cytogenetics for karyotyping remains so the reference technique for the diagnosis of HLTs in low incomes countries.

This article aims to fulfil two objectives: First, to provide an overview of the different types of HLTs that have presented to the cytogenetic laboratory of the Pasteur Institute of Morocco in Casablanca. Secondly, to highlight demographic indicators such as age, sex and local incidence as well as recurrent abnormalities present in our population in a context of limited resources. To do so, a retrospective statistical study was carried out on patients suspected of having haematological disorders, recruited at the cytogenetic laboratory of the Pasteur Institute of Morocco in Casablanca between 1992 and 2021.

Materials and Methods

Study Design

A retrospective cross-sectional study, based on the review of karyotype examination results, from the archive reports of the cytogenetic laboratory was conducted over the period from January 1992 to October 2021. Ethical approval was granted by the Rabat Ethics Committee CERB 62-21 for Biomedical Research in accordance with the Helsinki Declaration. Informed consent was waived because of the retrospective nature of the study and the analysis of anonymous clinical data.

Participants

This retrospective descriptive study focused on the activity of the cytogenetic laboratory of the Pasteur Institute of Morocco - Casablanca over the last 29 years and included all the files of patients seen for bone marrow karyotype analysis between January 1, 1992 and October 31, 2021, in whom a diagnosis of HLTs was formally retained based on cytogenetic examinations.

The patients were referred to the cytogenetic laboratory Pasteur Institute for suspicion of HLTs. The clinical picture varied according to the pathology with mainly abnormalities of the complete blood count, cytopenia, anaemia, hepatomegaly, splenomegaly and primary myelofibrosis (PMF).

Karyotype

The conventional karyotype analysis consists of 5 steps: (1) cell culture - (2) metaphase blocking - (3) chromosome preparation - (4) denaturation and staining - (5) microscopic observation of chromosomes under visible light. Primary karyotype analysis was performed on bone marrow samples collected in heparin tubes. The blastocysts culture was achieved in a combination of fetal bovine serum (FBS) and Roswell Park Memorial Institute medium (RPMI-1640). The rest of the methodology was similar, as published in previous studies [13-15]. For each patient a total of 50 to 100 cells were selected and analyzed. All HLTs were diagnosed in accordance with the World Health Organization guidelines by screening t (9;22) in CML, t (8;21) or t (15;17) in AML, t (12;21) or t (1;19) in ALL; trisomy 8, deletion of chromosomes 7,5q in MDS and deletion of chromosomes 11q,17p in CLL/SLL. The obtained karyotypes were reported in compliance with the international system of human cytogenetic nomenclature (ISCN 2016) [16].

Statistical Analysis

Were excluded from the analysis the incomplete bone marrow records and the blood or tissues records in accordance with the World Health Organization guidelines [4]. Patients with a diagnosis or suspicion of plasma cell myeloma (PCM), chronic myeloid leukaemia (CML), B- or T- lymphoblastic acute leukaemia/lymphoma (ALL), acute myeloid leukaemia (AML), acute leukaemia of ambiguous lineage (ALAL), myeloproliferative neoplasm (MPN), chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL), aplasia, mature B-cell and T-cell neoplasm, chronic myelomonocytic leukaemia (CMML), lymphoproliferative disorders (LPDs), myelodysplastic neoplasm (MDS), clonal cytopenia of undetermined significance (CCUS), bone marrow failure syndromes (BMFS) and Unclassifiable HLTs were included in this cohort [3, 4]. The data for each patient was recoded and the studied parameters were mean age, sex, local annual

rate, local incidence, and distribution of chromosomal abnormalities according to nosological subtypes.

The parameters of our study were collected directly from the department's archive files. Incomplete records were excluded from the analysis. Data analysis was performed using SPSS version 20 software (IBM SPSS Inc. Chicago, IL, USA). The Chi-square test was used to analyze the association between qualitative variables and the comparison of quantitative variables was conducted using the Anova test. The significance level was set at a p-value ≤ 0.05. Local annual rate was obtained by dividing the number of cases by the length of the study period (29 years). The local crude incidence was calculated by relating the local rate to the number of inhabitants of the Greater Casablanca region provided by the general population census of 2004 [17] carried out by the Moroccan High Commission for Planning.

Results

This study was initiated in 2021 at the Pasteur institute of Morocco in Casablanca, where the karyotype can be proceeding on blood – bone marrow or tissues samples. Out of a total of 15080 samples processed between 1992 and 2021, distributed as follows: 85% (12830/15080) whole blood karyotypes and 15% (2250/15080) bone marrow (BM) karyotypes. In 28.84% cases, the files were incomplete or unusable and only 71.15% (1601/2250) marrow karyotype records were retained for our study. During this period in the cytogenetic department, 30.2% (483/1601) normal BM karyotype and 69.8% (1118/1601) karyotype with cytogenetic abnormalities were recorded, which corresponded to an average recruitment of 38.5 new cases per year with 51.3% men for 48.7% women and a 1.05 sex ratio (M/F) in favor of Male gender. The patients were aged between 01 and 95 years and the median age at diagnosis was 44 years. The maximum observations are under the age of 60 years. The analysis of the results shows that the most frequent HLTs seen in our laboratory are myeloid neoplasms. CML and AML account for the largest share with 82.3% of observations (Table 1). Table 2 summarizes the distribution of the two sub-groups of HLTs (leukaemia and lymphoma) according to sex, age and chromosomal abnormalities. The Anova test shows that the age distribution is significantly different in leukaemia sub-group, while in lymphoma and HLTs the p-value is superior to 0.05 (Table 2). In contrast, there is no significant association between sex and nosological sub-groups (p = 0.382). MPN (70.21%) are the most recurrent HLTs with a local annual rate of 27 new cases/year, followed by AML and MDS with respectively 4.82 and 2.13 new cases/year. CML was the main pathology with 780 cases, all participants being Philadelphia chromosome positive (Table 3), with other myeloid

Table 1. Comparison of Frequencies and Percentages of the Different Nosological Groups and Statistical Associated Parameters

Clinical Information	Number of Cases	Percentage	Percentage Cumulative	Median Age	Mean Age	Standard Deviation
CML	780	69.8	69.8	45	45.46	15.499
AML	140	12.5	82.3	27	30.68	18.119
MDS	62	5.5	87.8	61	56.73	20.108
ALL	55	4.9	92.8	16.5	20.58	15.959
ALAL	45	4	96.8	30	34.17	20.246
CLL/SLL	14	1.3	98	60	61.09	60.332
BCR-ABL negative MPN	5	0.4	98.5	23.5	27	16.391
OTHER	4	0.4	98.8	19	28.5	31.3
PCM	4	0.4	99.2	68	65.67	10.693
CMML	3	0.3	99.5	29.5	29.5	14.849
Unclassifiable HLTs	2	0.2	99.6	26.5	26.5	17.678
NHL	2	0.2	99.8	35	35	-
Bone marrow failure syndromes (BMFS)	1	0.1	99.9	22	22	-
LPD	1	0.1	100	64	64	-
Leukaemia	1105	98.8	-	44	42.7	18.12
Lymphoma	13	1.2	-	37	40.42	25.71
Total HLTs	1118	100	-	44	42.68	18.207

Table 2. Analysis of the Distribution of Pathologies According to Demographic and Cytogenetic Parameters

	Age	Sex	Isochromosomes	Deletion	Addition	All abnormalities
Leukaemia	< 0.001**	0.694*	0.223*	< 0.001*	< 0.001*	< 0.001*
Lymphoma	0.372**	0.091*	-	0.786*	0.119*	0.405*
All HLTs	0.666**	0.382*	0.223*	< 0.001*	< 0.001*	< 0.001*

(*) $\chi 2$ test. (**) Anova T test.

Table 3. Distribution of Chromosomal Rearrangement in Six of the Most Recurrent Haematolymphoid Tumours

Chromosomal Rearrangement	Abnormality	AML	B-ALL / T-ALL	ALAL	MDS	CML	CLL/SLL
Translocation	t (8 ;21)	45	-	-	-	-	-
	t (15 ;17)	4	-	-	-	-	-
	t (10 ;14)	2	-	-	-	-	-
	t (9 ;11)	3	-	-	-	-	-
	t (2 ;10)	3	-	-	-	-	-
	t (2 ;11)	1	-	-	1	-	-
	t (12 ;13)		4	-	-	-	-
	t (13 ;14)	3	-	-	-	-	-
	t (9 ;22)		-	-	-	780	-
	t (10 ;11)	1	1	2	-	-	-
Partial Deletion	Del 6q	-	3	-	-	-	-
	Del 4q	-	-	-	-	-	-
	Del 5q	-	-	-	11	-	-
	Del 7q	4	-	-	-	-	-
	Del 9q	9	-	3	-	-	-
	Del 11q	4	-	2	3	-	3
	Del 12p	2	2	-	-	-	2
	Del 13q	-	-	-	4	-	-
	Del 20q	-	-	-	2	-	-
Monosomy	-9	-	2	-	-	-	-
	-10	5	-	-	-	-	-
	-19	2	2	-	-	-	-
	-21	4	1	1	2	-	-
	-22	2	-	-	-	-	-
	-X	4	-	-	-	-	-
	-Y	9	-	-	2	-	-
Partial Addition	Add 4 (p/q)	1	1	1	-	-	-
	Add 5p	-	-	-	1	-	1
Trisomy	+2	-	5	3	-	-	-
	+4	5	3	2	-	-	-
	+7	2	2	-	-	-	-
	+8	9	5	2	13	-	-
	+12	-	-	-	-	-	5
	+16	2	1	-	-	-	-
	+21	6	9	4	4	-	-
Inversion	Inv 16 (p13 ;q22)	3	-	-	-	-	-
	Inv 7 (p22 ;q23)	-	1	-	-	-	-
	Inv 9 (p11 ;q13)	1	-	-	-	-	-
Isochromosome	Iso 8q10	1	-	-	-	-	-
	Iso Xq10	1	-	-	-	-	-
	Iso 17q	-	-	-	1	-	-
Derivative Chromosome	Der 2	3	1	-	2	-	-
	Der 9	2	1	-	-	-	-
	Der 12	-	4	5	-	-	-
	Der 19	3	2	-	-	-	-
Others	Complex Karyotype**	15	20	12	16	-	2

** More than three unrelated chromosomal aberrations in the same karyotype

neoplasms accounting for less than a third of observations. BCR-ABL negative MPN, PCM, CMML and NHL have the lowest local annual rates, less than one new case per year (Table 4 and 5).

On all the collected data, 98.84% (1105/1118) were diagnosed with PCM and 1.16% (13/1118) with chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). CLL/SLL was the only type of lymphoid neoplasms. The mean age of study participants diagnosed with leukaemia was 42.69 ± 18.12 and 32.6 ± 23.31 years for lymphoma. Among the lymphoma patients, there were 3 cases (0.3%) of CMML, 2 cases (0.2%) of NHL and 8 cases (0.7%) of other rare lymphoma; while in leukaemia, the distribution was as follows: CML 69.8 % - AML 12.5 % - MDS 5.5% - ALL 4.9 % - ALAL 4.0 % - BCR-ABL negative MPN 0.4 % and CLL/SLL 1.3% (Table 1). The maximum rate of HLTs places CML in pole position, followed by acute leukaemia (ALAL + AML + ALL). The age distribution was unimodal regardless of sex and significantly related to the pathologies with a peak in the [41-50] age group, i.e. 22.1% (247/1118) of the study population. The average age of our sample at diagnosis was 42.68 ± 18.20 years.

No patients with ALL, CMML, BCR-ABL negative MPN or NHL were observed after the age of 60, while PCM does not appear to occur before the age of 50. Similarly, no cases of PCM were recorded after 2013. There were 63 cases (8%) of CML in 2013, the highest number of cases in our observations. MDS shows the greatest increase in frequency over the study period, from 2 (3.2%) cases in 1992 to 13 (20.9%) in 2021. AML, ALL and ALAL revealed a similar evolution over the study period.

Cytogenetics Abnormalities

Files with incompletes (name, age or karyotype result) data were not included in the analysis. The most recurrent abnormalities were found in adults and consisted mainly of translocations, deletions, addition, derivatives and iso-chromosomes (Tables 3 and 4). All chromosomes are affected by these structural abnormalities, but the majority of monosomy are linked to chromosomes -7, -24 and -21, with 21.3%, 15.9% and 11.6% of complete deletions respectively. Trisomy are mostly found in chromosome +21, 16.7% of all chromosomal additions. In our study 21's trisomy isn't specific, it can occur in children with Down syndrome, children without Down syndrome, and adults. Microdeletions of chromosome 9 (15%) and micro-additions of chromosome 4 (37.5%) as well as chromosome 8's trisomy (20.5%) complete the classification of the most affected chromosomes in structural abnormalities associated with HLTs.

The majority of structural abnormalities observed remain translocations (74.2%) and deletions (12.5%). With 780 observations, the t (9;22) translocation is the most recurrent structural abnormality, accounting for 88.4% (780/882) of all translocations, followed by the t (8;21) translocation, 52 (5.9%) observations. The frequency of translocations t (9;22) was higher in the [41-50] class age. Chromosomal abnormalities as deletions and additions are significantly associated with leukaemia, contrary to lymphoma with a p-value greater than 0.05 (Table 2). ALL, ALAL, and MDS are HLTs with the most disease-associated abnormalities. Of the 140 AML cases, there were 32.14% (45/140) t (8;21) - 2.85% (4/140) t (15;17) - 1.42% (2/140) t (13;14) and 1.42% (2/140) t (9;11). No t (12;21), t (1;19) or chromosome 16 inversion have been observed in ALL, but nine karyotypes were associated with 21's trisomy. A partial deletion of chromosomes 7q or 9q are part of the AML's recurrent rearrangement. Total or partial trisomy's of chromosomes +4, +8, +16 and +21 (24/140) as well as polyploidy and mosaic monosomy have been found in AML. Five cases with chromosomal inversion (inv

Table 4. Distribution of the Different Subtypes of Haematolymphoid Tumours According to Sex

	Absolute (n)	Number of Men H (n)	Percentage of Men %	Number of Women (n)	Percentage of Women %	Rate of Males (cases/year)	Rate of Women (cases/year)	Crude incidence in Males (cases per 100 000 inhabitants/year)	Crude incidence in Women (cases per 100 000 inhabitants/year)
CML	780	402	70	378	69.5	13.86	13.03	0.778	0.711
AML	140	73	12.7	67	12.3	2.52	2.31	0.141	0.126
MDS	62	26	4.5	36	6.6	0.9	1.24	0.05	0.068
T-ALL/ B-ALL	55	30	5.2	25	4.6	1.03	0.86	0.058	0.047
ALAL	45	27	4.7	18	3.3	0.93	0.62	0.052	0.034
BCR-ABL negative MPN	5	2	0.3	3	0.6	0.07	0.1	0.004	0.006
CLL/SLL	14	8	1.4	6	1.1	0.28	0.21	0.015	0.011
PCM	4	1	0.2	3	0.6	0.03	0.1	0.002	0.006
Other	8	3	0.5	5	0.9	0.1	0.17	0.006	0.009
NHL	2	1	0.2	1	0.2	0.03	0.03	0.002	0.002
CMML	3	1	0.2	2	0.4	0.03	0.07	0.002	0.004
Total	1118	574	100	544	100	19.79	18.76	1.111	1.023

χ^2= 3.881; p= 0.382

(16), inv (9) and inv (11)), four with duplications (1q, 13q and 17q) and eleven with derivatives chromosomes complete the list of abnormalities recorded in AML. Acute leukaemia (AML+ALAL+ALL) accounted for approximatively 22% of the chromosome additions and deletions. Respectively, twelve and six cases of monosomy in the sexual chromosomes were reported in male and female, with an association between sexual chromosome's (X or Y) deletion and t (8;21) translocation in 4/140 (-X) and 8/140 (-Y) cases of AML's karyotypes (Table 3). In MDS, a 5q deletion in 17.7% (11/62), 21's trisomy in 6.45% (4/62), and 8's trisomy in 20.9% (13/62) of cases have been noted. In ALL, four karyotypes had Der12 and two carried Der19. CLL/SLL phenotype was associated in five cases with trisomy 12 and, isochromosomes, the least represented abnormalities with only four cases, were observed in AML and MDS. Complex karyotypes are concentrated in adult patients with myeloid neoplasms.

Local Rate and Incidence

The incidence observed in our study can be defined as: the proportion of individuals in a population who were diagnosed with a HLTs during the period of 1992-2021. The incidence of HLTs increased with age between 1 and 59 years and decreased after 60 years. To estimate the crude incidence, we used the direct method by taking into account the population distribution according to the census of the Moroccan High Commission for Planning 2004 estimated to 3 615 903 inhabitants with respectively 1 782 255 males and 1 833 648 females. The number of cases shows a discontinuous evolution other the years. The crude incidence (per 100,000 inhabitants/year) by sex and total are presented in Tables 5 and 6.

The local incidence and rate values vary according to the pathological subtype, with an overall average of 1.066/year/100,000. As expected, the subtypes with the lowest number of cases had the lower incidences. CML had the highest local incidence and annual local rate with respectively 0.744 cases per 100,000 inhabitants/year and 26,897 new cases/year and NHL, the lowest local incidence and annual local rate with 0.002 cases per 100,000 inhabitants/year and 0.069 new cases/year. Ultimately, a significant variation ($p < 0.001$) between pathologies and age group repartition have been illustrated (Table 6).

Discussion

The evolution of molecular biology techniques and the discovery of new markers such as micro additions/deletions or single nucleotide polymorphisms (SNP), have improved the diagnosis of cancers, making chromosome analysis an insufficient technique on its own. Cytogenetic for HLTs analysis have limitations, mainly due to its low sensitivity (15-25%) resulting in generation of false negative results. Therefore, our data were only carried on karyotype as the laboratory do not afford the resources for others technics. During the 29 years of activity of the Cytogenetics Department of the Pasteur Institute of Morocco and out of a total of 15080 recorded karyotype files, there were 1118 cases of HLTs, i.e. a frequency of 7.4% and a local rate of 38.55 new cases per year reflecting the youth of our population. The annual distribution of HLTs shows a sawtooth pattern, with maximum frequencies in 1995 (61 cases), 2013 (77 cases) and 2021 (73 cases). The mean age at diagnosis being 42.68 years. The year 2013 with 6.88% patients, represent the highest number of HLTs observations. Conversely, the number of new cases in 2004 was inferior to 12 (1.15%). This irregular distribution of the number of cases per year of HLTs has also been observed in other countries [18]. Indeed, with variability due to major geographical disparities, the frequencies fluctuate from one region to another. More than a quarter of HLTs are diagnosed in Europe [19] although the continent has only one tenth of the world's population. It can be assumed that the difficulty of access to care in third world or developing countries is a hindrance, both in the management of these diseases and in the access to epidemiological data.

With regard to the nosological subgroups, the three major pathologies observed are myeloid neoplasms. Leukaemia represents the first subgroup with more than

Table 5. Local Rate and Incidence of the Different Subtypes of Haematolymphoid Tumours

	Absolute (n)	Relative (%)	Mean age (years)	Sex-ratio (M/F)	Global rate (Cases/year)	Crude incidence (Cases per 100,000 inhabitants/year)
CML	780	69.77	45	1.06	26.897	0,744
AML	140	12.52	28	1.09	4.828	0.134
MDS	62	5.55	60	0.72	2.138	0.059
ALL	55	4.92	17	1.2	1.897	0.052
ALAL	45	4.03	32.42	1.5	1.552	0.043
BCR-ABL negative MPN	5	0.45	32	0.67	0.172	0.005
CLL/SLL	14	1.25	61.41	1.33	0.483	0.013
PCM	4	0.36	67.72	0.33	0.138	0.004
Other	8	0.72	24.5	0.6	0.276	0.008
NHL	2	0.18	36.7	1	0.069	0.002
CMML	3	0.27	40	0.5	0.103	0.003
All HLTs	1118	100	44	1.06	38.552	1.066

Table 6. Age Distribution of all the Haematolymphoid Tumours Identified between 1992-2021

Clinical Information	AGE_CLASS										
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	Total
CML	9	35	86	163	208	147	96	29	7	0	780
AML	17	30	28	18	24	9	10	1	0	0	137
MDS	2	4	1	3	8	12	16	10	3	1	60
T-ALL/B-ALL	15	18	7	3	3	4	0	0	0	0	50
ALAL	3	9	9	8	3	3	4	0	2	0	41
CLL/SLL	0	0	0	0	0	7	3	1	0	0	11
OTHER	1	1	1	0	0	0	0	1	0	0	4
BCR-ABL negative MPN	0	2	0	1	1	0	0	0	0	0	4
PCM	0	0	0	0	0	1	1	1	0	0	3
Unclassifiable HLTs	0	1	0	1	0	0	0	0	0	0	2
CMML	0	1	0	1	0	0	0	0	0	0	2
NHL	0	0	0	1	0	0	0	0	0	0	1
LPD	0	0	0	0	0	0	1	0	0	0	1
Bone marrow failure syndromes (BMFS)	0	0	1	0	0	0	0	0	0	0	1
All HLTs	47	101	133	199	247	183	131	43	12	1	1097

χ^2= 448.381; p < 0.001.

2/3 of HLTs diagnosed between 1992-2021 ahead of lymphoma and PCM, this recalls the results of Hossain et al. (2014) [20].

The HLTs show much more variation than most other cancers. The study of Elidrissi Errahhali et al. (2016) [21], which discussed the epidemiological profile of HLTs in the eastern region of Morocco from 2008 to 2012, gave a local rate of 10.9%, which is in line with our results and the global average of 6.6% [22]. Like previous publications, our analysis shows a male predominance in HLTs with a mean sex ratio between (1.06 - 1.12), depending on the nosological subtype [23-25]. The affected populations presenting a predominance in young adults [23, 26, 27]. In Western countries, HLTs affects a majority of men [28] between 0-59 years old while above 60 years, the sex ratio is close to 1. The data of this study (Table 5 and 6) are in accordance with those observation as we identified a predominance of HLTs in young adults (56.2%) with a sex ratio of 1.06. The demographic distribution of the population affects the age at diagnosis. This plays an important role in the incidence.

In 2020, about 474,519 new cancer cases (2.5% of all new leukaemia cases) with an average sex ratio of 1.4 [6, 29]. Based on GLOBOCAN [5, 6, 30], the incidence of leukaemia and PCM is respectively estimated to 2.4/100,000 and 0.65/100,000 in Morocco as in Africa. These rates are six times higher in developed countries such as France (18/100,000 and 10.7/100,000) or Germany (16.5/100,000 and 8.5/100,000). In the presented study, leukaemia was estimated at 1.05/100,000 inhabitants in the Greater Casablanca region, which raises the question of an under-evaluation of these diseases in Morocco, as there is no data available for some rural area. The crude incidence as well as the local rate showed that the three main forms of HLTs were CML, AML, MDS (Table 4 and 5). The same observations have been reported in Mexico [15]. However, other studies such as Elidrissi Errahhali et al. 2016 [21] in eastern Morocco, Awan et al. (2023) [26] in Pakistan and Ugwu et al. (2021) [24] in Sub-Saharan Africa give prominence to CML but have described a majority of acute leukemia. The variability in the results may be explained by differences in the method of diagnosis or the variable accessibility to screening tools in the different laboratories. The study material could also differ according to the articles, ranging from bone marrow puncture, to tissue biopsy, to peripheral whole blood. However, our results remain lower than those described in developed countries; even for CML [31]. This significant variation between countries could be explained not only by the higher proportion of patients admitted and the existence of a more efficient epidemiological surveillance system in these regions, but also by the higher survival rate in these diseases allowing a better diagnosis [32]. Differences in exposure to carcinogens such as pesticides, occupational cancers, genetics and nutrition are other factors of variability.

Of the 140 positive AML cases, 41.4% (58/140) were in the age group [11-30] years. In accordance with the current results, Al-Kahiry (2012) [33] described in their article that acute leukaemia was the second most common HLTs, in contrast to the observations reported in Yemen [34] and in the United States by Siegel et al. (2020) [35] where AML was the most common HLTs in adults followed by CML. AML is the most investigated pathology in this study, while CML is the most diagnosed with 50% of the suspicious cases carrying a cytogenetic abnormality. In the years 2013 and 2021, CML reached its highest local rate with 63 and 46 new cases diagnosed respectively. Between 1994-1995, 52 samples were analyzed for suspected AML, of which only 12 cases returned positive, i.e. a failure rate of 77%. The high rate failure in cultured AML is due to the presence of recurrent

Table 7. Comparison of the Frequencies of Haematolymphoid Tumours between the Pasteur Institute of Morocco-Casablanca and other Regions

Study period	1992-2021	2008-2012		1980-2004			2008-2012			2005-2014		
Reference	Our study	Eastern Morocco (Elidrissi Errahhali et al. 2016) [21]		Côte d'Or – France (Maynadié et al. 2011) [69]			Bangladesh (Hossain et al. 2014) [20]			Bahrain (Ismaeel et al. 2022) [68]		
Pathologies	Median age	Sex ratio (M/F)	Percentage (%)	Median age	Sex ratio (M/F)	Percentage (%)	Median age	Sex ratio (M/F)	Percentage (%)	Median age	Sex ratio (M/F)	Percentage (%)
Total number	2250			6075			5086			5338		NA
Total number of	1118			660			1549			5013		272
Haematolymphoid tumours	49.68%			10.90%			30.50%			NA		NA
Percentage of all cancers												
All HLTs cases	44	1.06	1118 (100)	42	2.2	660 (100)	NA	NA	1549 (100)	42	2.2	5013 (100)	42	1.5	272 (100)
CML	45	1.06	780 (69.8)	NA	NA	NA	56	1.5	141 (9.1)	40	2.1	912 (18.2)	39.5	1.1	38 (14)
AML	28	1.09	140 (12.5)	42.5	0.9	32 (4.9)	62-63	1.3	468 (30)	35	1.9	1417 (28.3)	39	1.6	71 (26.1)
T-ALL/B-ALL	17	1.2	55 (4.9)	48	1.3	16 (2.4)	NA	NA	NA	27	2.1	706 (14.1)	9	1.8	62 (22.8)
CLL/SLL	61-62	1.3	14 (1.3)	67	2.8	38 (5.8)	NA	NA	NA	60	2.9	183 (3.7)	65	0.9	15 (5.5)
MDS	60	0.7	62 (5.5)	62	0.7	20 (3)	74-76	2	345 (22)	57	1.9	225 (4.5)	56	3.3	34 (12.5)
BCR-ABL negative MPN	32	0.6	5 (0.4)	53	0.7	84** (12.7)	63-64	1.4	443 (38)	NA	NA	NA	44.5	0.3	8 (2.9)
PCM	67-68	0.3	4 (0.4)	63.5	1.2	82 (12.4)	NA	NA	NA	55	2.1	528 (10.5)	57	1	44 (16.2)
NHL	36-37	1	2 (0.2)	55	1.3	196 (29.7)	NA	NA	NA	48	3.6	846 (16.9)	NA	NA	NA

** Includes CMLs; NA= Not Available

bone marrow aplasia and a poor survival rate, compared to CML where cell proliferation is disease-related and survival scores are better.

With a total of 62 cases and a local rate of 2.13 new cases/year, MDS, the third most recurrent HLTs in this cohort, is a myeloid neoplasm with a tendency to acute leukaemic transformation. Given a mean incidence of 1.6/100,000 in Asia [36], [2.1 - 8.1]/100,000 in Europe [37] and 4/100,000 in America, [38] MDS is among the least common HLTs. The outcomes of the current study are lower than those reported by Maaroufi et al. (2020) [39] 7.6 new cases/year between 2008-2018 at the Rabat Military Hospital, but match the Romania's [40] where an incidence of 0.3/100,000 was reported. The median age at diagnosis is similar to that observed in Western countries [41] with a maximum frequency between 60-70 years 25.8% (16/62). There is also a predominance in gender, 58.1% women and 41.9% men. The demographic distribution of the population of Greater Casablanca, where the sex ratio over 60 years of age is around 0.8 (Male/Female), would justify these results.

The frequency of ALL was 4.9% with a 1.2 (M/F)

sex ratio, which is much lower than previously reported. The low proportion of ALL in the pathological landscape of HLTs described here is consistent with the observations of Elidrissi Errahhali et al. (2016) [21] where only 0.3% of all cancers were ALL, i.e. 2.4% of the HLTs described. Despite an unimodal distribution between [0-59] years of age, children aged [0-20] years remain the most affected population 67.2% (37/55) in ALL. Similar observations have been made in the American population, with 60% of the under-14s affected [35].

Lymphoma are solid tumors, most often lymph nodes, whose cytogenetic diagnosis requires cell sorting before culture, a technology that is not currently available at the Cytogenetic Laboratory of the Pasteur Institute of Morocco-Casablanca. Of all our observations, only 0.17% (2/1118) NHL were included. This is in contrast to the sub-Sahara Africa [18, 42] literature where lymphoid neoplasm were more frequent, with a majority of Hodgkin's lymphoma (HL). In HL and NHL, the results of the complete blood cell count and anatomo-pathology of affected lymph nodes are often the only tests performed because they allow the diagnosis to be made without having to include the karyotype. Diagnosis by biopsy analysis reduces both costs and time delays. This could explain the absence of solid tumors in our results.

In this cohort, both PCM and BCR-ABL negative MPN contributed to 0.4% of all HLTs. Other rarer malignancies like Down's syndrome or Burkitt's lymphoma represent 0.7%. In other cohorts such as the studies conducted a the Ethiopian hospital [1] and in Martinique [43] a majority of lymphoma especially PCMs have been describe.

During data collection we observed a high mortality rate for lymphocytic leukaemia searches, which affects the relative proportion of diagnosed acute leukaemia. This is consistent with previous studies that have reported the preponderance of chronic leukaemia over acute leukaemia in hospital. While acute leukaemia are usually sudden in onset and may not allow the patient to present to hospital, chronic leukaemia have an increased survival rate [32]. This brings to mind issues of the social and ethnic-racial paradigm of the disease. Survival rate was not recorded in the archives as an epidemiological parameter and was therefore not studied as it was considered irrelevant due to the unsufficient number of complete files available.

Karyotype, a pioneering technique in cytogenetics, allows the identification of prognosis indicators that serve to identify biologically distinct subsets of dysmorphic-sexual-haematological pathologies. In this study, we report the cytogenetic results of 1118 Moroccan patients from the records of the Pasteur Institute of Morocco, the first institution with a cytogenetic platform for the diagnosis of HLTs in Casablanca. Due to the similarity between the population distribution of Greater Casablanca and Morocco, these results may represent a partial view of what may have existed in Morocco between [1992 - 2004]; however, beyond this period, the existence of new private testing laboratories limits expectations. With different subtypes dominating at different ages, HLTs can be diagnosed at any time, ranging in the studied cohort from 1 to 95 years. Of the total clinical research prescriptions for HLTs collected, 69.8% (1118/1601) were abnormal in number and/or structure compared to 52.5% in Yaghmaie et al. (s. d.) [44] 49% in Awan et al. (2023) [26] and 33.3% in Arana Trejo et al. (2017) [15]. The distribution of chromosomal abnormalities according to HLTs shows a predominance of CML with a majority of translocations, especially the t (9; 22) translocation, the first one sought according the WHO diagnosis criteria. Next we have ALAL, AML, MDS, ALL and CLL/SLL, with deletions, additions and derivatives chromosomes respectively as their major abnormality. Translocation (74.2%) followed by aneuploidy (20.6%) are the most frequent chromosomal rearrangement. The age distribution of cytogenetic abnormalities shows a peak between [41-50] years. Surprisingly, the variability of genomic lesions increased with age below 60 years and decreased above 60 years. The most affected age group being around [31-50] years, i.e. 40.7% of our sample, with 51.34% of men and 48.66% of women.

Translocation t (9,22) was the only abnormality described in CML as it is a major diagnostic criteria according to the WHO classification of MPN [3, 4, 45]. A high frequency of this translocation has also been reported in South American patients in contrast to Western patients [15]. In this cohort the most representative age range carrying t (9;22) was [41-50] years, i.e. 26.66% (208/780), suggesting a low median age of disease detection. Our results are in agreement with the Haematology Unit of Internal Medicine at the King Saud University Medical City, Riyadh, KSA [46] who reported a median age at diagnosis of 43.4 ± 18.1 years in the Saudi population well below the 65 years documented in Western countries [47, 48]. No significant difference was observed between gender and the t (9;22) translocation.

The indicative AML karyotypes represent a frequency of 52.2%, which is average when knowing that in 60% of AMLs at diagnosis, there isn't any chromosomal abnormalities [49]. Therefore, AML was the second malignancy diagnosed in our study; this is consistent with the clinical observation reporting a large proportion of MDS cases transformation to AML [50]. A large variability of chromosomal rearrangements and abnormalities are associated with the AML phenotype [51, 52]. In fact, deletions are frequent in AML and affect chromosomes 7q and 9q, resulting in decreased expression of transcription factors involved in gene regulation, replication and DNA damage repair, as well as in cell cycle progression [53, 54]. Deletions of the short arm of chromosomes 7 or 9 have previously been described as responsible for an intermediate prognosis factor in AML patients, while 8's trisomy is considered a risk factor. The t (15;17) translocation was observed in 2.85% (4/140) of cases, which is near to the 3.9% reported in Boujmia et al. (2021) [55] study. About (24/45) 53.33% of t (8;21) translocations occur in AML, mostly in children (0-20 years), in contrast to the Gulf States and Pakistan which described a population of young adults aged 20-39 years as being at risk. Recent studies mentioned the presence of a second modality after 50 years of age, which was not observed in the current study [20, 21, 42].

These chromosomal rearrangements are among the most common in AML and our rates are lower compared to those reported in Mexico (16%) [15] Australia (15.3%) - Japan (33.1%) [56] and China (14.3%) [52]. We assumed in our study that the frequency of AML's characteristics translocations should have been underestimated by conventional cytogenetic analysis as, the yield of cell cultures in AML was lower than in the other diseases. Techniques such as Fluorescence in Situ Hybridization (FISH) and/or reverse transcriptase polymerase chain reaction (RT-PCR) being not applicable in our laboratory, the possibility of false negatives results is still present as the sensitivity of cytogenetics remains limited to 15%. Another consideration is the accessibility of care, which stills difficult in view of the high rate of early mortality due to haemorrhage during the diagnostic period.

The association between 5q deletion, 21q trisomy and MDS has already been described as responsible for a poor prognosis [14, 57, 58]. A complete trisomy of chromosome +8, the most frequent numerical abnormality in MDS appears in 20.9% (13/62) karyotypes. This association is strongly correlated to AML's transformation. Our observations in MDS are similar to those from Pakistan [59] and Tunisia [36] but remain lower than those found in the work of Hosono (2019b)[60] and Xia et al. (2019) [61] in China. Derivatives chromosomes, inversions and duplications, while rarer, have also been found in the MDS (Table 3).

Children aged [0-20] years represented 60% (33/55) of ALL patients; this is consistent with the literature but is higher than the earlier described Moroccan studies, in which young adults (20-39 years) were the most affected age group [21]. This difference can be explained by the fact that in their study, the authors underestimated the proportion of junior population, as their center did not treat children's diseases. In ALL, twenty cases were carrying complex karyotypes and nine had derivatives chromosomes in their chromosomal formula.

Trisomy 12 was observed in 35.7% of CLL/SLL. It is the second most common abnormality in this disorder. This percentage is probably underestimated as only 30% of trisomy 12 are detected by conventional cytogenetics against 70% by FISH [62]. Trisomy12 is associated with an intermediate prognosis.

Only four karyotypes carried isochromosome: three with a diagnosis of AML carrying iso (Xq10), iso (8q10), iso (11q10) and one karyotype carrying iso (17q) with a diagnosis of MDS. Iso (17q) has been identified in the literature in almost 2.5% [63] cases associated with both myelo/lymphoproliferative malignancies. Studies attribute a prognosis and survival marker value to iso (17q) as it is associated with rapid disease progression in AML, as well as an intermediate score in the revised International Prognosis Scoring System (IPSS) when present in the karyotype in general [63]. Iso (11q) in association with t (8;21) represent a risk factor with a poor prognosis, [64] while iso (8q) is one of the isochromosome involved in leukaemogenesis and transformation to secondary AML [65]. The complexity of karyotypes associated with these rearrangements support the hypothesis of poor prognosis and a susceptibility to acuitization (transformation of de novo MPN to acute leukaemia). This category of chromosomal lesion has not been found in any other disease.

Rarer abnormalities were identified in leukaemic malignancies, with some karyotypes carrying several markers at the same time. Complex karyotypes are considered as a risk factor and poor prognosis [13]. They are not exclusive to any cell line and the frequency of complexity increases with age. A complex karyotype is defined according to the 2022 WHO classification [3, 4] by the presence of three or more abnormalities. In 9.9% (111/1118) of pathological karyotypes and 6.9% (111/1601) of all karyotypes analyzed more than three chromosomal rearrangements have been observed. These findings are comparable to previously published data, where [3-15%] complex karyotypes were recorded [14, 26]. AML was the disease with the highest proportion of complex karyotypes, about 18.5%. In other malignancies, the frequency varies between 0.3 and 1.8%.

Sexual chromosome monosomy (45X, -Y/-X, t (8;21)) was found in 8.57% AML with a male predominance (sex ratio = 2). This association occurs in children [0-20] years and young adults [21-40] years [66] although it can appear at any age. Loss of the X chromosome (-X) have been describe in 30-40% of female and loss of the Y chromosome (-Y) in an average of 50% male with AML in association with the t (8;21) translocation [49]. In HLTs patients, it is not uncommon to observe sexual chromosome's monosomy, although these frequencies are higher than those found in our study. Where Y's chromosome deletion in male in association with translocation t (8;21) is known to improve prognosis, chromosome X deletion does not appear to influence prognosis in female. However, patients with a loss of chromosome X would have a better survival rate than those without it [66, 67].

The results of this study compared to several regions [68, 69] are combined in Table 7. The differences in frequency may be explained by the geographical, ethnic and age distribution of each cohort from which they were drawn [70]. Compared to local annual rate, the relative contribution of HLTs increases when longer periods of time are considered [71]. The distribution of HLTs present variations according to the study population but generally, MPN are part of the most common malignancies.

Strengthens and Limitations

The strength of this study lies in the fact that it is the very first step in understanding the distribution pattern and rate of HLTs in patients received at the Pasteur Institute of Morocco in the Greater Casablanca region. However, the limitations of the current study include the fact that it was a single-center retrospective study - without patient follow-up - with a relatively small sample size. Therefore, information bias is unavoidable. Some cases may have been omitted due to lack of sufficient documentation and/or missing data. Furthermore, the diagnosis of HLTs in our institution was mainly based on the cytogenetic aspect of these diseases. The absence of other diagnostic methods

such as complete blood count (CBC), anatomopathological or molecular biology (FISH, PCR or microarray analysis) was also an important limitation of the study, as some pathologies might have been misdiagnosed, undiagnosed or misfiled.

In conclusions, Haematolymphoid tumours karyotypes have an important diagnostic value when combined with haematological, cytological and anatomopathological measurement. The study is the largest to be conducted in the region. In summary, a range of HLTs were identified with a majority of myeloid neoplasm and an increasing local annual rate. We determined that CML with t (9;21) was the most common cytogenetic abnormality in our department followed by acute leukaemia (AML, ALL and ALAL) with 21.4% and myelodysplastic neoplasm (MDS) 5.5%. The sex distribution wasn't significantly associated to the two sub-groups (leukaemia and lymphoma) or with HLTs while, chromosomal abnormalities were significantly associated with leukaemia and not to lymphoma. In addition, the local incidence in our cohort was 1.1 per 100,000 for male and 1.023 per 100,000 for female with MPN being the most common HLTs diagnosis. Geographically, our results are more similar to those from low-income countries than developed countries. Cytogenetically normal HLTs are a heterogeneous group that requires investigation of other abnormalities such as point mutations (SNPs), copy number variations (CNVs), or transcription/translation abnormalities. Clearly, relying solely on the rate of our institution will not be sufficient to provide a meaningful estimate of the relative burden of HLTs in the general Moroccan population.

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What Is Known About This Topic

• Haematolymphoid tumours are cancers affecting both mature and immature blood cells from both lineages lymphoid and myeloid;

• Haematolymphoid tumours are associated for some of them with genetic markers investigated in developed countries by molecular biology techniques, while in Africa the technique of reference remains karyotype;

• The epidemiology of haematolymphoid tumors is well known in Europe, compared to Africa where data on their incidence and prevalence are limited.

What This Study Adds

• Our study reports the highest cohort with HLTs in a Moroccan population;

• This is a preliminary study carried out in view of the paucity of data on the question in our country;

• The local incidence rate founds are lower and the median age at diagnosis is higher than in other countries.

Competing Interest

The authors declare that they have no financial or non-financial competing interests.

Author's Contributions

S.G.C.S designed the research, was the principal investigator, and took primary responsibility for the paper. S.G.C.S and S.B collected, interpreted the data and wrote the manuscript. H.C. supervised the statistical analysis and gave conceptual advice. A.E.H reviewed the manuscript and gave conceptual advice. J.A, L.R, L.Z, C.E and L.L.R, performed the experiments and reported the results. R.S, H.L, S.N, gave the final approval of the version to be submitted. The manuscript was reviewed and approved by all authors.

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