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Epidemiological and Disease Burden Profiles of Leukemias and Malignant Lymphomas: Overview and Trends in the Republic of Moldova and Worldwide

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Abstract

Introduction: Hematological malignancies (HM) are relatively frequent nosological entities within the structure of morbidity by malignant tumors, exhibiting a severe evolution, restrained prognosis and negative socio-economic impact in the advanced stages and phases. **Objective:** The objective of the study was to identify the epidemiological patterns, and to evaluate the epidemiological trends and disease burden issues of HM in the Republic of Moldova and worldwide. **Materials and Methods:** The following research methods were used: epidemiological, descriptive statistics, clinico-analytic. The diagnosis was proved in all cases by histopathological, cytological, cytogenetic, molecular and immunophenotyping examinations. The qualitative type researches were performed and enriched by the narrative synthesis of the data. From the specialized international bibliographic sources and official statistics concerning HM. The narrative review of the reference sources was fulfilled in the form of a synthesis. **Results:** The number of newly diagnosed and followed-up patients with HM at the Institute of Oncology in 2016, 2017, 2018, 2019, 2020 and 2021 amounted respectively to 725, 802, 613, 628, 536 and 528, the incidence (new cases per 100,000 population) being 17.6, 19.5, 14.9, 17.7, 15.1 and 20.3. In 2021 HM constituted 6.2% of all newly-diagnosed cases with malignant tumors in the Republic of Moldova. In the same year Hodgkin lymphoma was diagnosed in 10.04% of cases, non-Hodgkin's lymphomas—in 31.63%, multiple myeloma and plasma cells neoplasms—in 7.77%, lymphoid leukemias—in 17.42%, myeloid leukemias—in 12.31%, monocytic leukemias—in 0.95%, and other leukemias—in 16.29%. In 2019 the male rate was 51.5%, and the female rate—48.5%. Within 2 years males were 266 (50.4%), females—262 (49.6%). The age of 50 - 79 years prevailed in

both genders (males—65%, females—72.5%). The children constituted 4.0% of the newly diagnosed cases, 4.8% of those under the follow-up at the end of the year 2019 and 6.4% of the newly diagnosed cases in 2021. The disease span from the onset to diagnosis ranged between 1 - 24 months and constituted on average 5.63 months, without a significant difference as compared to 2019 (5.76 months). The incidence of HM in Western countries is 14 - 19 new cases per 100,000 population (4% of all cases with malignant tumors). The incidence of non-Hodgkin's lymphomas increased by 45% between 2006 and 2016, from 319,078 to 461,000 cases. Between 2006 and 2016, the incidence of leukemias increased by 26%, from 37,000,000 to 467,000 cases. **Conclusions:** The epidemiological study revealed slightly lower morbidity by HM in the Republic of Moldova as compared to the West European countries mainly due to the migration of a workable population. The patients with malignant lymphomas, male gender and age categories of 50 - 79 years proved to be commonly registered epidemiological patterns. The narrative analysis of the literature revealed that patients with HM may experience a considerable disease burden with a negative impact on their employment status, working productivity and annual household income.

Keywords

Hematological Malignancies, Epidemiological Patterns, Incidence, Mortality, Disability-Adjusted Life-Years, Disease Burden, Management

1. Introduction

Hematological malignancies (HM) are relatively frequent nosological entities within the structure of morbidity by malignant tumors, exhibiting a severe evolution, restrained prognosis and negative socio-economic impact in the advanced stages and phases. HM comprises around 9% of all cases of cancers and is the 4th most commonly diagnosed cancer in males (after prostate, lung and colorectum) and females (after breast, lung and colorectum) in the economically developed countries and regions of the world. HM may be considered an actual issue of public health and oncology at the national, regional and global levels due to the severe relapsing evolution, restrained prognosis and unfavorable socio-economic impact in the advanced stages and phases. Over the decades, there has been a growing trend in the incidence and prevalence of leukemias and malignant lymphomas both in industrialized countries globally and in the majority of the administrative territorial units of the Republic of Moldova. Malignant lymphomas are malignant monoclonal proliferations of the lymphoid tissue cells [1] [2]. Currently, non-Hodgkin's lymphomas are a more frequent group of malignant haematologic diseases, the incidence continuously increasing [1] [3] [4]. The incidence of non-Hodgkin's lymphomas in the USA and European countries is 14 - 19 new cases per 100,000 population (4% of malignancies) [1] [5]. The increased morbidity by extranodal B-cell lymphomas, follicular lymphomas,

and T-cell lymphomas [6] is found in the majority of specialty references. In 2016, there were 461,000 newly diagnosed cases of non-Hodgkin's lymphomas and 240,000 deaths due to the progression of these malignant lymphoproliferations. The incidence of non-Hodgkin's lymphomas increased by 45% between 2006 and 2016, from 319,078 to 461,000 cases. Between 2006 and 2016, the incidence of leukemias increased by 26%, from 370,000 to 467,000 cases [3]. Chronic myeloproliferative neoplasms are the clonal leukemic neoplasms of the hematopoietic system, accounting for 40% - 50% of all leukemias in adults. These pathologies are characterized by the uncontrollable multiplication of myeloid, megakaryocyte and/or erythrocyte cell lineages, with an increase of the total and circulating cell pools. Morbidity due to chronic myeloid leukemia varies between 0.6 - 1.6 cases per 100,000 population [4] [7] [8]. The incidence of primary myelofibrosis is 0.5 - 1.5 cases per 100,000 population [4] [9] [10]. The morbidity by polycythemia vera varies between 0.2 - 1.3 cases per 100,000 population [4] [9]. The morbidity by HM increases with age, with a maximum incidence between 45 and 65 years [5], the diseases thus affecting the working-age population. The increase in morbidity and disability in the working population, the weighted rate of late diagnosis of malignant hematological diseases argued the need to study their epidemiological aspects, indicating the priority of the topic under discussion for oncology hematology and public health.

2. Objective

The objective of the study was to identify the epidemiological patterns, and to evaluate the epidemiological trends and disease burden issues of HM in the Republic of Moldova and worldwide.

3. Materials and Methods

The patients were followed-up between 2016-2022 at the comprehensive cancer center—Institute of Oncology. We applied the following research methods: epidemiological, observational, descriptive statistics, clinical-analytic, cross-sectional [11]. All patients from the National Cancer Register were enrolled in the study. The epidemiological data about patients with HM were generated and processed in cooperation with the Medical Statistics unit and Monitoring, Evaluation, Quality and Integration of Health Care Services (SMECISAM). The diagnosis was proved by histopathological, immunohistochemical, cytological, cytogenetic, molecular and immunophenotyping examinations of the bone marrow, peripheral blood, and biopsied lymph nodes. The type of haematologic malignancies was identified according to the criteria of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue revised in 2017 [2] [12]. Therefore, the diagnosis of acute leukemia was morphologically confirmed by complete blood count, bone marrow aspiration with cytological, cytochemical and cytogenetic examination, and determination of the percentage (≥20%) and type of blast cells. In cases of uncertain diagnosis, the type of acute leukemia was identified by performing immunophenotyping and cytogenetic examination of the venous blood

and bone marrow aspirate [13]. Quantitative real-time PCR was applied in chronic myeloid leukemia cases in order to determine the expression of p210 and p190 chimeric BCR-ABL gene transcripts at the step of diagnosis [7] [8]. In cases with polycythemia vera and idiopathic myelofibrosis, the major diagnostic option was the bone marrow biopsy and the detectyion of JAK2 V617F mutation in the peripheral blood [9] [14]. The diagnosis of multiple myeloma was proved by the bone marrow aspiration, which revealed the presence of malignant plasmacytic cells over 10% in cases of bone lesions. The relevant diagnostic percentage of myeloma cells should exceed 20% in cases of the absence of bone lesions [15]. Quantitative immunoglobulins assay, M serum gradient and immunophenotyping were performed in the uncertain diagnostic cases. The qualitative type researches were performed and enriched by the narrative synthesis of the data. The accumulation of information for our researches was done by studying data from the specialized international bibliographic sources and official statistics concerning variables of HM. The narrative review of the reference sources was fulfilled under the form of a synthesis in the Discussion section of the article. In order to realize the study objectives, the scientific publications were searched over the Google Search, PubMed, NCIB, Medscape, Z-library, Hinari database. More than 70 reference bibliographic sources were analyzed. Forty-one relevant and significant primary sources were identified and selected according to the impact score, with a scientific, reproducible and transparent approach to the topic under discussion, with subsequent data selection and evaluation. The following indicators and variables related to HM were investigated: incidence and structure of morbidity, disease span from the onset to diagnosis, age-adjusted prevalence, global burden of the disease, age-standardized incidence rate, age-standardized rate, estimated annual percentage changes disability-adjusted life-years. With the aim to minimize the error, a copy of the data sheet was initially produced, listing the items to be extracted from the primary studies.

4. Results

The cooperation with the Medical Statistics unit and SMECISAM allowed generation and processing of the statistical data that revealed the epidemiological situation and trend in the field of HM in the Republic of Moldova during the years 2016-2021. The number of newly diagnosed and followed-up patients with HM at the Institute of Oncology in 2016, 2017, 2018, 2019, 2020 and 2021 amounted respectively to 725, 802, 613, 628, 536 and 528, the incidence (new cases per 100,000 population) being 17.6, 19.5, 14.9, 17.7, 15.1 and 20.3 per 100,000 population (**Figure 1**). After two intermittent years of decrease, the incidence of HM, thus, exhibited a slight increasing trend.

In 2020 Hodgkin lymphoma was diagnosed in 10.26% of all cases with HM, non-Hodgkin lymphomas—in 34.89%, multiple myeloma and plasma cells neoplasms—in 8.40%, lymphoid leukemias—in 18.28%, myeloid leukemias—in 9.51%, monocytic leukemias—in 2.24%, and other leukemias—in 15.86%. In 2021 HM constituted 6.2% of all newly-diagnosed cases with malignant tumors

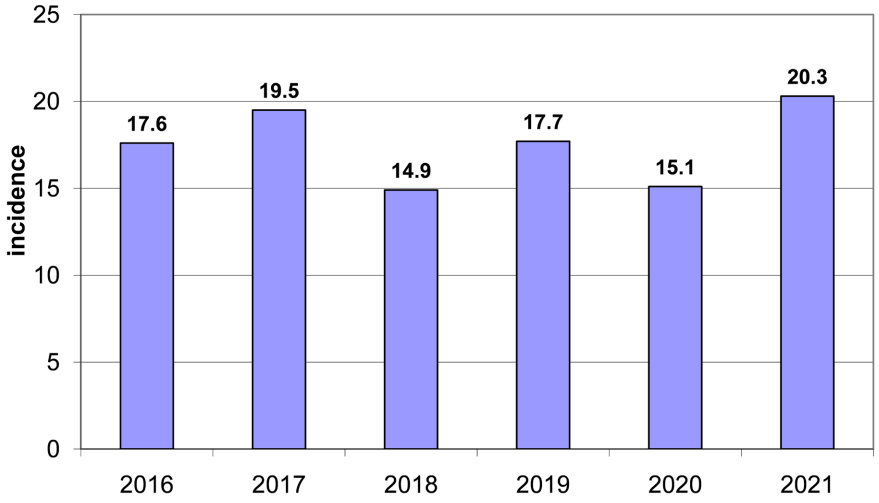

Figure 1. The incidence trend of hematologic malignancies per 100,000 of population in the Republic of Moldova.

in the Republic of Moldova. In the same year Hodgkin lymphoma was diagnosed in 10.04% of cases, non-Hodgkin lymphomas—in 31.63%, multiple myeloma and plasma cells neoplasms—in 7.77%, lymphoid leukemias—in 17.42%, myeloid leukemias—in 12.31%, monocytic leukemias—in 0.95%, and other leukemias—in 16.29% (**Figure 2**).

In 2021, the incidence of Hodgkin's lymphoma (C81) was 2.0, non-Hodgkin's lymphomas (C82-C85; C88, C96)—6.4, multiple myeloma and plasma cell tumors (C90)—1.6, lymphoid leukemias (C91)—3.5, myeloid leukemias (C92)—2.5, other leukemias (C93-C95)—4.2 per 100,000 (**Figure 3**).

The decrease of the incidence of HM in 2020 as compared to 2016 and 2017 can be explained by labor population migration and the impact of the COVID-19 pandemic on patients' addressability. The average age of men was 54.7 years, of women—57.9 years. In both gender groups, the patients aged between 50 and 79 years prevailed (males—65%, females—72.5%), partially fitting the category of a workable population. The gender analysis of morbidity showed that the male's rate was 51.5%, the female's rate—48.5% in 2019. Within 2 years males were 266 (50.4%), females—262 (49.6%). The children constituted 4.0% of the newly diagnosed cases, 4.8% of those under the follow-up at the end of the year 2019 and 6.4% of the newly diagnosed cases in 2021. As in 2019, the disease span from the onset to diagnosis ranged between 1 - 24 months in the newly diagnosed advanced cases and constituted on average 5.63 months, without significant difference as compared to 2019 (5.76 months). In the advanced cases, the diagnosis of HM was established within 1 - 6 months in 74.3%, within 7 - 12 months—in 20%, and within 12 - 24 months—5.7% ($p > 0.05$).

5. Discussion

The narrative review of the published world experience was performed with the aim to assess the epidemiological trends, disease burden and financial impact of

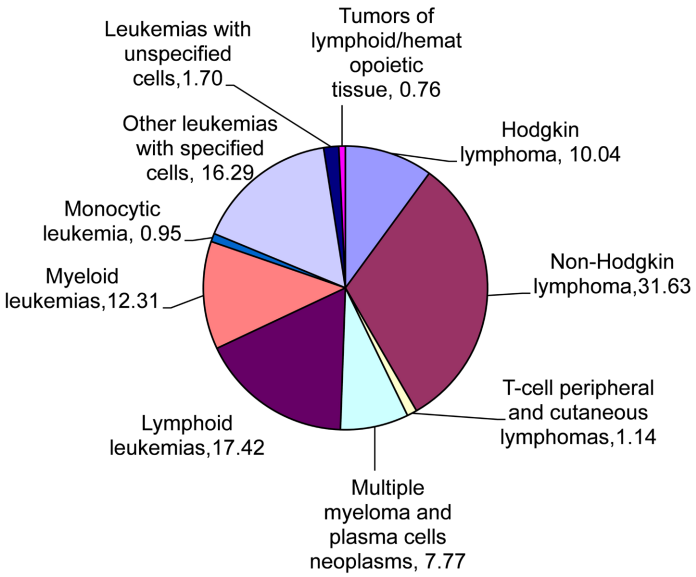

Figure 2. The structure of morbidity by hematological malignancies in the Republic of Moldova in 2021.

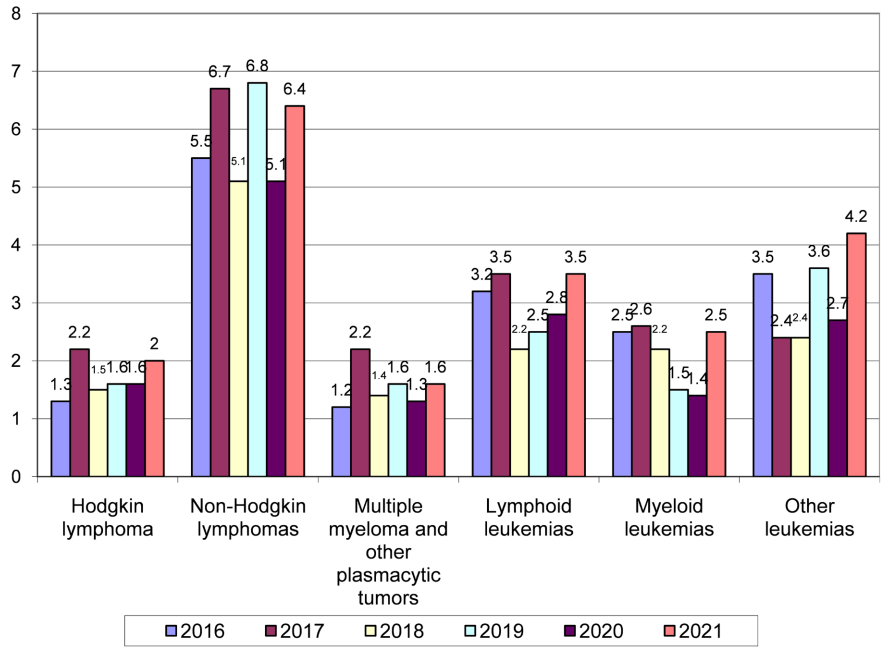

Figure 3. The incidence trend of hematologic malignancies per 100,000 of population in the Republic of Moldova with regard to nosological entity.

HM on public health. To perform the situational analysis, the global studies used the statistical indicators of the GLOBOCAN database, obtained for the year 2018 from 185 countries, as well as the incidence records from Cancer Incidence in Five Continents (CI5) in order to examine dynamic trends [16] [17]. Currently, non-Hodgkin's lymphomas are considered the more common group of HM, the incidence continuously increasing. The incidence of Western cancers is 14 - 19 new cases per 100,000 inhabitants and equal to 4% of all cases with malignant

tumors [1] [5]. Increased morbidity in extra-ganglionic B-cell lymphomas, follicular lymphomas, and T-cell lymphoma lymphomas is found in the majority of specialty references. In 2016, there were 461,000 (95% UI, 428,000 - 482,000) newly diagnosed cases of non-Hodgkin lymphoma and 240000 deaths (95% UI, 221,000 - 248,000) due to the progression of these lymphoproliferative malignancies [3]. The incidence of non-Hodgkin's lymphomas increased by 45% between 2006 and 2016, from 319,078 to 461,000 cases. Globally, the newly diagnosed cases between 2006 and 2016 increased by 45% (95% UI, 38% - 48%), of which 17% were due to the increasing age-specific incidence rates, 15% – to changing population age structure, and 12% – to population growth. Worldwide in 2018, NHL constituted the 5-9th most frequent group of malignant neoplasms, with nearly 509,590 new cases and 248,724 deaths [18]. Incidence rates at the beginning of the last decade varied significantly by geographical region, being higher in males, especially in Israeli Jews (age-standardized incidence of 17.6 per 100,000 inhabitants), in white Americans (14.5 per 100,000), in Australia (15.3 per 100,000), Canada (13.7 per 100,000) and Portugal (13.3 per 100,000). The similar geographical pattern was also observed in females, with the highest incidence rates recorded in the population of Israel (13.0 per 100,000), white Americans (10.4 per 100,000), in Canada (10.0 per 100,000), Australia (12.3 per 100,000) and the lowest – in Middle Africa (2.8 per 100,000), South Africa (1.6 per 100,000), Vietnam (3.5 per 100 100,000), India (3.6 per 100,000). Higher incidence rates of non-Hodgkin's lymphomas were frequently found in countries classified as having a very high Human Development Index, while many countries rated as having a low and medium Human Development Index showed a lower incidence. The authors summarized that the relationship between the incidence rate of non-Hodgkin's lymphomas and the level of the Human Development Index seemed to be determined by countries with a very high level of this composite statistical indicator. Compared with Western countries, Asian patients have an increased rate of marginal zone lymphoma and a decreased rate of follicular lymphoma and chronic lymphocytic leukemia/small cell lymphocytic lymphoma [19] [20] [21]. Those differences likely reflect known variations in genetic susceptibility to B-cell non-Hodgkin's lymphomas between Asian and Western populations [22] [23]. For some histopathological subtypes, the existence of certain molecular pathways or etiological factors is assumed, which may contribute to regional differences in incidence rates. For example, despite the low incidence of follicular lymphoma in Asia compared to Western populations, the frequency of the bcl-2 translocation, characteristic of this histopathological type, is similar in healthy populations from both regions, suggesting that the development of follicular lymphoma may be triggered in Asia and in western countries through different mechanisms [24]. However, the incidence of non-Hodgkin's lymphomas is increasing both globally and regionally. The epidemiological study, performed in South Korea, demonstrated that the age-standardized incidence of B-cell non-Hodgkin's lymphomas increased dynamically from 5.74 (95% CI, 5.51 to 5.98) per 100,000 inhabitants in 2011 to 6.96 (95%

CI, 6.72 to 7.20) per 100,000 inhabitants in 2015. The age-standardized incidence rates of diffuse B-macrocell lymphoma, marginal zone lymphoma and of follicular lymphoma were significantly increased ($p < 0.001$), with similar increases seen in men and women [25]. Between 2011 and 2015, the incidence of diffuse B-macrocell lymphoma increased by 11%, of marginal zone lymphoma—by 32%, and of follicular lymphoma—by 25%. The age-standardized incidences of mantle cell lymphoma and Waldenstrom's macroglobulinemia remained relatively stable between 2011 and 2015, although in Waldenstrom's macroglobulinemia there was some annual variation in morbidity in women and men. The crude and age-standardized prevalence of B-cell non-Hodgkin's lymphomas increased steadily every year and was about 2.5 times higher in 2015 than in 2011. The South Korean epidemiological study shows that the prevalence indices of each subtype of B-cell non-Hodgkin's lymphomas also increased. The age-adjusted prevalence of diffuse large B-cell lymphoma increased 1.8 times, of chronic lymphocytic leukemia/lymphocytic lymphoma—1.7 times, of follicular lymphoma—2.6 times, of mantle cell lymphoma—4.0 times, marginal zone lymphoma—11.3 times and Waldenstrom's macroglobulinemia—1.6 times ($p < 0001$). These increases are considererd to be similar in women and men across all B-cell non-Hodgkin's lymphomas subtypes.

Despite the implementation of new antineoplastic agents, the available bibliographic sources reported about a dynamic increase of gross and age-standardized mortality rates. Recent researches revealed that age-standardized mortality increased by 42% from 1.33 per 100,000 inhabitants in 2011 to 1.89 per 100,000 population in 2015. Non-Hodgkin's lymphomas mortality rate was also growing before this period, estimated at 143,000 deaths in 1990 and 210,000 deaths in 2010 [26]. The highest mortality rate from non-Hodgkin's lymphomas was reported in New Zealand and Canada. The mortality rate in the USA was estimated at 1910 cases in 2018 [27] and at 3125 cases in Canada during the years 1984-2014 [28]. The similar trend from the mortality rate was observed in China, with 52,100 deaths caused by this malignant tumor (32,700 men and 19,400 women) in 2015 [29]. According to another publications, the death rate from non-Hodgkin's lymphomas increased by 2.5% annually from 1975 to 1991, with a downward trend during 1991-1997 (1.6% annually). Subsequently, during the period 2006-2011, the mortality rate decreased annually by 3.1% [30] [31]. In 2016, there were 467,000 (95% UI, 423,000 - 489,000) new cases of leukemias worldwide and 310,000 (95% UI, 286,000 - 324,000) deaths. Between 2006 and 2016, the newly diagnosed cases increased by 26% from 370,000 (95% UI, 344,000 - 385,000) to 467,000 (95% UI, 423,000 - 489,000). The main contributors to this increase were population growth by 12%, population aging by 10%, and an increase in age-specific incidence rates with 3% [3]. In 2011, an estimated 44,600 patients were diagnosed with acute and chronic leukemia in the United States, and in 21,780 cases death occurred due to the progression of these diseases. The growing interest is attributed to the epidemiological patterns and diseases burden of the BCL/ABL1-positive and BCL/ABL1-negative myeloprolifera-

tive neoplasms. The incidence and prevalence of these HM varies worldwide, but exhibit a trend of slow increase. Morbidity due to chronic myeloid leukemia varies between 0.6 - 1.6 cases per 100,000 population. The incidence of primary myelofibrosis is 0.5 - 1.5 cases per 100,000 population. Morbidity due to polycythemia vera varies between 0.2 - 1.3 cases per 100,000 population. Morbidity due to malignant hematological diseases increases with age, with a maximum incidence between 45 and 65 years, the diseases thus affecting the working-age population.

In 2017 the study of the global burden of disease (GBD) analyzed and systematized data on the incidence and annual mortality of CML, DALYs, risk attributive factors, as well as information on age, geographical distribution and sex. Globally, non-Hodgkin lymphomas caused 6.8 million (95% CI, 6.2 - 7.1 million) DALYs (disability-adjusted life-years) in 2016, with 98% arising from years of life lost and 2% from years lived with disability [3], placing these lymphoproliferative malignancies in a favorable position as compared to leukemias. Worldwide in 2016 leukemias caused 10.2 million DALYs (95% UI, 9.3 - 10.8 million). The GBD 2017 study classified the countries of the world into 5 quintiles (high, high-medium, medium, low-medium, low) of social-demographic index (SDI). With regard to CML, the GBD has varied significantly from country to country due to different possibilities for early screening, accessibility of new antineoplastic agents and medical resources [32] [33]. In order to describe the CML burden, annual incidence cases, death cases, DALYs and the corresponding age-standardized rate (ASR) were analyzed. The estimated annual percentage changes (EAPC) were appreciated on the ASR base and used to quantify the ASR trend. In 1990, the age-standardized incidence rate (ASIR) was higher (1.34 per 100,000 population) in quintiles with high SDI. By 2017, there was a significant upward trend of ASIR in low SDI quintiles (0.65 per 100,000 population, 95% IU), which exceeded high SDI quintiles (0.53 per 100,000 population, 95% IU). Regarding the geographical distribution, in 2017 Western Europe with an incidence of 61.62×10^2 (95% IU) of cases and South Asia with an incidence of 80.44×10^2 (95% IU) of cases remained at the top of the higher morbidities among regions of the world. In the same year in these geographical areas the highest number of deaths and DALYs was found – respectively 42.45×10^2 (95% IU) and 66.60×10^2 (95% IU), 68.46×10^3 (95% IU) and 207.79×10^3 (95% IU). In 1990 the age-standardized death rate (ASDR) (0.92 per 100,000, 95% IU) and the ASR of DALYs (24.23 per 100,000, 95% IU) proved to be superior in quintiles with high SDI. In 2017, the situation was considerably opposed, with a comparatively high level of ASDR (0.6 per 100,000 population, 95% IU) and ASR of DALYs (16.71 per 100,000 population, 95% IU) in quintiles with low SDI. The study found that ASIR ($\rho = -0.610$, $p < 0.01$), ASDR ($\rho = -0.471$, $p < 0.01$) and age-standardized DALYs rate ($\rho = -0.403$, $p < 0.01$) in 1990 exhibited a negative correlation with the corresponding EAPC. The correlations between SDI and EAPC incidence ($\rho = -0.509$, $p < 0.01$), deaths ($\rho = -0.620$, $p < 0.01$) and DALYs ($\rho = -0.632$, $p < 0.01$) were also negative. Herewith, the referring study could

demonstrate a faster decreasing trend of ASR in countries with weightier disease reservoir baseline in 1990 or with higher SDI in 2017. The trends in the CML burden revealed by the GBD study provided important information for the promotion of medical services and public health. Despite the declining overall trend of ASIR, ASDR, and age-standardized DALYs in quintiles with high SDI, the CML burden remains stable due to increased population growth in emerging region countries and an aging population in developed countries [3]. Between 1990-2017, the incidence decreased by 34.9% in quintiles with high SDI, increasing by over 60% in quintiles with low SDI, medium-small and medium SDI. Developing countries continue to bear the substantial burden of CML mainly due to reduced access to the newest targeted antineoplastic therapy [34].

The issue of medical costs of treating HM, especially non-Hodgkin's lymphomas, is a subject of regular concerns in the scientific literature. A retrospective cohort analysis of direct costs was undertaken in patients primarily diagnosed with non-Hodgkin's lymphomas and in the control group (subjects without an oncological diagnosis) using the MarketScan® medical and drug claims database from the eligible employers [35]. The analysis was carried out in order to demonstrate the dynamics of costs related to aggressive non-Hodgkin's lymphomas by examining the costs associated with the remission induction, secondary and palliative phases of treatment, as well as to evaluate the economic consequences of treatment failure. Patients with aggressive (n = 356) and indolent (n = 698) non-Hodgkin's lymphomas were found to receive health services with high associated costs compared to control group. The primary determinants of costs were hospitalizations (aggressive non-Hodgkin's lymphomas—44%, indolent non-Hodgkin's lymphomas—50% of total costs) and outpatient visits (aggressive non-Hodgkin's lymphomas—39%, indolent non-Hodgkin's lymphomas—34% of total costs). A study of the USA working population [36] may be considered of scientific and practical values, which assessed the indirect costs and workplace productivity losses associated with non-Hodgkin's lymphomas using The MarketScan® Commercial Claims and Encounters and Health and Productivity database Management Databases (2007-2013). As compared to the control group, patients with non-Hodgkin's lymphomas sustained the most significant loss of workplace productivity (31.99 days; 95% CI: 25.24 days, 38.73 days; $p < 0001$). After 12 months from diagnosis, indirect costs associated with non-Hodgkin's lymphomas were increased (6302.34$; 95% CI: 4973.40$, 7631.28$; $p < 0001$). In aggressive non-Hodgkin's lymphomas, the mean monthly costs of induction treatment (10,970$) and palliative care (9836$) exceeded those related to the secondary phase of treatment (3302$). The average cost of treatment failure in the respective histopathological types was 14,174$ per month and 85,934$ over the entire study period. Therefore, the treatment-related expenses were higher in aggressive non-Hodgkin's lymphomas compared to indolent ones, especially in the induction phase and palliative care. The authors concluded that treatment failure proved to be the most costly aspect of medical care.

The degree of utilization of health system resources was studied in cases of

progression of non-Hodgkin's lymphomas. Patients with tumor progression had 23% more frequent outpatient visits compared to patients in remission ($p < 0001$). In the group of patients with progression, the frequency of referral for laboratory investigations was twice as higher ($p < 0001$) in outpatient conditions. The proportion of patients who received chemotherapy increased significantly (72%) as compared to those without progression (29%; $p < 0001$). In the group of patients with progression, the authors found the higher frequency of visits for combined infusional chemotherapy (1610.86) as compared to the group without progression (166.07; $p < 0001$), suggesting the administration of more intensive chemotherapy regimens, since the majority of responded patients followed the maintenance therapy with Rituximab. Follicular non-Hodgkin's lymphoma progression was associated with a higher frequency (18%) of hospitalizations and emergency department's visits as compared to cases with remissions or tumor stabilization (4%; $p < 0.001$). The obtained results supported the authors' hypothesis, according to which the treatment strategies that postponed or prevented the progression of follicular non-Hodgkin's lymphoma not only improved clinical balances, but also ensured the substantial economic benefits in terms of costs reduction of the provided medical services. Another study [37] demonstrated that, based on the standard monthly cost for a patient, the mean costs of treatment failure in aggressive NHL were 14,174$, being significantly higher than those estimated in follicular non-Hodgkin's lymphoma. The improved survival rates indicate that more patients are living with the disease. The patients with progression of the tumor process and conventional treatment registered a relatively long life span [38].

An analysis of the Living with MPNs survey was conducted to assess the impact of chronic myeloproliferative neoplasias on employment, career potential and work productivity [39]. This cross-sectional survey included respondents between the ages of 18 and 70 living in the US. The survey included ~100 questions related to the diagnosis of chronic myeloproliferative neoplasia, medical history of the disease, symptoms and functional status determined by chronic myeloproliferative neoplasia, changes in employment and work productivity, impact on daily activities from the date of diagnosis. The Chronic Myeloproliferative Neoplasia Symptom Assessment Form Total Score (MPN-SAF TSS) was used to assess symptom burden. The Work Productivity and Activity Impaired by Specific Health Problem Questionnaire (WPAI-SHP) was used to assess the effects of chronic myeloproliferative neoplasia on work productivity and activity. Of the 904 respondents, 592 were employed at the time of diagnosis. About half (50.5%) of the 592 respondents reported ≥ 1 change in their employment status due to diagnosis, the most common being "left a job" (30.2%), "went on leave medical leave due to disability" (24.8%) and "had reduced working hours for at least 3 months" (21.8%). Among respondents who remained employed at the time of survey participation ($n = 398$), mean WPAI-SHP scores were as follows: absenteeism—6.9%, presenteeism—27.4%, total work impairment—31.1% and activity impairment—32.8%. WPAI-SHP scores correlated positively with MPN-SAF

TSS (correlation coefficients—0.37 - 0.70; P < 0.001). Analysis of the Living With MPNs study indicated that chronic myeloproliferative neoplasms exert a substantial negative impact on patients' employment, career potential and work productivity. The degree of work productivity impairment caused by chronic myeloproliferative neoplasia was comparable to that in other chronic pathologies. Patients with moderate to severe rheumatoid arthritis reported impairments regarding productivity and work activity (range of mean scores: absenteeism—2.4 - 11.8; presenteeism—13.7 - 39.7, total work impairment—15.2 - 43.2, activity impairment—19.1 - 56.2), which were similar to values recorded from respondents in the Living with MPNs survey.

An extensive study of the financial burden of chronic myeloproliferative neoplasms on patients was conducted in the USA in 2014 [39]. For analysis, 369 subjects were eligible, with the diagnosis established in 2013 and the age between 16 - 65 years at the time of diagnosis (primary myelofibrosis—85, polycythemia vera—172, essential thrombocythemia—112). Almost all patients (99%) had health insurance, including commercial insurance by an employer (primary myelofibrosis—46%, polycythemia vera—53%, essential thrombocythemia—57%) and Medicare (primary myelofibrosis—40%, polycythemia vera—34%, essential thrombocythemia—24%). The average household income in 2013 for patients with primary myelofibrosis, polycythemia vera, and essential thrombocythemia was similar to each other (79,800$, 80,200$, and 80,400$, respectively) and slightly higher than the total income per capita in 2013 (75,839$). A significant proportion of patients in each group of chronic myeloproliferative neoplasms reported that their disease led to reduced working hours, interruption of activity and medical disability: primary myelofibrosis—38%, 35%, 33%, polycythemia vera—33%, 28% and 15%, essential thrombocythemia—28%, 21% and 4%, respectively. The patient's medical and social aspects, such as age and health insurance status, were similar among patients who reported effects associated with chronic myeloproliferative neoplasms on employment and patients who were not related to each group of chronic myeloproliferative neoplasms. In each group of chronic myeloproliferative neoplasms, the average percentage of loss of household income in patients with reduced working hours, discontinuation of employment and medical disability were in primary myelofibrosis—16%, 18%, 28%, polycythemia vera—15%, 24%, 17% and essential thrombocythemia—0%, 24%, 37%, respectively, compared to patients who did not have any impact of chronic myeloproliferative neoplasms on their employment status. Discontinuation of employment and medical disability tended to have a wider negative impact as compared to reduced working hours in all chronic myeloproliferative neoplasms [39] [40]. Nevertheless, the degree of impairment of occupational productivity, caused by chronic myeloproliferative neoplasms, proved to be comparable to that in other chronic non-oncologic pathologies.

A relevant study of multiple myeloma related costs was performed by the university hematology centers in Italy [41]. The study enrolled 236 patients with this common and disability HM. In 164 (69.5%) cases the period of disease

monitoring and reporting did not exceed 5 years. Patients treated with autologous hematopoietic stem cell transplantation were younger (average age— 58.7 years) as compared to those managed with chemotherapy and immunomodulatory drugs (average age—67.8 years). The total costs of the disease reached the value of 19267.1€ ± 25078.6 (asymptomatic patients—959.3€ ± 1091.6; symptomatic patients receiving medication—21707.8€ ± 21785.3; symptomatic patients treated with autologous transplantation of stem cells –59243.7 € ± 4214.0; patients in plateau/remission—8130.7€ ± 15092.5). The main determinants of the total costs of the disease were medication and hospitalizations (46.1% and 29.4%, respectively). Antineoplastic and immunomodulatory preparations constituted 21.6% and 21.1% of the total costs of the disease. The list of costs of antineoplastic drugs was led by bortezomib (97.4%), while lenalidomide (99.4%) served as the determining cost factor in immunomodulatory therapy. The cost of hospitalization ensured by the Italian National Health Service was mainly influenced by transplantation (94.6%), while chemotherapy and treatment of skeletal fractures did not exceed 1% and 2%, respectively. The financing of health care costs, pocket expenses and lost productivity accounted repectively for 83.8%, 3.1% and 13.1% of the total costs of the disease. The lowest and highest occupational productivity losses were reported by asymptomatic patients (21.9€ ± 95.3) and patients after autologous stem cell transplantation (9538.3€ ± 17612.4). These amounts were equal respectively to 2.3% and 16.1% of the total costs of the disease. The same groups of patients required the lowest and highest costs for informal care: 51.3€ ± 147.7 (5.4% of the total cost of illness) and 1015.4€ ± 2100.1 (1.7% of the total cost of the disease), respectively.

The narrative analysis of the recently published studies revealed, that the socio-economic impact of HM depended on the nosological entity, and was determined by the degree of emerged disability, the treatment complexity and the need for hospitalizations. Prevention or reversal of unfavorable medical and social patterns of HM can be considered as a factor in the improvement of patients' management, which reduces the negative impact on their individual productivity.

6. Conclusion

The epidemiological study revealed slightly lower morbidity by HM in the Republic of Moldova as compared to the West European countries mainly due to the migration of a workable population. The patients with malignant lymphomas, male gender and age categories of 50 - 79 years proved to be commonly registered epidemiological patterns. Asian patients had an increased rate of marginal zone lymphoma and a lower rate of follicular lymphoma and chronic lymphocytic leukemia/small cell lymphocytic lymphoma, as compared to Western countries. The narrative analysis of the literature revealed that patients with HM, especially those with aggressive non-Hodgkin's lymphomas, acute leukemias, multiple myeloma and chronic myeloproliferative neoplasms, may experience a

considerable disease burden with a negative impact on their employment status and working productivity, which in turn may be associated with low annual household income. The synthesis of bibliographic references showed the increase in expenses related to the treatment of aggressive non-Hodgkin's lymphomas as compared to those indolent, especially in the induction phase and within the framework of the palliative service. Treatment failure proved to be the most costly issue of medical services provided to patients with non-Hodgkin's lymphomas. The prevention or reversal of the unfavorable medical and social patterns of HM can be considered as an optimizing factor of patients' management, which reduces the negative impact on their individual productivity.

Author's Contribution

Vasile Musteata conceptualized and designed the researches, collected and interpreted the data, and drafted the manuscript.

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Conflicts of Interest

The author has no conflict of interest to declare.

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