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Managements of Special Health Care Needs Patients from Dental Assistant Point

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Abstract

The main role of this article is to describe dental assistants and the dental department's role in the dental delivery system for Special health care needs (SCHN) by creating a structure to educate the dental assisting profession and project factors that have a significant impact on the dental assistant. The dental assisting management of SCHN patient's profession including dental Assistance general responsibilities, regulation credentialing, and education. The SCHN patient's management creates a challenge in all area of the dental department. Handling patient with a SCHN is underexplored throughout the dental staff especially when there is not enough theoretical foundation, education and training to deal with this category of patients. SCHN patients are defined as individuals who have abnormal behavioral impairments, mental conditions or/and chronic disease or abnormal laboratory results. Thus, the aim of this article is to guide all dental assistance staff in the best dental management choice for SCHN patients. All health care teams are part of patient care in most medical settings. A work environment supportive ensures positive outcomes for patient care. This article was considered as those categories of patients required more care and special way to deal with, moreover language, age, gender and education level of the patient are also considered significant parries. Not Many studies were found to support the care of SCHN patients in dentistry department. Taking experience from other area help to design a system to handle the SCHN even if it requires hiring a Dentist who is specialized in that filed.

Keywords

Dental Management, Dental Assistant, Dentist, Special Needs, Special Health Care Need

1. Introduction

1.1. What Does a Dental Assistant Mean and What Is Their Job Descriptions

Dental assistants are specialized health care workers who provide direct support to the dentist. Well Educated dental assistants may be delegated to do other procedures that do not require the professional skill and judgment of a dentist. Dental assistants may require a minimum education which includes two academic years [1].

A Dental Assistant can work with different dental professional categories. A Dental Assistant can cover duty with Dentists, Hygienists, Prosthetists, Specialists or oral Health Specialists. Generally, any professional working in dentistry may need a Dental assistant during their daily clinic. Dental assistant usually has the most diverse role in a dentistry practice, and really need to stay on their toes [2]. The primary responsibility of the assistant is to prepare the Clinic and the examination room for patient appointments by sterilizing instruments and ensuring all necessary materials and equipment are ready for the doctor to start the work. They also assist during their procedures by handling the instruments and anticipating the equipment and the materials needed throughout the appointment. The Dental Assistant may also be responsible for greeting patients as they arrive, submitting billing details to the insurance company and scheduling the patient's next appointment before they leave the clinic [3]. Other duties and responsibilities include:

- Update and maintain client's dental records and take and process X-rays of patients.
- Perform routine dental cleanings and assist the dentist with any procedure.
- Schedule patient appointments and help to advise patients on recommended oral hygiene.

The job description of the dental assistant like other medical health workers involves direct contact with the patient and their legal grading. It is easy to do the job if you deal with an educated patient, more difficulty rise when there is a gap in the explanation either from the dental assistant's side or the patient side. The dental department may hire a coordinator to deal with the patient who will have significant benefits to the department and the patient [4]. The department of the dentist may hire a special dentist who is specialized to deal with SCHN patients [5] [6].

1.2. What Is Special Health Care Need Mean (SHCN)

SHCN patients are defined by any physical, developmental, mental, sensory, or behavioral, condition that requires specialized services or programs. The condition may be congenital, developmental, or acquired through disease, trauma, or environmental cause and may impose limitations in performing daily self-maintenance activities or substantial limitations in a major life activity [7] [8].

2. Methods

PubMed®/MEDLINE search using the terms: special needs patient, disability,

disabled patients/persons/children, Special patients/Dental treatment dentistry, Special care health needs and oral health; fields: all; limits. Papers for review were selected from the result list of articles and from references within the selected search. The article search was done during the period of 2009-2021. When data did not appear sufficient or were inconclusive, recommendations were based on expert and/or consensus opinions by experienced researchers and clinicians. Systematic and non-systematic reviews, studies on a series of cases and research articles were considered to structure this article.

3. Literature Review

Passed on the National Survey of Children's Health in 2017-2018, approximately 13.6 million children (18.5 percent) had a special health care need [9]. 26.6% had functional limitations, 19.9% were consistently or significantly impacted by their health condition, and 46.0% were sometimes/moderately impacted by their health condition(s). Since there is a significant improvements and development in medical cares SHCN are living longer and require extended medical and oral care [10].

SCHN patients at childhood age increase the risk of having urgent medical care including oral health care [11]. Difficulties may be due to serious reasons which may include finding a dentist who is willing to provide care, child's cooperation, and transportation and communication issues [12] [13].

SHCN patients rely mostly on free government coverage to pay for their medical and dental care. Lack or delay of treatment may lead to an increase in the need for costly care health issues [14].

Language and cultural considerations and other barriers may interfere with the oral health care of SCHN patients. Communication skills are essential for SCHN patients and can be accomplished by trying different methods which may include interpreters, written materials, and lip-reading [8]. Lack of knowledge from parents, Dentists and dental assistant also play a significant role in dealing with SCHN patients [15].

SHCN patients significantly require additional considerations for behavior guidance which include the patient's mental development, level of education, patient cooperation in medical procedure, type of therapy or procedure as these can complicate or delay the delivery of the needed care. The use of basic behavior guidelines may help to recognize and manage SCHN patients [16] [17].

4. Recommendations

The management of SCHN may include several steps which need to be implemented and consider. Steps may include the Evaluation of the General Health issues of the patient and then the Evaluation of the Oral Health process. Evaluation of behavior difficulties of the patient, Planning and establish the best dental treatment case by case. The evaluation of General Health issues help the dental assistant to provide a complete health history which can be obtained or fulfilled

by the parents of the patient this information may include medical history, medications in use, abnormal laboratory test or any health problems. Clear medical history is essential before moving to the treatment process plan. Evaluation of Oral Health process and the reasons of consultation must be considered before performing the clinical examination. X-ray or At least one panoramic must be taken before the exam. Evaluation of Behavior difficulties of the patient is the most relevant aspect in this protocol. For that, So we suggest that the behavioral will be based on the amended Frankl scale (**Table 1**), which considers the level of cooperation of the patient; and the scale developed by Houpt and co-workers (**Table 2**), based on patient movement during the procedure or examination The application of the scales can give a good indicator as to whether outpatient care can be performed or not [18]. After completing the steps of the clinical assessment, the best treatment plan for each patient must be drawn and classified. During the planning and establishing the best dental treatment the dental assistant and the dentist should not assume that patients with difficult communication skills have associated intellectual disability, unless it is specified and reported [19].

Table 1. Frankl scale for evaluating behavior modified by De Nova Garcia, 2007 [18].

Category 1	Clearly Negative	Total lack of cooperation
Category 2	Negative	Signs of lack of cooperation
Category 3	Positive	Accepts treatment with caution. May require reminders (open mouth, hands down, etc.)
Category 4	Very Cooperative	No sign of resistance. Very cooperative

Table 2. Scale for evaluating movement (Houpt and Co-Workers 1985). Modified by De Nova Garcia, 2007 [20].

1. Violent movement constantly interrupting examination
2. Constant movements that hinder examination
3. Controllable movements that do not interfere with the procedure
4. Lack of movement

5. Conclusion

This article is made to set the challenge that dental assistants face when dealing with s SHCN patients. Like other parts of the community, a system must be designed for this category of patient. A Well trained dental assistant can handle the multi task and perform a significant role in the dental department. The number of this category of patients significantly increased every day with new and rear cases. The dental assistant must keep herself self-updated about the patient's situation and adopt a technique to deal with SCHN patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Daily Lifestyle Habits as Risk Factors for Plaque-Induced Gingivitis and Periodontitis Severity and Grading among Samples of Dental Students at King Khalid University

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Abstract

Objective: To assess daily lifestyle habits as risk factors for plaque-induced gingivitis and periodontitis severity and grading among samples of dental students at King Khalid University. **Material and Methods:** This study included 150 male participants. They were divided according to the levels into three equal groups: levels 5, 6, and 7 (group I), levels 8, 9, 10 (group II) and levels 11, 12, and interns (group III). This study consisted of questions related to age, gender, educational level, father's education, mother's education, home ownership, brushing teeth more than or twice a day, in addition to daily lifestyle habits that were daily smoking, daily use of sugary drinks, and daily use of sugary foods. Some clinical parameters of plaque-induced gingivitis and periodontitis and the percentage of radiographic bone loss were recorded. All data were collected and analyzed using Tukey's test and Chi-square test. A P-value of less than 0.5 ($p < 0.5$) was considered a statistically significant difference, and less than 0.001 ($p < 0.001$) was a highly statistically significant difference. **Results:** One hundred fifty male dental students of different levels in the college of dentistry at King Khalid University participated in the study in three groups (I, II, and III). The mean age of group III is more than that of group II and group I, with highly statistically significant differences ($p < 0.001$). There are significant differences in periodontal clinical parameters in the comparison between group I, group II, and group III ($p < 0.05$). The plaque index score (2.1 - 3) and the gingival bleeding index score (>30%) were more among the participants in group I than the participants in groups III and II. There was an increase in the percentage of affected participants with stages III and IV of clinical attachment loss (CAL), periodontal

pocket depth (PPD), radiographic bone loss (%RBL), tooth mobility, as well as glycated hemoglobin (HbA1c) test values (>7%), and the number of cigarettes smoked per day (>10 cigs) in group III more than in group II and I. **Conclusion:** We conclude that the severity and grading of plaque-induced gingivitis were higher among the participants in group I, while the severity and grading of periodontitis were higher among the participants in group III due to the different impact of their daily lifestyle habits.

Keywords

Daily Lifestyle, Dental Students, King Khalid University, Periodontitis, Plaque-Induced Gingivitis

1. Introduction

Periodontal disease is a group of inflammatory diseases of the surrounding periodontal tissues that have a multifactorial etiology with a dental plaque as the primary factor [1]. They may be more common in developing countries than in developed countries [2] [3], where 10% - 15% of the world's population suffers from the periodontal disease [4].

The incidence of periodontal diseases is associated with health-related risk behavior factors such as carbohydrate-rich diets, alcohol intake, smoking, and inadequate oral hygiene, which are prevalent in developing countries, and other factors, including poor access to healthcare services and low socio-economic status [5] [6]. Thus, the severity and progression of periodontal diseases are influenced by various factors [7].

Some studies have shown that incorrect tooth brushing frequency/technique and frequent sugar intake increase inflammation of periodontal tissue [8] [9] [10]. In contrast, another study reported that periodontal tissue inflammation among individuals with homeownership, higher parental education, and family income or who owned a car was lower [11].

Lifestyle has been described as an individual daily activity including healthy and risky behaviors. Recently, lifestyle is gaining importance in maintaining periodontal health because it reflects the way people live, their attitudes, and their activities that may have a direct or indirect effect on the severity and progression of periodontal disease [12]. Belloc and Breslow's research was the first study that revealed the strong relationship between lifestyle exercise and physical health status [13]. Moreover, another study detected that individuals who have an active lifestyle have good oral hygiene [14].

In Saudi Arabia, there are lifestyle changes that occur, and they have passive effects on public health due to their association with various systemic and oral diseases such as increased sweetened beverages and consumption of fruit juices as well as increased smoking and irregular tooth-brushing among young Saudi people [15] [16] [17].

The relationship between the severity and progression of periodontal diseases

and daily lifestyle habits in the population should be assessed through practical diagnostic methods to promote periodontal health. Public health organizations rely on community oral health promotion programs to detect periodontal diseases early in younger age groups to prevent the progression and severity of periodontal diseases. Therefore, the aim of this cross-sectional study was to evaluate daily lifestyle habits as risk factors for plaque-induced gingivitis and periodontitis severity and grading among samples of dental students at King Khalid University.

2. Material and Methods

2.1. Study Samples and Design

One hundred and fifty male participants in this cross-sectional study were counted as the minimum sample size. They have been selected from a list of students from the college of dentistry at King Khalid University, Saudi Arabia, from October 2021 to January 2022. They were divided into three equal groups from levels 5 to 12 and interns (20 - 27 years old). Group I (50 participants from levels 5, 6, and 7), group II (50 participants from levels 8, 9, and 10), and group III (50 participants from levels 11, 12, and interns).

2.2. Ethical Considerations

This study was performed with the understanding and consent of the participants and in compliance with the ethical standards of the Declaration of Helsinki of the World Medical Association. This study was approved by the Institutional Review Board (IRB) of the college of dentistry at King Khalid University. Informed consent was obtained from participants before the start of the study.

2.3. Inclusion Criteria

Inclusion criteria include: 1) Participants with periodontal diseases, 2) Participants with at least 20 remaining teeth in a minimum of four sites in the oral cavity with bleeding on probing (BOP), probing pocket depths (PPD) more than 3 mm, and clinical attachment loss (CAL) more than 1 mm [18], 3) Patients who did not receive periodontal treatment during the 6months before the start of this study [19].

2.4. Exclusion Criteria

Exclusion criteria include: 1) Students of the other King Khalid University colleges, 2) Levels 1, 2, 3, and 4 for students of the college of dentistry, King Khalid University, 3) Participants who did not answer the lifestyle questions or refused the clinical examination, 4) Students who suffer from any local or systemic diseases that can affect the periodontal tissues, 5) Students who did not provide informed consent.

2.5. Participants' Interview

Participants were interviewed to assess their attitudes toward oral and peri-

odontal health. A self-administered, close-ended, and structured questionnaire was used to collect the personal data (age, father's education, mother's education, homeownership, daily brushing teeth, smoking status, and medical status) of the participants.

2.6. Clinical Examination

A periodontal examination was performed for each participant and recorded on a periodontal chart. This clinical examination included **plaque index (PLI)** [20], gingival bleeding index (GBI) [21], probing pocket depth (PD) [22], clinical attachment level (CAL) [23], and tooth mobility (present or absent).

2.7. Glycated Hemoglobin (HbA1c) Levels

Participants' medical reports were used to record glycated hemoglobin (HbA1c) levels. The National Glycohemoglobin Standardization Program (NGSP) system was applied in the assessment of HbA1c levels [24].

2.8. Radiographic Examination

The percentage of radiographic bone loss was obtained from extra-oral digital panoramic radiographs (GendexOrthoralix 9200 DDE, Georgia-USA) according to the severity of alveolar bone assessed by the American Academy of Periodontology (AAP) as mild (<15%), moderate (15% - 33%), and severe (>33%) [25].

2.9. Statistical Analysis

Statistical analysis was performed with the ANOVA test. Data analysis included descriptive statistics on the age of the participants. A Tukey's test was used to evaluate the comparison between group II & group III, group I & group III, and group I & group II.A Chi-square test was performed on the periodontal parameters and lifestyle habits in group I.II and III comparison and the P-value calculation. The P-value was considered as a statistically significant difference of less than 0.5 ($p < 0.05$) and a highly statistically significant difference of more than 0.001 ($p < 0.001$).

3. Results

The study was conducted on 150 dental students of different levels within three equal groups (n = 50), groups I, II, and III (response rate = 100%). The ages of groups I, II, and III ranged from 20 - 23 years with a mean (standard deviation) of 21.43 (0.88) years, 22 - 25 years with a mean (standard deviation) of 23.01 (1.68) years, and 23 - 27 years with a mean (standard deviation) of 25.79 (6.84) years, respectively (Table 1 & Figure 1).

Table 1 and Figure 1 also showed no significant relationship between the ages of the participants. There was a highly significant difference in the comparison between group II & Group III, and group I & group III as well as group I & group II ($p < 0.001$).

Table 1. The mean and standard deviation (±SD) of the participants age groups.

Groups	Age of the patient		ANOVA	
	Mean ± SD	Range	F	P-value
GI	21.43 ± 0.88	20 - 23		
GII	23.01 ± 1.68	22 - 25	129.31	1.07
GIII	25.79 ± 6.84	23 - 27		
Tukey's test				
Group II & Group III		Group I & Group III	Group I & Group II	
<0.001**		<0.001**	<0.001**	

GI: Group I, GII: Group II, GIII: Group III, **: Highly significant differences.

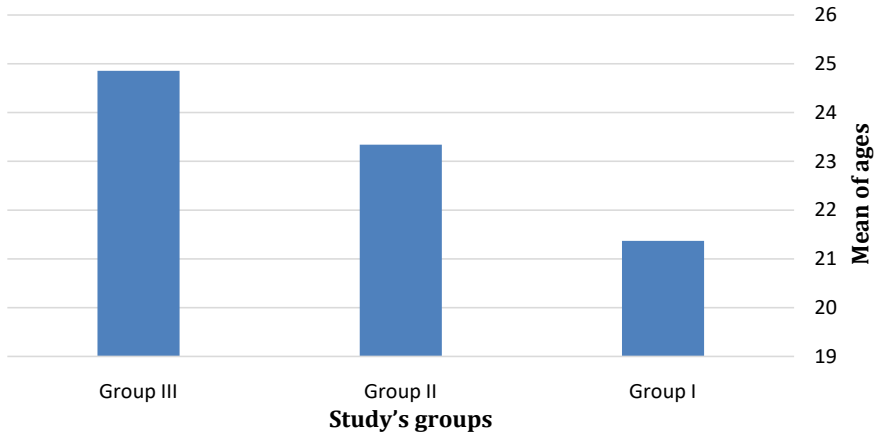

Figure 1. Mean of the participants ages groups.

The distribution of study participants according to their lifestyle characteristics is summarized in Table 2 and Figure 2. Most of the participants in group I had fathers with university education (52%) brushed their teeth ≥ 2 times daily (58%) and daily used sugary drinks (78.%) more than in groups II and III, whereas the participants in group II had more university-educated mothers (38%) and home ownership than groups I and III. Moreover, the participants in group III currently smoke more daily (34%) than the participants in groups I and II. Table 2 showed significant differences in lifestyle characteristics during the comparison between groups I, II, and III ($p < 0.05$).

Table 3 and Figure 3 shows that more than half of the participants in group I had a high average plaque index (56%) and a gingival bleeding index at ≥30% of the probing sites (54%). This table showed statistically significant differences in plaque index and gingival bleeding index during the comparison between groups I.II and III ($p < 0.05$).

Table 4 and Figure 4 show the distribution of participants according to the values of periodontal pocket depth and clinical attachment loss. The values of clinical attachment loss and periodontal pocket depth were more among group III participants than in groups I and II. Clinical attachment loss was 3 - 4 mm in 36% of participants and ≥5 mm in 12% of participants, while periodontal pocket

Table 2. Distribution of study participants according to lifestyle characteristics.

		Groups			Total N (%)	Chi-square	
		I N = 50	II N = 50	III N = 50		X^2	P-value
Father's education	**UE**	26 (**52.00**%)	13 (26.00%)	17 (34.00%)	56 (37.34%)	**6.14**	**0.063***
	LUE	22 (44.00%)	32 (64.00%)	30 (60.00%)	84 (56.00%)		
	NE	2 (4.00%)	5 (10.00%)	3 (6.00%)	10 (6.66%)		
Mother's education	UE	18 (36.00%)	19 (**38.00**%)	11 (22.00%)	48 (32.00%)	**22.18**	**p < 0.01***
	LUE	28 (56.00%)	22 (44.00%)	31 (62.00%)	81 (54.00%)		
	NE	4 (8.00%)	9 (**18.00**%)	8 (16.00%)	21 (14.00%)		
Home Ownership	**Rented**	28 (56.00%)	23 (46.00%)	35 (70.00%)	86 (57.34%)	**7.81**	**0.033***
	Owner	22 (44.00%)	27 (**54.00**%)	15 (30.00%)	64 (42.66%)		
Brushing teeth ≥ 2 times daily	**≥2 Ts/D**	29 (**58.00**%)	26 (52.00%)	13 (26.00%)	67 (44.66%)	**13.88**	**p < 0.01***
	<2 Ts/D	21 (42.00%)	24 (48.00%)	37 (74.00%)	83 (53.34%)		
Currently smoking on a daily basis	**D**	11 (22%)	15 (30%)	17 (**34**%)	43 (28.7%)	3.88	p < 0.01*
	ND	39 (78%)	35 (70%)	33 (66%)	107 (71.3%)		
Daily use of sugary drinks	D	39 (**78**%)	36 (72%)	37 (**74**%)	112 (74.66%)	0.7866	p < 0.01*
	ND	11 (22%)	14 (28%)	13 (26%)	38 (25.34%)		

UE: University educated, LUE: Less than university educated, NE: Not educated, Ts/D: Times daily, D: Daily, ND: Not daily. *: Significant differences.

Table 3. Distribution of participants according to the average of plaque index and gingival bleeding index.

		Groups			Chi-square	
		I	II	III	X^2	P-value
PI	0.1 - 1	10 (20%)	27 (54%)	17 (34%)	16.11	0.008*
	1.1 - 2	12 (24%)	8 (16%)	13 (26)		
	2.1 - 3	28 (**56**%)	15 (30%)	20 (40%)		
GBI	< 10%	13 (26%)	10 (20%)	15 (30%)	6.81	0.0035*
	10-30%	10 (20%)	15 (30%)	16 (32%)		
	>30%	27 (**54**%)	25 (**50**%)	19 (38%)		

GI: Group I, GII: Group II, GIII: Group III, PL: Plaque index, GBI: Gingival bleeding index.

depth was ≤5 mm and >5 mm in 10% of participants. There were significant differences in the comparison between the groups of participants depending on the values of clinical attachment loss and periodontal pocket depth ($p < 0.05$).

Table 5, Table 6 and Figure 5, Figure 6 show the distribution of participants according to the values of some parameters of periodontitis complexity and clinical findings of periodontitis modalities, which assessed the severity and progression

Table 4. Distribution of participants according to the values of periodontal pocket depth and clinical attachment loss.

		Groups			Chi-square	
		I	II	III	X^2	P-value
CAL	1 - 2 mm	41 (82%)	38 (76%)	26 (52%)	8.89	0.01
	3 - 4 mm	9 (18%)	10 (20%)	18 (**36**%)		
	≥5 mm	0 (0%)	2 (4%)	6 (**12**%)		
PPD	≤4 mm	48 (96%)	46 (92%)	40 (80%)	8.14	0.02
	≤5 mm	2 (4%)	3 (6%)	5 (**10**%)		
	>5 mm	0 (0%)	1 (2%)	5 (**10**%)		

CAL: Clinical attachment loss, PPD: Periodontal pocket depth.

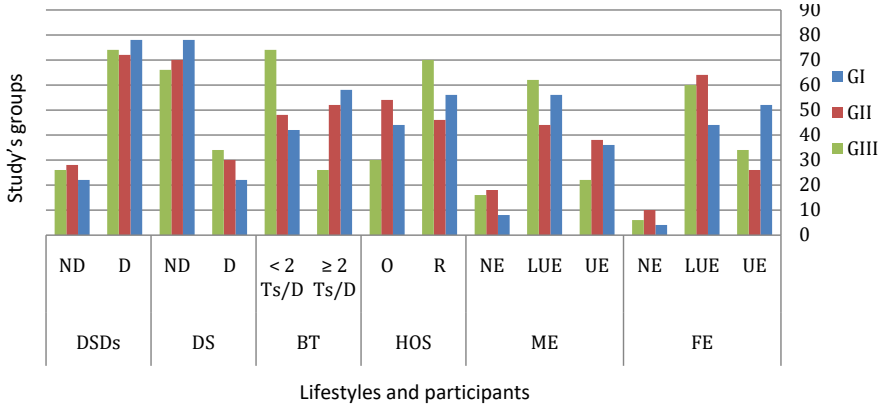

Figure 2. Participants' distributions according to lifestyle characteristics. GI: Group I, GII: Group II, GIII: Group III, FE: Father's education, ME: Mother's education, UE: University educated, LUE: Less than university educated, NE: Not educated HOS: Home Ownership, O: Owner, R: Rented, DS: Brushing teeth ≥ 2 times daily, Ts/D: Times daily, D: Daily, ND: Not daily, D: Daily, ND: No-daily, DS: Currently smoking on a daily basis, DSDs: Daily use of sugary drinks.

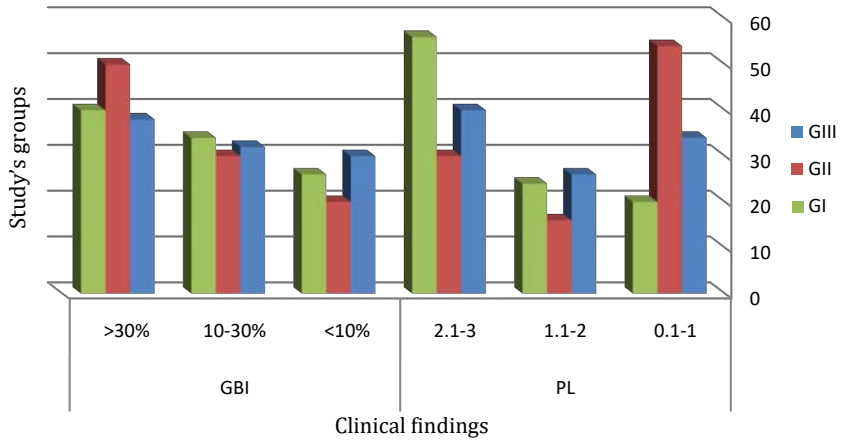

Figure 3. Participants' distribution according to plaque index and gingival bleeding index. GI: Group I, GII: Group II, GIII: Group III, PL: Plaque index, GBI: Gingival bleeding index.

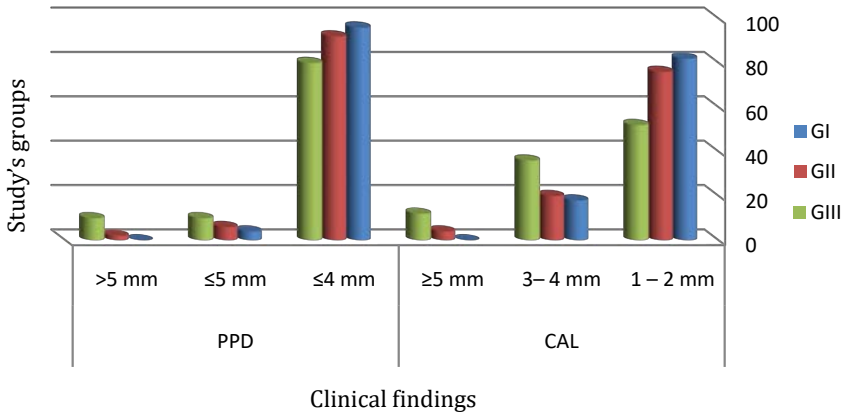

Figure 4. Participants' distribution according to the values of clinical attachment loss and periodontal pocket depth. GI: Group I, GII: Group II, GIII: Group III.

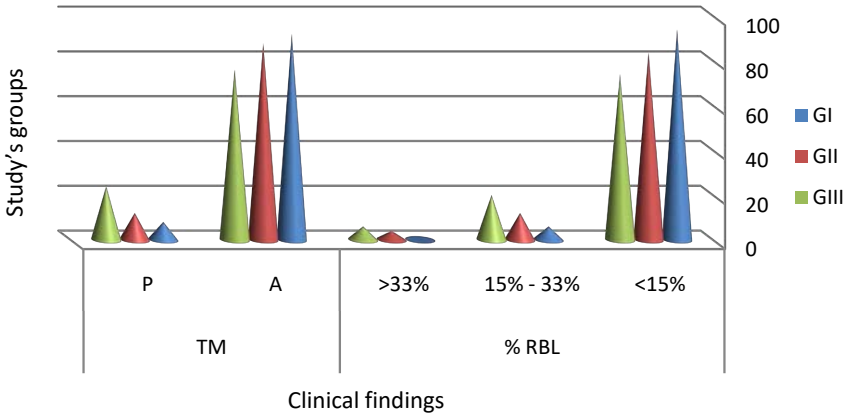

Figure 5. Participants' distribution according to the values of some parameters of Periodontitis Complexity. % RBL: Parentage of radiographic bone loss, TM: Tooth mobility.

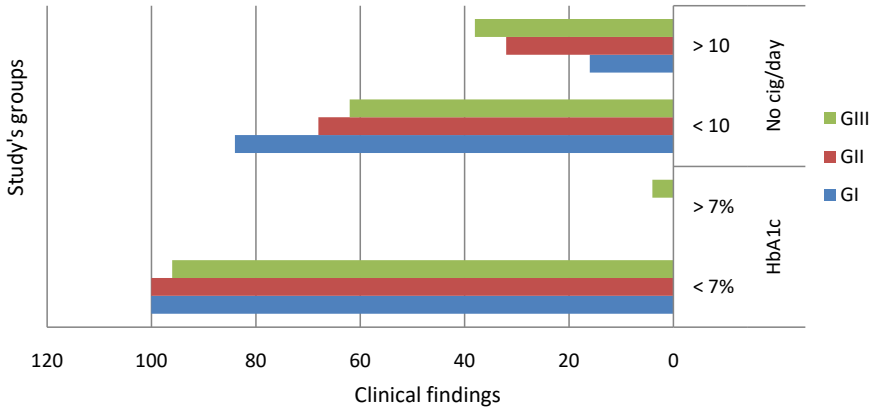

Figure 6. Distribution of study participants according to values of periodontitis modalities. HbA1c: glycated hemoglobin test; No cig/day: number of cigarettes smoked per day.

of periodontitis among the participants' groups in this study. In group III, the percentage of radiographic bone loss was 15% - 33% in 20% of the participants and >33% in 6% of the participants, and values of glycated hemoglobin test were

Table 5. Distribution of study participants according to the values of some parameters of Periodontitis Complexity.

		Groups			Chi-square	
		I N = 50	II N = 50	III N = 50	X^2	P-value
% RBL	<15%	47 (94%)	42 (84%)	37 (74%)	13.43	<0.051*
	15% - 33%	3 (6%)	6 (12%)	10 (**20**%)		
	>33%	0 (0%)	2 (4%)	3 (**6%**)		
Tooth mobility	Absent	46 (92%)	44 (88%)	38 (76%)	**9.82**	**0.063***
	Present	4 (8%)	6 (12%)	12 (**24**%)		

% RBL: Parentage of radiographic bone loss.

Table 6. Distribution of study participants according to values of periodontitis modalities.

		Groups			Total N (%)	Chi-square	
		I N = 50	II N = 50	III N = 50		X^2	P-value
HbA1c test	<7% HbA1c	50 (100%)	50 (100%)	48 (96%)	148 (98.6%)	13.43	<0.001*
	>7% HbA1c	0 (0%)	0 (0%)	2 (**4%**)	2 (1.4%)		
No cig/day	<10 cig	42 (84%)	34 (68%)	31 (62%)	107 (71.33%)	**9.82**	**0.063***
	>10 cig	8 (16%)	16 (32%)	19 (**38%**)	43 (28.66%)		

HbA1c: glycated hemoglobin test; No cig/day: number of cigarettes smoked per day.

>7% in 4% of the participants, as well as the number of cigarettes smoked per day, was >10 cigarettes in 39% of the participants. The parameters of periodontitis complexity and clinical findings of periodontitis modalities in the current study were higher in group III, with significant differences during the comparison between groups I, II, and III ($p < 0.05$).

4. Discussion

Lifestyle habits are associated with periodontal diseases, and their risk factors may affect the condition of oral mucosa and periodontal tissues. Moreover, different lifestyle habits and cultures vary according to the regions in the world [26]. This cross-sectional study included 150 students selected from the college of dentistry, King Khalid University. As far as we know, there is no published study regarding the influence of lifestyle habits as risk factors on some clinical parameters of plaque-induced gingivitis and periodontitis severity and grading among samples of dental students of different levels at King Khalid University. In this study, it was detected that increasing age was significantly associated with periodontitis more than plaque-induced gingivitis, as the severity and grading of periodontitis among the participants in group III were more than in groups I

and II, which is consistent with other previous studies [27] [28] [29]. However, the severity and grading of periodontitis are considered to be cumulative destruction throughout the lifespan, not due to increasing age which is insignificant when good oral hygiene is present. Moreover, the impairment of tissue integrity and the immune system increases the susceptibility of periodontal tissues to diseases [30]. Thus, the severity of periodontal disease changes among individuals according to various factors through their interaction with parents and society and may have a direct or indirect effect on the grading of periodontal diseases [12] [31]. This result is consistent with the clinical findings of our study, where we found that the less periodontal destruction among the participants in group I and group II compared to the participants in group III may be due to the higher parental education levels of the participants in group I and group II and the risky behaviors of the participants in group III.

On the other hand, previous studies revealed that lower educational levels and poor behavioral practices are risk factors for periodontal diseases, and people with higher income and higher education are less affected by severe periodontal diseases [32] [33]. These results are consistent with the results of the current study, where we found that brushing teeth was less than two times a day among the participants of group III compared to group I and group II, and it is also consistent with another study that revealed that more than 95% of participants with good oral hygiene did not have periodontitis [34].

This study revealed that male dental students in group I consumed sugary drinks daily (78%) more than groups III and II, which led to modifying the effect of their current daily smoking and increased gingivitis severity. These clinical findings influence oral health instruction for young adults of this age. Thus, lifestyle habits should be evaluated to solve health problems that have combined causes [35].

Plaque accumulation, oral hygiene, and gingivitis among group I in this study were heavy, with poor oral hygiene, and severe gingivitis consistent with the clinical findings of another Saudi study [36].

Brushing teeth ≥ 2 times daily for participants in group III of this study (44.66%) is consistent with the clinical findings of another Brazilian study (41%) [37].

In this study, PLI, GBI, PPD, CAL, %RBL and TM were significantly associated participants' lifestyle habits. Lower parental education, rented home living, brushing teeth less than twice a day, daily smoking, and daily use of sugary drinks were significantly related to greater severity and grading of periodontitis among participants in group III more than participants in groups I and II. Where most of the participants in the present study had generalized severe grade 3 plaque-induced gingivitis (group I and II more than III) and generalized periodontitis stage IV grade C (group III more than I and II). The clinical findings in this study revealed that education of the father and mother, having home ownership of living, non-smoking daily and non-daily use of sugary drinks, and brushing teeth reduced the possibility of progression periodontitis and twice or

more daily tooth brushing significantly more effectively than brushing less than twice daily.

These clinical findings are consistent with those of two previous studies conducted in Korea and Saudi Arabia [38] [39]. Concerning daily smoking, 28.7% of the participants in group III reported that they are smoking daily, which is the cause of the increased severity and progression of gingivitis and periodontitis. These results are consistent with another Saudi study that reported that 20% of participants with severe periodontal diseases were daily smokers and not consistent with another Sweden study that revealed that the severity of periodontal diseases among non-smokers and smokers was similar [40] [41]. Moreover, the clinical finding of this study is consistent with those of other studies, which reported that smokers had more gingival bleeding and severe periodontal diseases than non-smokers [42] [43].

5. Strength and Limitations

Participants in this study were selected from male students in the college of dentistry. Thus, it cannot be an accurate representative sample of the influence of lifestyle habits on the severity and progression of periodontal diseases among the Saudi population. Therefore, participants were selected from different cities in Saudi Arabia to increase generalizability. At the end of this study, to more accurately assess the impact of lifestyle habits on the severity and progression of periodontal diseases among dental students, it is recommended that future studies rely on the longitudinal relationship between lifestyle and severity and progression of periodontal diseases.

6. Conclusion

Within the limits of the current study, we concluded that the severity and grading of plaque-induced gingivitis were more among the dental students of low levels (groups I and II), while the severity and grading of periodontitis were more among the dental students of high levels (group III) due to the impact of lifestyle among the participants of group III particularly irregular tooth brushing, daily smoking, and daily use of sugary drinks.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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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

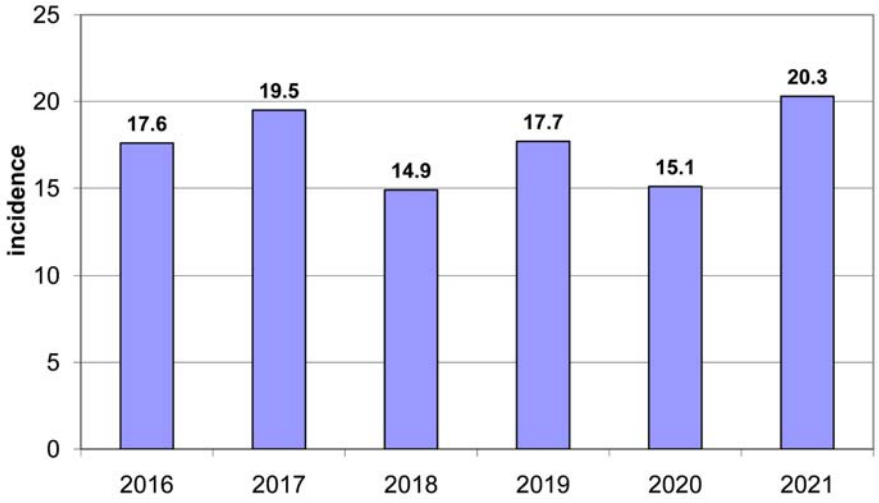

Figure 1. The incidence trend of hematologic malignancies per 100,000 of population in the Republic of Moldova.

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

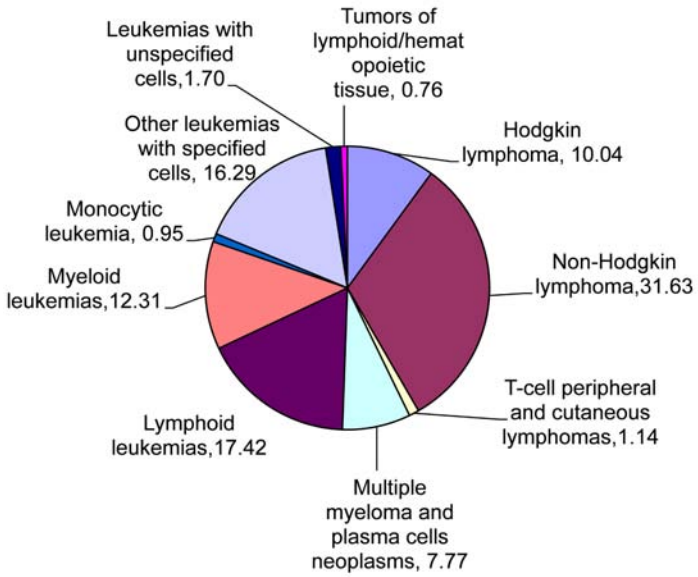

Figure 2. The structure of morbidity by hematological malignancies in the Republic of Moldova in 2021.

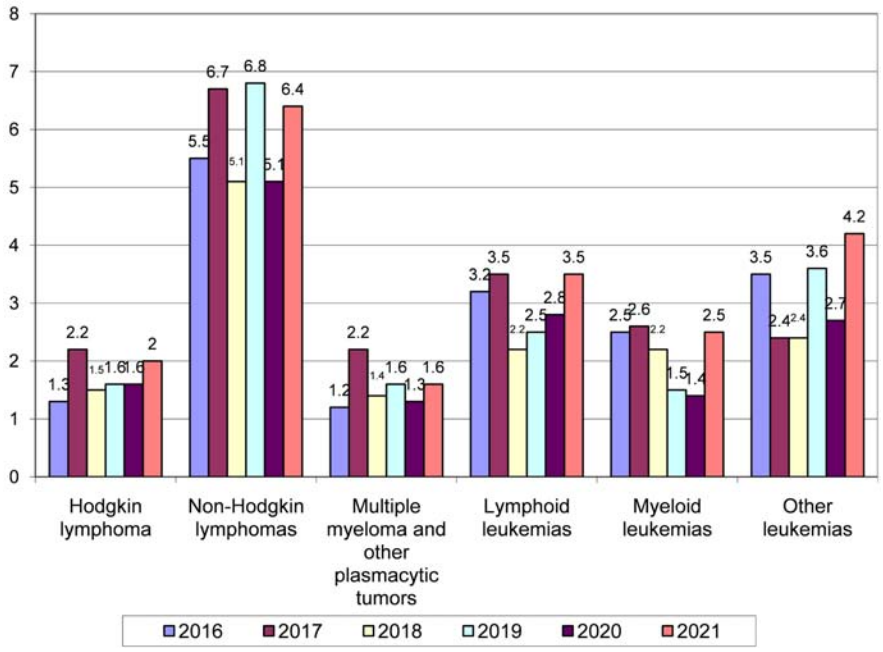

Figure 3. The incidence trend of hematologic malignancies per 100,000 of population in the Republic of Moldova with regard to nosological entity.

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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Factors Associated with Non-Adherence to Treatment in Sickle Cell Patients Monitored at the National Reference Center for Sickle Cell Disease in Niger

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Abstract

Introduction: Sickle cell disease is a real public health problem in the world and particularly in Niger where the prevalence of the S gene is estimated at 25% and that of the homozygous forms at between 1% and 2%. Treatment combines quarterly follow-up of patients and management of complications. The objective of this study was to identify the potential explanatory factors of non-adherence to treatment in sickle cell patients followed at the national reference center for sickle cell disease in Niger. **Methods:** This is a cross-sectional study of sickle cell cases followed at the CNRD in Niger. The population consisted of all sickle cell patients followed in this center in 2021. The data collection techniques were individual interviews and documentary reviews. Non-adherence was assessed with the Girerd test. Descriptive statistical tests and simple and multiple logistic regression models were performed. **Results:** A total of 368 patients were enrolled. The median age is 7 years (4; 10) and the sex ratio is 1.04. Ninety-eight (98) or 26.6% were compliant and 270 (73.4%) were non-compliant. In multivariate analysis, the factors independently and negatively associated with non-adherence to treatment were schooling (adjusted OR [95% CI], p-value), 0.17 [0.10 - 0.30]; $p < 0.0001$); discontinuation of treatment [OR = 0.15 [0.05 - 0.43], $p < 0.0004$; the distance from the Center 0.58 [0.33 - 0.99)], $p \leq 0.0489$. Unawareness of the disease was positively and significantly associated with non-adherence 7.68 [2.20 - 26.72], $p \leq$

0.0014. **Conclusion:** The factors influencing treatment compliance identified in this study are all modifiable. To prevent the complications of sickle cell disease, we must fight against ignorance, make care services accessible and make care free.

Keywords

Associated Factors, Sickle Cell Disease, Non-Adherence to Treatment, Niger

1. Introduction

Sickle cell disease is one of the most important hemoglobinopathies (thalassemia, sickle cell disease, etc.) in the world in terms of frequency (with approximately 50 million people affected) and social impact, recently recognized as a global public health problem by the World Health Organization (WHO) [1].

The management of sickle cell disease like any chronic disease is lifelong and requires good compliance. To ensure this good compliance requires both clinical and psychosocial care.

Indeed, therapeutic compliance refers to the concordance between the behavior of the patient vis-à-vis his treatment and the recommendations of his doctor [2].

With regard to compliance with medication prescriptions, 30% to 60% of patients with a chronic disease including sickle cell disease can be categorized as being poorly or non-compliant. Several factors can influence this parameter. The characteristics of the patient, the particularities of the disease, the methods of treatment, the attitudes of the doctor or the organization of the healthcare system are the main incriminated factors [2]. Other factors can also be considered, in particular the psychological dimension of the treatment, which we will not discuss in this study.

As a result, compliance with treatments prescribed for chronic diseases represents a major public health issue worldwide. In addition, in its latest report, the World Health Organization highlighted that poor adherence to long-term treatments is a growing problem [3].

Thus, several studies have been carried out on therapeutic compliance in the world. Some of them have found that there is an association between adherence and the main demographic, medical and psychosocial correlates others have found that the association depends on the patient's age [4] [5] [6].

In Niger so far, no study has focused on treatment compliance in sickle cell patients in order to determine the factors associated with it. This study is however necessary to explain the level of therapeutic observance and to research the factors associated with this observance.

The objective of this study was to identify the potential explanatory factors of non-adherence to treatment in sickle cell patients followed up at the national reference center for sickle cell disease in Niger.

2. Methods

2.1. Type of Study

This is an analytical cross-sectional study conducted among sickle cell patients monitored at the national reference center for sickle cell disease in Niger. The collection was made from June 14 to July 24, 2021, *i.e.* a period of forty (40) days. Informed consent from patients was always required and the study did not expose patients to additional risks.

2.2. Study Population

The population consisted of all patients with major sickle cell syndrome who are followed at the national reference center for sickle cell disease in 2021.

Prop nt included in our study patients aged 18 and over with more than one year of follow-up at the center and patients aged under 18 with more than one year of follow-up at the center whose parent or caregiver in charge gave his consent to participate in this work.

The only non-inclusion criterion was a no target, but who interrupted monitoring at the CNRD for more than 3 months

The sample size was calculated on the basis of the prevalence (P) of non-adherence estimated at 64.74% [7]. The sample size of the primary targets is defined by OpenEpi®: n = 368.

2.3. Data Collection

The survey took place over a period of 40 days from June 14 to July 24, 2021. Patients meeting the inclusion criteria were recruited during the follow-up consultation for sickle cell patients. The collection of information was done through a questionnaire completed by the investigator according to the answers of the patient or his tutor and the information of his follow-up sheet for certain data. The questionnaire had two parts; the first part included the identification of the patient, the socio-demographic characteristics (age, sex, marital status of the parents, number of children with sickle cell disease in the family, place of residence, educational level of the parents, socio-economic level of the parents, status at with regard to social security), the therapeutic characteristics (specific features of the disease, treatment methods, organization of the healthcare system, knowledge of the disease). The second part was made up of questions relating to the assessment of therapeutic compliance, taken from the Girerd questionnaire, which consists of 6 questions. The questions take into account the aspects of regularity in taking medication, discontinuation of treatment, forgetfulness and the quantity of medication to be taken.

Assessment of the GIRERD test score

Total yes	Assessment of the level of compliance
0	Good compliance
1 - 2	Minimal compliance issue
3	Poor compliance

This questionnaire was administered in the local dialect, and tested beforehand with 10 patients to detect any comprehension problems.

2.4. Analysis Plan

At the end of the inclusion period, the data was entered into Excel software with prior coding of the various responses and then analyzed using EPI info and SPSS software.

2.5. Descriptive Study

First, a descriptive analysis was performed by calculating the confidence interval (95% CI) around a percentage for a risk = 0.05. There is a 5% risk that the percentage obtained will be outside this interval.

2.6. Study of Factors Associated with Non-Adherence to Treatment

The second part of the study concerns the identification of factors associated with non-adherence to treatment. Two groups of patients were formed for this purpose: the group of non-compliant patients and the group of compliant patients. In the univariate analysis, the associations between the dependent variable (therapeutic non-adherence) and all of its determinants were tested by the Chi2 test or Fisher's exact test when the Chi2 validity conditions were not fulfilled. A p-value of less than 0.05 was considered statistically significant. Double contingency 2×2 cross tables were established for the calculation of the odds ratio (OR) as an epidemiological association factor with calculation of the confidence intervals (95% CI) of the risk. A multivariate analysis by logistical regression was carried out by choosing as dependent variable the binary variable "non-compliance" with two modalities: non-observant and observing. The explanatory variables included in the multivariate model are those for which the association with the dependent variable has a statistical significance level below 0.20 during the univariate analysis. Multivariate analysis was used to calculate the adjusted odds ratios and their confidence intervals for each of the factors studied. The explanatory variables included in the multivariate model are those for which the association with the dependent variable has a statistical significance level below 0.20 during the univariate analysis. Multivariate analysis was used to calculate the adjusted odds ratios and their confidence intervals for each of the factors studied. The explanatory variables included in the multivariate model are those for which the association with the dependent variable has a statistical significance level below 0.20 during the univariate analysis. Multivariate analysis was used to calculate the adjusted odds ratios and their confidence intervals for each of the factors studied.

2.7. Description of the Variables to Be Studied

The non-compliant patient is the one with poor compliance or a minimal compliance problem, *i.e.* having a yes score greater than or equal to 1, and the pa-

tient who is therapeutically compliant is the one with good compliance.

Sociodemographic characteristics (age, sex, marital status of parents, number of children in the family, place of residence, level of education of parents, socioeconomic level of parents, social security status) and perception to be informed about sickle cell disease were informed on the declaration of the patients. Therapeutic characteristics (particularities of the disease, treatment methods, organization of the healthcare system, knowledge of the disease) were obtained from declarations by patients confronted with the content of the follow-up sheets.

3. Results

3.1. Epidemiological Characteristics of Patients

A total of 368 patients were investigated, 51% of whom were female, the sex ratio was 1.04F/H, the median age was 7 years (4.10), 92.1% had the SS form, the majority of patients resided in Niamey, *i.e.* 79.1%. Two hundred and thirty-eight (238) or 64.6% of the parents surveyed are educated and 35.3% of them had no level of education, 206 of the parents worked in the private sector or 55.9%.

Three hundred and eight (308) parents of the children, or 83.7%, lived as a couple, 61.4% of whom were polygamous. The family's monthly income is more than 100,000 CFA francs in 60.9% of cases and 286 or 77.7 did not have health insurance (Table 1).

3.2. Clinical Features

Specifics about the disease

Among the patients, 61.7% had known their status for 5 years, 63.6% had less than 5 attacks per year and 91.3% had been hospitalized less than 3 times a year.

Modality of treatment

Compared to treatment, 14.9% of sickle cell patients had stopped their treatment, 3.8% thought that there were no risks associated with stopping treatment, 24 or 43.6% mentioned traditional treatment as due to discontinuation of their medical treatment. 197 or 53.5% of sickle cell patients took only 2 tablets per day and 278 or 75.5% performed less than 5 examinations per year.

Knowledge about the disease

Three hundred and twenty-three (323) or 87.8% had knowledge of their disease, 92.7% of them had been informed by their doctor, 64.7% mentioned forgetting as a reason for not knowing the disease (Table 2).

System organization

50.8% of sickle cell patients were located less than 10 kilometers from the care center, only 76 or 20.6 used their own personal means of transport to get to the center, 35.6% admitted to having experienced a drug shortage linked to a lack of resources in 79.3% of cases (Table 2).

Level of Therapeutic compliance in sickle cell patients

It emerges from this distribution that the patients are compliant in 26.6% of cases and the non-compliant represent 73.4% (Figure 1).

Table 1. Socio-demographic and clinical characteristics of sickle cell patients followed.

Socio-demographic and clinical characteristics		Number, n	Percentage (%)
Sex	F	188	51
	M	180	49
Place of residence	Other regions	76	20.6
	Niamey	292	79.3
Schooling	No	130	35.3
	Yes	238	64.7
Educational level	Primary	47	12.8
	Primary	100	27.1
	Superior	91	24.7
	No Level	130	35.3
Parents' occupations	Without	59	16
	Private sector	206	56
	Public sector (civil servants)	103	28
Marital status	Couple	308	83.7
	Separated	52	14.1
	Widow	8	2.2
Matrimonial regime	Monogamy	189	61.4
	Polygamy	119	38.6
Monthly income	<100,000	144	39.1
	≥100,000	224	60.9
Health Insurance	No	286	77.7
	Yes	82	22.3
Form of sickle cell disease	CS	29	7.9
	SS	339	92.1
Total		368	100

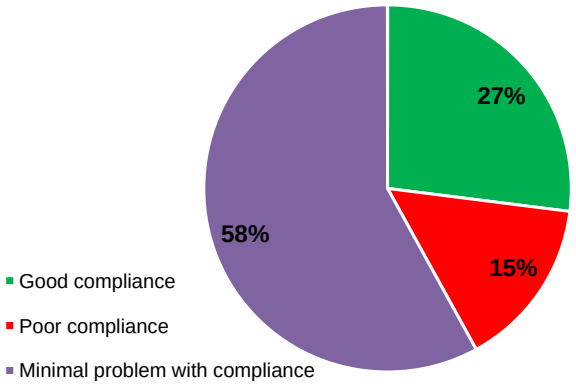

Figure 1. Distribution of sickle cell patients according to the level of therapeutic compliance.

Table 2. Distribution of patients according to knowledge about sickle cell disease & health system organization.

Knowledge about the disease & health system organization		Number, n	Percentage (%)
Knowledge of the disease	No	45	12.2
	Yes	323	87.8
Person who informed the patient of his illness	Other practitioner	27	7.3
	Doctor	341	92.7
Reasons for the ignorance of the disease	Lack of information	4	11.8
	Oversight	22	64.7
	No information	8	23.5
Reasons for drugs shortage	Lack of means	79	61.7
	Neglect	5	3.9
	Out of stock	44	34.4
Distance from center	<10 KM	187	50.8
	≥10 KM	181	49.2
Means of transport used (staff)	No	292	79.3
	Yes	76	20.7
Break in drugs	No	237	64.4
	Yes	131	35.6
Total		368	100

Particularity of the disease in sickle cell patients

Among the patients, 61.68% had known their status for 5 years, 63.59% had less than 5 attacks per year and 91.30% had been hospitalized less than 3 times a year (Table 3).

Factors associated with non-adherence to treatment in sickle cell patients: univariate analysis

The univariate analysis shows that the socio-demographic and clinical factors which influence compliance with treatment are: age OR = 0.56 (0.33 - 0.95), p = 0.032, residence OR = 2.50 (1.26 - 4.98) p = 0.007, health insurance OR = 0.44 (0.23 - 0.84) p = 0.012, schooling OR = 0.19 (0.11 - 0.32) p < 0.001, distance from the center OR = 0.38 (0.23 - 0.62) p < 0.0001, Stopping treatment OR = 0.29(0.16 - 0.51) p = 0.0001 and the number of analyzes requested per year OR = 0.33 (0.17 - 0.63) p = 0.0006 (Table 4).

Multivariate analysis

The multivariate analysis showed that there is a significant association between non-adherence to treatment and the following factors: Stopping treatment OR = 0.15 (0.05 - 0.43) p = 0.0004, knowledge of the disease OR = 7.68 (2.20 - 26.72) p = 0.0014, distance from the health center OR = 0.58 (0.33 - 0.99) p = 0.04, schooling OR = 0.17 (0.10 - 0.30) p = 0.0001 and Health Insurance OR = 0.36 (0.16 - 0.84) p = 0.01 (Table 5).

Table 3. Distribution of patients according to the particularity of the disease in sickle cell patients at the national reference center for sickle cell disease of Niamey in 2021.

Specifics about the disease		Number, n	Percentage (%)
Duration of sickle cell status	<5 years	141	38.3
	≥5 years	227	61.7
Number of crises per year	<5	234	63.6
	≥5	134	36.4
Number of hospitalizations per year	≤3	336	91.3
	>3	32	8.7
Total		368	100

Table 4. Distribution according to treatment in sickle cell patients at the at the national reference center for sickle cell disease modalities in Niamey in 2021.

Processing methods		Number, n	Percentage (%)
Discontinuation of treatment	No	313	85
	Yes	55	15
Existence of risk when stopping treatment	No	14	3.8
	Yes	354	96.2
Number of drugs taken per day	≤2	197	53.5
	>2	171	46.5
Reasons for stopping treatment	Lack of means	17	30.9
	Neglect	9	16.3
	Oversight	5	9.1
	Traditional treatment	24	43.6
Number of analyzes requested per year	Without	59	16
	≤5	278	75.5
	>5	90	24.5
Total		368	100

Table 5. Socio-demographic and clinical characteristics of sickle cell patients in univariate and multivariate analyses.

Variables		Observation level		ORb (95% CI)	p-value	ORa (95% CI)	p-value
		Watching	Non-observant				
Age range	<5 years	68	216	1			
	≥5 years	30	54	0.56 (0.33 - 0.95)	0.032	0.96 (0.46 - 1.97)	0.91
Residence	Niamey	87	205	1			
	Other regions	11	65	2.50 (1.26 - 4.98)	0.007	1.81 (0.66 - 4.98)	0.24
Sex	M	44	136	1			
	F	54	134	0.80 (0.50 - 1.27)	0.35		
Monthly income	>100,000	59	165	1			
	≥100,000	39	105	0.9725 (0.6 - 1.54)	0.87		

Continued

Health Insurance	Yes	13	69	1			
	No	85	201	0.44 (0.23 - 0.84)	0.012	**0.36 (0.16 - 0.84)**	**0.01**
Diet	Monogamy	53	136	1			
	Polygamy	77	231	1.54 (0.8 - 2.67)	0.12	1.45 (0.74 - 2.82)	0.27
Schooling	Yes	36	202	1			
	No	98	270	0.19 (0.11 - 0.32)	<0.001	**0.17 (0.10 - 0.30)**	**0.0001**
Knowledge of the disease	Yes	95	233	1			
	No	3	37	5.02 (1.51 - 16.70)	0.0037	**7.68 (2.20 - 26.72)**	**0.0014**
Distance from center	<10 km	33	153	1			
	≥10 km	65	117	0.38 (0.23 - 0.62)	<0.0001	**0.58 (0.33 - 0.99**	**0.04**
Number of children with sickle cell disease in the family	≤ 2	7	39	1			
	>2	91	231	0.45 (0.19 - 1.05)	0.06	0.98 (0.35 - 2.76)	0.98
Occupation					0.007		
	Without			1			
	Private sector			1.93 (0.96 - 3.87)			
	Public sector			0.82 (0.36 - 1.86)			
Educational level					<0.001		
	No level			1			
	Primary			0.10 (0.03 - 0.30)			
	Primary			0.30 (0.17 - 0.55)			
	Superior			0.13 (0.06 - 0.29)			
Number of hospitalizations/year	≤3	9	23	1			
	>3	89	247	1.08 (0.48 - 2.43)	0.84		
Number of crises per year	≤5	21	86	1			
	>5	77	184	0.58 (0.33 - 1.00)	0.05	0.70 (0.32 - 1.53)	0.38
Number of drugs per day	≤ 2	55	142	1			
	>2	43	128	1.15 (0.72 - 1.83)	0.0014	1.91 (0.90 - 4.06)	0.09
Use of personal vehicle	Yes	18	117	1			
	No	80	153	0.74 (0.41 - 1.31)	0.30		
Stopping treatment	Yes	18	117	1			
	Boop	80	153	0.29 (0.16 - 0.51)	0.0001	**0.15 (0.05 - 0.43)**	**0.0004**
Form of sickle cell disease	SS	91	7	1			
	CS	248	22	1.15 (0.47 - 2.79)	0.75		
Number of analyzes requested per year	<5	**12**	80	1			
	≥5	86	190	0.33 (0.17 - 0.63)	0.0006	1.06 (0.42 - 2.70)	0.88
Duration of sickle cell status	<5 years	46	52	1			
	≥5 years	181	89	0.43 (0.27 - 0.69)	<0.001	0.51 (024 - 1.10)	0.088

ORb: Gross odds ratio. **ORa**: Adjusted odds ratio.

4. Discussion

4.1. Therapeutic Compliance

In our study, 73.37% were non-compliant and 26.63% had good compliance. Oudin Doglioni *et al.* [8] found that 74.4% of respondents had poor compliance, 24.2% average compliance and 1.4% good compliance [8], Candrilli *et al.* [7] found non-adhesion at 64.7% in their study. As Adewoyin *et al.* in a study carried out in Nigeria which finds a high proportion of non-adherence 80% [9]. This could be explained on the one hand by the cost of taking charge of the disease and on the other hand by the chronic nature of the disease. The more the disease becomes chronic, the more the financial resources are exhausted, the more the patience of the parents to support the attendance of the care centers is reduced.

4.2. Factors Significantly Associated with Non-Adherence to Treatment in Sickle Cell Patients

We had found a significant association between non-adherence and the level of schooling OR = 0.17 with ap < 0.0001. This could be explained by the fact that 64.67% of the children's parents were educated. The more parents are educated, the more they know about the disease and its socioeconomic and health consequences.

We also found a significant association between knowledge of the disease and non-adherence to treatment (ORa = 7.68, p = 0.0014). In this study 87.77% of the parents knew about the disease of their children. According to Lainé, 71.4% know their diseases in West Africa and 83.3% in Central Africa [10], the more worrying the disease becomes, the more parents seek to know it better.

This study also showed an association between stopping treatment and non-adherence to treatment (ORa = 0.15, p = 0.0004). Stopping the treatment causes serious complications in the patients suddenly, when the parents return to the center they become more observant for fear of inflicting the same suffering on the child.

Finally, we found a significant association between non-compliance and the distance from the treatment center (ORa = 0.58, p = 0.04). The closer the center, the easier the accessibility and above all that in the study more than three quarters (3/4) of the patients had no means of personal transport, which made accessibility difficult. In this study only 20.65% of the patients come from other regions, which testify to the inadequacy in the accessibility to care.

Our study had limitations in the methodology and type of study. Indeed, the methodology for evaluating therapeutic compliance used is that proposed and validated by Girerd. This Girerd questionnaire has not been validated in sub-Saharan populations and not translated into language, we had to make an approximate translation in order to adapt it to our realities. While our study has highlighted certain factors that influence treatment compliance, a larger cohort study over a longer period would certainly provide more reliable information on the management of this chronic condition, sickle cell disease.

5. Conclusions

At the end of this study, it turns out that non-adherence to treatment in sickle cell patients is a frequent and multifactorial phenomenon. Therapeutic non-adherence is associated with factors such as knowledge of the disease, discontinuation of medical treatment, distance from the care center and level of schooling. In view of our results and to improve this observance, we must necessarily fight against ignorance, and make sickle cell treatment services accessible, make treatment free, because one third of people who have stopped treatment had done for lack of means.

Identifying the factors associated with non-adherence allows governments and practitioners to identify bottlenecks and intervene to improve adherence. Therapeutic education and psychosocial support are necessary to motivate the patient to face this disease.

6. Limit of Study

Our study allowed a punctual evaluation of the therapeutic observance in patients followed at the national reference center for sickle cell disease in Niamey. Although analytical cross-sectional, our study made it possible to include about twenty variables in the study and to identify certain factors associated with non-compliance with treatment in sickle cell patients.

However, it has limitations:

- ✓ Indeed, an important variable (ethnicity) is not entered in this study. The fact that the ethnic data were not collected while we know the conservation of genetic defects in the frequency/presence of sickle cell disease.
- ✓ The methodology for evaluating therapeutic compliance used is that proposed and validated by Girerd. This Girerd survey has not been validated in sub-Saharan populations and not translated into language, we had to make an approximate translation in order to adapt it to our realities.
- ✓ If our study has highlighted certain factors that influence treatment compliance, a study of a larger cohort over a longer period would certainly provide more reliable information on the management of this chronic condition that is sickle cell disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Questionnaire

I) Socio-demographic and epidemiological characteristics

Age [ ]

Age < 5 years [ ] >5 years [ ]

Gender M [ ] F [ ]

Place of residence: Niamey other regions to be specified……

Parents' profession: civil servant [ ] private [ ] without [ ]

Health insurance yes [ ] No [ ]

Marital status: [] Couple [ ] Widowed [ ] separated [ ]

Regime: Monogamy [ ] Polygamy [ ]

Education: Yes [ ] No [ ]

If yes level: Primary [ ] Secondary [ ] Higher [ ]

Monthly household income: <XOF 100000 [ ] >XOF100000 [ ]

What form of sickle cell disease do you have? SS [ ] SC [ ], S b thalassemia [ ]

Number of children with sickle cell disease in the family……

II) Particularity of the disease

- How long have you known your sickle cell status < 5 years [ ] >5 years [ ]

How many hospitalizations per year? …

How many crises per year? ……..

III) Method of treatment

Are you currently on treatment? yes no

How many medications do you take? (Number) ……

Have you ever stopped treatment once? Yes [ ] No [ ]

If yes, why?

Do you think there is a risk in stopping your treatment?

Have you had any tests for your illness: Yes [ ] No [ ]

How many times have you been asked for tests?

How many times have you made them?

Why have you not been carried out all the analyzes:

- High Cost [] Oblivion [] Distant Lab [ ]

- Lack of information [ ] Other [ ] specify .

IV) Knowledge about the disease

- Do you know your disease? Yes [ ] No [ ]

If not why ? Never got information [ ] Forgot [ ] Doesn't care [ ]

Who told you about your illness? Your doctor [ ] Another practitioner [ ] Other:

V) Organization of the system

Distance from the center: <10 km [ ] >10 km [ ]

Means of transport used: Personal Yes [] no [ ]

Have you ever had any drug shortages? yes [ ] No [ ]

If yes, why? lack of means [ ] Out of stock at the pharmacy [ ] others……

VI) GIRED compliance assessment test

Did you forget to take your medicine this morning? YES [ ] NO [ ]

Since the last visit, have you run out of medication? YES [ ] NO [ ]

Have you ever taken your treatment later than usual?

YES [ ] NO [ ]

Have you ever not taken your treatment because some days your memory fails you? YES [ ] NO [ ]

Have you ever skipped your medication because some days you felt like your medication was doing you more harm than good? YES [ ] NO [ ]

Do you think you have too many tablets to take? YES [ ] NO [ ]

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Huu S. TIEU's Predicting Outcome of Severe Acute Respiratory Syndrome (SARS) and Preparing the Treatment for COVID-19 (Coronavirus) and Other Viral Pandemics

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Abstract

This project paper is to give a prediction for the future of other viral pandemics and to provide recommendations for preparing therapies that could help in the success of effective treatments and benefits for patients in life-threatening situations. The theory of prediction was proposed by Huu S. TIEU on March 25, 2019, and he hypothesized that any malfunctioning cell in the body could have a damaging effect. This paper discusses the prediction that Localized Oxygen Deprivation could be a contributing factor for a future epidemic or other viral pandemics that could affect body function. This paper is based on opinion and does not have sufficient evidence to support the claims made. Therefore, further in-depth study is needed to prove the findings. The author cites Hypoxia to support his idea, but he is not claiming that Hypoxia-Inducible Factor (HIF) has worked on his predictions. The author also tested a theory using cow blood curd for body function, but this test was not a structured test and the findings were not supported by other evidence. To further prove the idea or theory, further study into the subject should be conducted.

Keywords

COVID-19 (Coronavirus), Severe Acute Respiratory Syndrome (SARS), Viral Pandemics, Huu S. TIEU, Life Is Quantum Biology

1. Introduction

The COVID-19 crisis resulted in the infection of confirmed cases representing six hundred and fifty million people worldwide and the DEATHS confirmed to-

taling six million and five hundred thousand worldwide (World Health Organization on December 23, 2022 report) [1]. However, the death toll in India could be much higher because of the unconfirmed deaths (World Health Organization on December 21, 2022 report) [2]. It is estimated that another three and half million to almost five million deaths occurred but had gone unreported in India and because of this estimate, it could mean that other countries could be underreporting their numbers also. There was an uncanny similarity to the Severe Acute Respiratory Syndrome (SARS) outbreak [3] and respiratory illness of prior like flu infections [4]. Hypoxia [5] was a direct cause of fatality for COVID-19 infections as the Localized Oxygen Deprivation [5] [6] of the cells creates necrosis of tissues. The author had noticed patients were experiencing Hypoxia from a lack of proper lung function. Even a short period of time of Hypoxia can cause effects that could damage soft tissues (soft tissues are described as, organ tissues, veins, arteries, etc.). The author theory predicts that if a viral infection is severe enough to cause Hypoxia or Localized Oxygen Deprivation, then it results in a cascade effect in the body, including organ failure and blood clotting [7] [8].

2. Materials of Methods

New innovative research may be able to conduct a small well-designed study in a few subjects, there is still much to accomplish [9]. The paper includes only one subject and is not to be seen as a multiple subject article. The experiments that are included in this paper are from observation only [10]. The results from the author prediction or theory are forward thinking comments that are not sufficiently proven through the scientific method and are more opinions than evidence [11]. To provide evidence through proper studies would need to be done for proof in the future [12]. Though the prediction makes sense it is not a supported theory and should only be used as guidance for future study [13].

On November 01, 2018 the author tested this theory by purchasing two pounds of cow blood curd then on different day consumed different amounts of cow blood curd [14]. 1) Day #1 the subject consumed half (**1/2**) pound of cow blood curd and the author theorized that a small amount of cow blood curd would provide a nutritional balance to the body by providing nutrition to the cells (**Figure 1**). The author surmised that the benefits of not only the iron in the blood but the protein content could provide energy by improving the subjects' immune function. 2) Day #2 of the subject consuming about half (**1/2**) pound of cow blood curd it was noticed that the subject had improved his energy levels and felt a strong disposition (**Figure 1**). The subject noticed improved muscle strength and more endurance. 3) Day #3 the subject then consumed one pound of cow blood curds to test the high level (highly above the average of consumption) of nutrient intake (**Figure 2**).

3. Results and Discussion

On the third day the subject noticed that in a short time he felt nauseous and

Figure 1. Cow blood curd is solid cow blood jelly half (**1/2**) pound.

Figure 2. Cow blood curd is solid cow blood jelly one (1) pound.

had lost all the benefits that his previous intake of cow blood curd that had benefited his body. See (Figure 1) and (Figure 2) the subject received a total of two pounds of cow blood curd in three days. The side-effect or adverse effect of over producing antibodies included nausea, severe coughing, fever, headache, swelling or chronic inflammation, severe pain/ache, muscle pain, intense joint pain, sweating, dizziness, and confusion. This side-effect was also rib pain; the pain may be caused by an infection from excessive blood intake, a pulled rib muscle, and severe abdominal pain inside the muscle wall. Four days later, which allowed enough period of time to pass, the subject is level of antibodies began to decrease below a level that provides effective protection. The author concluded that an improper balance of nutrition would cause an imbalance in bodily function and cause a cellular malfunction in the body. The author further surmised that if a protein imbalance would occur by a viral infection, this can cause cell malfunction especially through Localized Oxygen Deprivation which is caused

by low lung function as seen in the cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [15] [16]. Localized Oxygen Deprivation impedes the body's ability to fight off infection, even in a mild case of a flu virus.

Subject have been claims that they first felt a painful feeling traverse down their back (spine) followed by a wrapping around to the front of the torso from their rids like they are being squeezed to death. There continues to be an extreme pain in their throat and this pain if untreated continues to worsen until the subject cannot breathe. This has been a fairly consistence feeling among many whom suffered from COVID-19.

On March 25, 2019 the Investigator's Brochure from Golden Sunrise Nutraceutical, Inc. (Golden Sunrise) was given to an Investigator for the U.S. Food and Drug Administration (FDA), which he in turn archived in the FDA Scientific and Technical Library to provide knowledge to the FDA of conditions that could benefit patients. For example, an overtaxed/overactive immune system results in body-wide "inflammation", which perhaps is the best way to describe decreased circulation, accumulation of metabolic waste such as radicals, acid-based imbalance, Localized Oxygen Deprivation, impaired energy production by the cells, and the list goes on. The Golden Sunrise Investigator's Brochure predicted cellular malfunction leading to Localized Oxygen Deprivation otherwise known as Hypoxia. Otto H. WARBURG had studied and theorized that Localized Oxygen Deprivation would cause a breakdown in tissues and this could cause a fermentation effect that would be a cause for cancer. He received the Nobel Prize & Laureate on Year-1931 [17], Corneille J. HEYMANS won the Nobel Prize in Physiology or Medicine on Year-1938 for showing how blood flowed to encompass the oxygenation of tissues and the importance of these discoveries [18], on October of 2019, William G. KAELIN Jr., Sir. Peter J. RATCLIFFE, and Gregg L. SEMENZA also received the Nobel Prize in Physiology or Medicine for their theory of Hypoxia or Localized Oxygen Deprivation in cellular response [19] [20]. The author prediction for the outcome of SARS disease risk on November of 2018. He then begins preparing for the treatment of COVID-19 (Coronavirus) and other viral pandemics on March 25, 2019. Golden Sunrise documents were archived in the FDA Scientific and Technical Library [7]. Their theory, research, and the treatment of Localized Oxygen Deprivation or Hypoxia helped to elucidate how the cells adjust to this threat and to their survival at a cellular level. It supports this as a common pathway in all cells which may lead to many illnesses including cancer, anemia, inflammatory pathways, and many more. The theories have supported Golden Sunrise dietary supplement products which correct this cellular malfunction and physicians documented successful treatment of fifty-four patients for COVID-19 with the Golden Sunrise dietary supplement products [7] [8].

4. Conclusion

When the subject conducted an experiment using cows' blood curb, they also

noticed a similar feeling when the intake of cow blood curb was excessive. The subject later applied this model when they experienced COVID-19, correlating the two using the same or similar pathways. This project aims to predict future viral pandemics, prepare for successful therapy, and determine the costs-effectiveness of treatment recommendations or decision-making.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Elevated Pulse Pressure Is a Risk Factor for Cerebral Microbleeds. A Single Center Case-Control Study

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Abstract

Recent developments in brain magnetic resonance imaging using advanced Susceptibility Weighted Imaging (SWI) have significantly increased the detection and prevalence of Cerebral Microbleeds (CMBs). Here, we aimed to explore the association between Pulse Pressure (PP) and CMBs. Having been implicated in various arteriopathies, we hypothesized that elevated PP could also be a risk for CMBs. A retrospective case-control study was conducted from August 2021 to September 2022 at Zhongnan Hospital of Wuhan University China. Extracted data were analyzed in SPSS. Chi-square test, binary logistic regression, and Spearman's correlation analysis were conducted.104 patients were analyzed. Univariate analysis showed no significant association between PP and CMBs, OR 1.65 (95% CI: 0.737 - 3.694; $p > 0.05$), while DBP and alcohol consumption were significant, ORs 2.956 (95% CI: 1.249 - 6.997, $p < 0.05$) and 2.525 (95% CI: 1.062 - 6.002, $p < 0.05$) respectively. Multivariate analysis, showed that PP was significantly associated with CMBs, OR 3.194 (95% CI: 1.024 - 9.964, $p < 0.05$) in combination with SBP, DBP, gender, age, smoking and alcohol consumption. Taken together, the study showed that elevated PP is associated with CMB, but is not an independent risk factor for CMBs.

Keywords

Cerebral, Microbleeds, Pulse, Pressure, Susceptibility Weighted Imaging, MRI, CMBs

1. Introduction

The recent use of Susceptibility Weighted Imaging (SWI) in brain MRI has dramatically increased the diagnosis of petechial cerebral hemorrhagic lesions

(CMBs) among patients with stroke, cognitive impairment, dementia, hypertension and the elderly [1] [2] [3] [4]. These lesions are clinically covert, yet they are radiological markers for small vessel diseases. CMBs occur in approximately 29.4% of the elderly patients [5], and are of increasing public health concern. They are majorly associated with; Cerebral Amyloid Angiopathy (CAA), Hypertensive arteriopathy, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), and Moyamoya disease [6]-[13]. Other risk factors include; Hypertension [14] [15] [16], advanced age (>60 years) [17] [18] [19] [20], gender (male) [19], diet [21], and antithrombotic therapy [22] [23] [24].

In principle, the origin of CMBs is considered to be microvascular fragility, which then promotes micro-hemorrhage within the cerebral vasculature [25]. In this case managing CMBs should involve identifying all the clinical and subclinical parameters linked to microvascular fragility. To this effect, studies have exposed hypertension as the most common risk factor for CMBs [16] [26] [27], although cases are also seen in normotensive subjects [28]. Other than hypertension, pulse pressure (PP), a derivative of the arithmetic difference between systolic and diastolic blood pressure, has also been implicated in a number of arteriopathies [29]-[36]. One study suggested that PP-induced arteriopathy could be due to the cerebrovascular stiffness common in advanced age, and the lack of an external elastic lamina by intracranial vessels [37]. Moreover, it is also suggested that elevated PP could promote endothelial dysfunction that concurrently with accumulation of proinflammatory cells and oxidative stress, induces cerebrovascular damage [38]. So elevated PP likely promotes the development and ultimate rupture of micro-aneurysms, hastens the development of atherosclerosis, and thrombotic events, and induces CMBs.

While various studies have explored the relationship between hypertension and CMBs [26] [39] [40], the relationship between elevated PP and CMBs has not been well elucidated. Considering that PP is an easily acquirable, non-invasive, low cost parameter, establishing its association with CMBs could offer a cheap and faster mechanism for determining risks for CMBs whether alone or in combination with other parameters like patient age, gender, blood pressure and alcohol consumption. On the basis of its implication in various arteriopathies, we hypothesized that elevated PP could be associated with CMBs, and so took advantage of the use of the advanced SWI imaging technique to explore this possible association.

2. Materials and Methods

We recruited a total of 104 patients (81 males and 24 females; aged 18 - 95 years, mean age 69.73 ± 8.74 years) from August 2021 to September 2022 at Zhongnan Hospital of Wuhan University. All recruited patients underwent brain MRI scan using SWI techniques. They were then divided into two groups based on their MRI results: 54 with CMBs, and 54 without CMBs. Patients were excluded if

they had the following: Those on hormonal replacement therapy that included estrogen, (evidence suggest that these drugs induce significant PP alterations [41]; those diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral amyloid angiopathy (CAA) or Moyamoya disease. The study was approved by the ethics committee of Zhongnan Hospital of Wuhan University, and patient consent was waived as the data were retrospectively collected. All recruited patients underwent MRI scan by MAGNETOM Avanto & Prisma 3T MRI systems (Siemens, Germany) using SWI sequence, and parameters set as follows: 800 ms repetition time, 20 - 50 ms echo time, 20 - 30 flip angles, 256 × 256 matrix, 240 × 100 vision, 7-mm scan slice thickness, and 2.5 mm spacing. MRI data were retrieved from the hospital Picture Archiving and Communication System (PACS), while other clinical information were got from the electronic medical database. Cerebral microhemorrhage was defined as loss of circular signal with a uniform diameter of 2 - 5 mm, with clear margin and no edema around the circular punctate non-sulcus area.

3. Blood Pressure Measurements and Comorbidities

Blood pressure measurements retrieved were single measurement recorded in the system for each patient. Hypertension was defined according to the International Society of Hypertension (ISH) [42] as blood pressure readings of ≥140/90 mmHg. Pulse pressure (PP) was derived as the arithmetic difference between Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) measurements. It was then divided in to three categories; low, normal and high with a threshold for normal being 40 to 60 mmHg [43] [44]. Other comorbidities collected were diabetes, hyperlipidemia, and stroke, all defined by the World Health Organization criteria for diagnosing hypertension, diabetes, and hyperlipidemia. In addition, history of smoking and alcohol consumption were also extracted. Confirmation of a stroke diagnosis was made based on definitive diagnosis and treatment from Zhongnan Hospital and image findings of obsolete cerebral lesions. Other data collected were: subject demographic information, clinical and medical characteristics, and treatment details.

4. Brain MRI Scan Results

All brain MRI results retrieved were conducted by highly qualified radiologists. When viewed on SWI, CMBs appear as small homogenous, and round foci with low signal intensity, having a diameter < 10 mm and without peripheral edema. Structures such as vascular gap, cavernous hemangioma, calcified plaque of atherosclerosis, hemosiderin deposition on the pia mater, and calcification of the globus pallidus are excluded. The number of CMBs located in the cortical region, sub cortical region, brain stem, cerebellum, and those that were diffuse were recorded. CMBs were defined as: non-CMB, (0), mild (1 - 2), moderate (3 - 10) and severe (>10) and patients grouped accordingly.

5. Statistical Analysis

Statistical analysis was conducted in SPSS version 25 software (IBM Inc. USA). Continuous variables were expressed as mean ± SD and categorical variables presented as counts and percentages. Independent student's t test was used to analyze the mean difference between groups of continuous data, while Pearson's Chi-square test was used for categorical data. Correlation analysis was conducted using the Spearman's rank test. A p-value ≤ 0.05 was considered statistically significant.

6. Results

Patient characteristics

A total of 104 patients were included in this study; 52 cases and 52 controls. Mean (± SD) age of the cases and controls were; 68.79 ± 9.104 vs 68.52 ± 9.359 years respectively ($p > 0.05$), and 69.2% were males ($p < 0.001$). Hypertension was the most frequent comorbidity accounting for 55.8% vs 44.2% ($p > 0.05$) of all comorbidities among cases and controls respectively, while limb disorders (hemiplegia, bradykinesia, limb weakness, numbness, and tremors) were the most notable primary complaints in both groups, though with a higher frequency amongst cases ($p > 0.05$). Average systolic BP and mean arterial pressure (MAP) were both higher in cases than controls (all $p < 0.05$), while average diastolic BP and pulse pressure (PP) though higher in cases than controls were not statistically different (all $p > 0.05$) (Figure 1). Detailed clinical and demographic information is presented in Table 1.

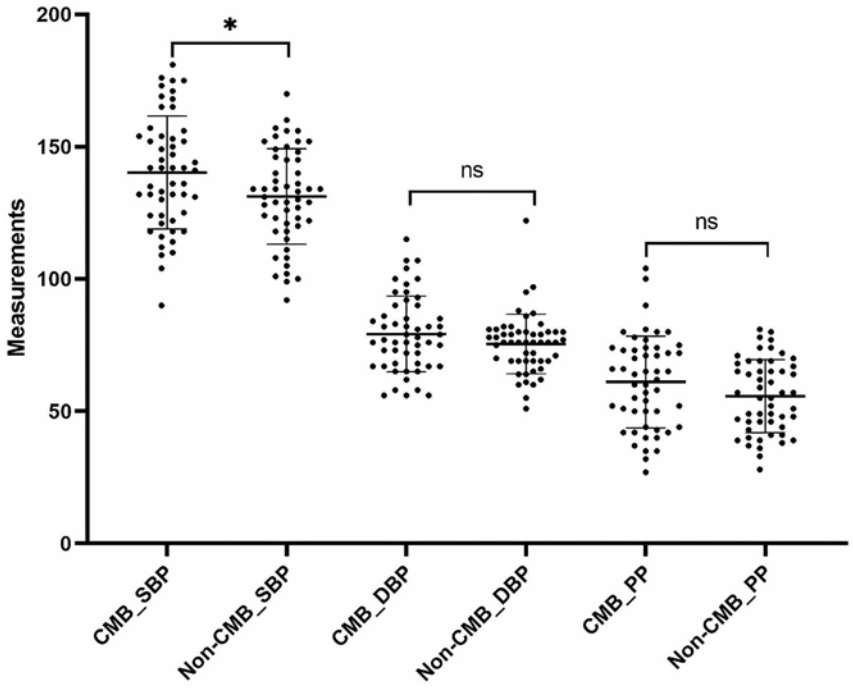

Figure 1. Mean difference in systolic BP, diastolic BP and pulse pressure among patients with CMBs and those without.

Table 1. Demographic and clinical characteristics of the patients.

Characteristic	Case, N = 52	Controls, N = 52	p
Gender (male), n %	43 (82.7)	38 (73.1)	<0.001*
Age, y (Mean ± SD)	70.6 ± 8.56	68.9 ± 8.93	0.76
SBP (mmHg)	140.0 ± 20.6	133.0 ± 19.2	0.02*
DBP (mmHg)	79.2 ± 14.2	76.8 ± 11.8	0.14
PP (mmHg)	61.0 ± 17.0	56.0 ± 14.0	0.06
MAP (mmHg)	99.4 ± 14.5	95.4 ± 13.1	0.04*
Co-morbidities			
Stroke n, %	4 (7.7)	2 (1.9)	0.16
Diabetes mellitus n, %	1 (1.9)	0 (0)	0.31
Hyperlipidemia n, %	4 (5.8)	3 (5.8)	0.98
Smoking, n (%)	22 (44.2)	31 (57.7)	0.18
Alcohol, n (%)	11 (21.2)	21 (40.4)	0.03*

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. MAP: Mean arterial pressure. *Significant result.

Association between pulse pressure and CMBs

Univariate and multivariate analyses were conducted to determine the association between PP and CMBs. SBP, DBP, age, smoking history and alcohol consumption history were also included in the multivariate analysis. Preliminary multicollinearity analysis showed no significant association between PP and the other blood pressure parameters. Univariate analysis revealed that PP was not significantly associated with CMBs, OR 1.65 (95% CI: 0.737 - 3.694; $p > 0.05$), while DBP and alcohol consumption were significant, ORs 2.956 (95% CI: 1.249 - 6.997, $p = 0.014$) and 2.525 (95% CI: 1.062 - 6.002, $p = 0.044$) respectively (Table 2). However, when PP was included in the multivariate analysis, it was significantly associated with the occurrence of CMBs, OR 3.194 (95% CI: 1.024 - 9.964, $p = 0.045$) (Table 3). These results suggest that PP is not an independent risk factor for CMBs but rather acts in combination with other risk factors to promote CMBs.

Correlations between pulse pressure and severity of CMBs

Pulse pressure (PP) was then divided into three categories; low, normal and high, while CMBs were ranked in severity according to number of micro bleeds (severity) as described by Ibrahim *et al.* [5], and the number of micro bleeds counted in each rank and the corresponding PP quartile, Table 4. Correlation among the CMBs ranks (CMBs severity) and the PP quartiles was then determined using Spearman's rank test, to ascertain whether severity of CMBs increased with increase in PP. The results showed a weak correlation, $r = 0.188$; and $p = 0.057$.

Correlation between pulse pressure and location of CMBs

The distribution of micro bleed lesions was not uniform across the brain,

Table 2. Univariate analysis of the association between pulse pressure and CMBs.

	B	SE	Wald	df	Sig	OR	95% CI
SBP	0.336	0.476	5.000	1	0.479	1.400	0.551 - 3.557
DBP	1.084	0.440	6.079	1	0.014*	2.956	1.249 - 6.997
PP	0.501	0.411	1.483	1	0.223	1.650	0.737 - 3.694
Gender	0.92	0.429	0.046	1	0.830	1.096	0.473 - 2.541
Age	0.217	0.467	0.216	1	0.642	1.242	0.498 - 3.102
Smoking	0.542	0.396	1,874	1	0.171	1.719	0.791 - 3.736
Alcohol	0.926	0.442	4.395	1	0.044*	2.525	1.062 - 6.002

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. *Significant result.

Table 3. Multivariate analysis of the association between pulse pressure and CMBs.

	B	SE	Wald	df	Sig	OR	95% CI
SBP	−1.115	0.724	2.375	1	0.123	0.328	0.079 - 1.354
DBP	1.604	0.563	8.109	1	0.004*	4.971	1.648 - 14.989
PP	1.161	0.580	4.002	1	0.045*	3.194	1.024 - 9.964
Gender	0.313	0.488	0.411	1	0.521	1.368	0.525 - 3.562
Age	−0.093	0.523	0.032	1	0.859	0.911	0.327 - 2.539
Smoking	0.134	0.469	0.082	1	0.774	1.144	0.456 - 2.867
Alcohol	1.086	0.529	4.212	1	0.040*	2.962	1.050 - 8.356

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. *Significant result.

Table 4. Correlation between pulse pressure and severity of CMBs.

CMB grade	Pulse pressure quartiles				N
	Q1	Q2	Q3	Q4	
0 (0)	13	16	16	7	52
1 (1 - 2) Mild	7	2	3	7	19
2 (3 - 10) Moderate	4	5	7	7	23
3 (>10) Severe	1	3	2	4	10
N	25	26	28	25	104

Spearman r = 0.188; p = 0.057.

Figure 2. 34.6% (18/52) were in the cortical region, 32.7% (17/52) in the sub cortical region, 19.2% (10/52) in the brain stem, 7.7% (4/52) in the cerebellum, and 5.7% (3/52) were diffuse. We used Spearman's rank test to determine the correlation among the CMBs distribution and PP quartiles. The result showed that no correlation existed (Spearman's r = −0.01; p > 0.05) (Table 5).

Table 5. Correlation between pulse pressure and location of CMBs.

Brain location	Pulse pressure quartiles				N
	Q1	Q2	Q3	Q4	
Cortical Region	6	2	3	7	18
Subcortical Region	4	4	3	6	17
Brainstem	2	3	4	1	10
Cerebellum	0	1	1	2	4
Diffuse	1	1	0	1	3
N	13	11	11	17	52

Spearman r = −0.01; p = 0.992.

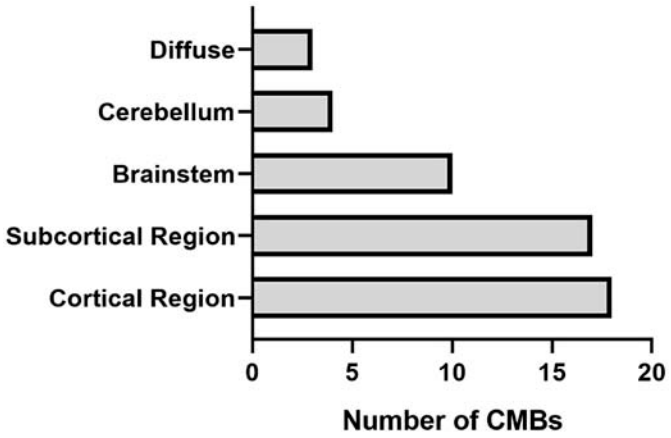

Figure 2. Brain distribution of CMBs.

7. Discussion

This study was conducted to mainly examine the association between pulse pressure (PP) and the occurrence of cerebral microbleeds (CMBs) in patients who underwent brain MRI using Susceptibility Weighting techniques. Blood pressure, gender, age, smoking and alcohol consumption were the other factors assessed. PP is often an overlooked parameter in clinical practice yet studies have demonstrated that it is involved in a number of arteriopathies [29]-[36]. Moreover, it is a rapidly acquirable, non-invasive, and economically cheap parameter that could be used as a predictor of vascular disease.

Our results revealed that PP is associated with the occurrence of cerebral microbleeds among the patients analyzed, ($p < 0.05$). However, the association occurred in combination with other risk factors *i.e.* SBP, DBP, age, gender, smoking and alcohol consumption, suggesting that PP is not an independent risk factors for CMBs. This result is consistent with those of Park *et al.*, [45] who found that long-term elevated PP in conjunction with high systolic blood pressure increased the risk of hemorrhagic stroke among stroke patients with cerebral microbleeds. Furthermore, like Emstahl *et al.*, [39], and Ding *et al.*, [46], we also showed that diastolic blood pressure and alcohol consumption are independent

risk factors for CMBs respectively, (all $p < 0.05$). Taken together, our results highlight the need to also consider elevated PP when assessing possible risk factors for CMBs in clinical practice.

In assessing how PP relates to the severity and brain location of CMBs, we considered the number of CMBs to show severity, and then mapped the brain location of the identified CMBs. The results revealed no distinct association between PP and the severity of CMBs or their location within the brain. This finding is in agreement with that of Lyu *et al.*, [40] who showed that there was no association between hypertension and the location of CMBs in the brain.

Evaluation of the patients' clinical characteristics revealed that limb disorder—which included hemiplegia, bradykinesia, limb weakness, numbness, and tremors—was the commonest primary complaint amongst the groups. Previously, White Matter hyper-intensities (WMHs), lacunas, and brain atrophy were confirmed to be associated with gait disorders. In general motor coordination relies on interrelated activity by distinct parts of the brain and injury to any of these parts may clinically manifest as limb disorder. CMBs are a manifestation of ongoing cerebral vascular disease which ultimately leads to injury of parts of the brain [47] [48]. In particular, the motor cortex plays the primary role in the motor activity of the body. Our results show that most CMBs amongst the cases were frequently noted in the cortical and subcortical regions, and this may explain the primary clinical observation of limb disorder. Indeed, Hou *et al.* [49] recently confirmed that CMBs are associated with lower gait velocity, wider stride width, longer Time-up-and-Go (TUG) test times, and other upper and lower extremity dysfunctions amongst patients with CMBs.

The results of our study offer significant insight into improved understanding of the risk factors for CMBs with the hope that early detection and subsequent intervention may prevent progression to worse outcomes such as stroke, cognitive impairment and dementia. Furthermore, our results offer grounds for possible consideration of PP as one of the risk factors, when assessing the risk of CMBs in clinical practice. Being a non-invasive, and easy to obtain parameter, its utilization could prevent CMBs and spare patients the need for invasive tests including cerebral angiography or brain biopsy.

This study had a few major limitations; first, we utilized only single blood pressure measurements extracted from the electronic database to determine PP, and yet a 24-hour ambulatory blood pressure could be a more reliable measurement to use. Second, the study was limited by sample size which affected the power. Third, being a retrospective study, it has inherent biases and limited parameters to analyze. We therefore think that a more robust, well designed, prospective cohort study is needed to validate our results.

8. Conclusion

In summary, this study revealed that there is an association between pulse pressure (PP) and cerebral microbleeds (CMBs). However, according to our analysis,

PP is not an independent risk factor for CMBs. The study also revealed that increased diastolic BP and alcohol consumption are independent risk factors for CMBs. The study limitations notwithstanding, including the assessment of PP among the other risk factors for CMBs could offer a cheap, non-invasive parameter that improves CMBs risk assessment and hence prevention of CMBs in patients at risk. To validate these results, a larger, well designed prospective cohort study is warranted.

Author Contributions

CN and HX conceived the study. CN: Conducted data collection. CN: conducted data curation and analysis. CN: Wrote the draft manuscript. HX reviewed the manuscript. HX: Supervised the study. Both authors have read and approved the final manuscript.

Ethical Approval

This study was approved by the Zhongnan Hospital of Wuhan University Research Ethics committee. Patients' permission was waived by the committee since the data were retrospectively collected.

Conflicts of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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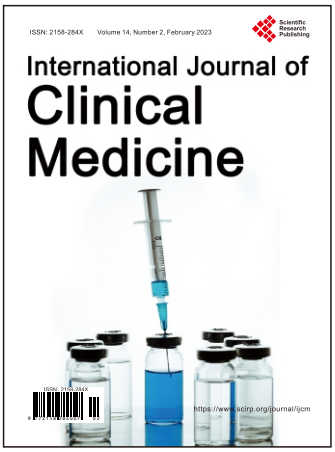

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