

Health Related Quality of Life in Patients with Chronic Disease in Lebanese Community Setting

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Abstract

Background:

The impact of chronic diseases on patient quality of life are becoming of high priority in healthcare system. There is an increased need of such data in Middle Eastern countries.

Objective:

To measure health related quality of life (HRQOL) in patients with chronic disease to associate this information with demographic data, socioeconomic status, and health satisfaction.

Setting:

Six community pharmacies in Beirut region.

Method:

A prospective cross-sectional study was conducted to gather information on socioeconomic status, health condition and quality of life of participants during their visit to their local pharmacy.

Main outcome measure:

Health related quality of life using the EQ5D instrument

Results:

Participants (n=103) gave an average of 6.8, and 7.4 over ten for their current health and for their satisfaction with their treatment, respectively. The mean utility score was 0.762 (SD 0.202). The number of prescribed medications per respondent indicated a significant impact on HRQOL ($p = 0.002$); with diuretic agents having a significant difference in utility scores ($p < 0.001$). On average, participants 75 years or older, hospitalized in the past 12 months, diagnosed with hypertension, had a lower utility score of 0.15 ($p < 0.001$), 0.111 ($p = 0.001$), and 0.065 ($p = 0.035$), respectively. For every unit increase in treatment satisfaction, the quality of life score increased by 0.036 unit ($p = 0.001$)

Conclusion:

HRQOL as measured by the EQ5D in this study was affected in patients with cardiac disease or diabetes. Male gender, advanced age, low socioeconomic status, frequent hospital and doctor visits were important risk factors for a poor HRQOL.

Impact On Practice:

- Revealing important data on the patient physical and emotional experience with a chronic disease would assist policy makers in their decision making on disease management.

- Measuring health related quality of life using EQ5D validated instrument would determine utility units of specific population with a certain disease, and such data is lacking in the region.

Introduction

In recent years, the competitive global market place has increasingly acknowledged the usefulness of Health-related quality of life (HRQOL) data to assist policy makers in reimbursement decisions by identifying the best alternative option among innovative medicines[1]. EQ5D is an instrument used to evaluate the generic quality of life developed in Europe and is a preference-based HRQOL measure This descriptive instrument has five questions each addressing one of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which are common problems in patients with chronic diseases[2].

Symptomatic management of chronic illness and their impact on health status are consistently ranked as the highest priorities for patients and healthcare providers[2, 3]. A negative impact of diabetes mellitus on patients' quality of life and satisfaction with their treatment has been reported in a recent study conducted in adult population in Jordan and Lebanon[4].

Furthermore, there is a growing emphasis on engaging the patient in his/her own care to optimize patient outcomes, while justifying whether the additional cost is worth the additional effectiveness of a new treatment option compared to standard options[1]. Thus, policy makers worldwide are supporting their decisions on providing patients access to innovative therapy based on cost effectiveness analysis using health outcomes that measure patient preference or HRQOL in addition to clinical surrogate endpoints[5]. There is an increase need for HrQOL data in Lebanon especially due to scarcity of resources and due to the impact of social determinant on health.

A special attention should be given to the increasingly epidemiological and economic burden of highly prevalent disease like cardiovascular disease, diabetes mellitus and non-communicable disease[6]. Measuring the impact of a disease or a treatment on the quality of life of the Lebanese patients helps assist healthcare providers and payers in their decision making upon selecting appropriate therapy.

The Lebanese healthcare sectors have been struggling with healthcare budget constraints, and facing challenges to support their decisions on reimbursement of interventions with evidence data on value of interventions, cost effectiveness evaluation, managed entry agreement schemes as well as health related quality of life. Lebanon is a small country in the Middle Eastern region, with a population size near 6,850,000 million in 2018, with almost 25% Syrian and Palestinians refugees, facing political, economical and social challenges. As share of Gross Domastic Product (GDP) for Lebanon, health expenditure was 6.4% in 2014 and increased to 8% in 2016[6–9]. The importance of pharmacoeconomics has been recognized in Lebanon and decision makers are seeking for information and tools to assist in reimbursement decisions and assessment of interventions. Despite recognizing this need, it has been very challenging to implement Health Technology Assessment due to a fragmented healthcare system and limited database on health outcomes and diseases prevalence[6, 10]. Furthermore and to our

knowledge, country specific EQ5D value set has not been determined in Lebanon and outcomes of interventions have been based on surrogate endpoints and factors related to health determinants without implementing the HRQOL instrument measures[11–14]. While this latter has been widely used to capture not only scientific but also social aspects on an interventions to guide decision makers in setting priority when choosing among alternative interventions (Rowen et al., 2017). In studies conducted in the region, other measurement tools were being developed based on existing instruments to capture quality of life and patient's satisfaction with their treatment[4].

Aim Of The Study:

The aim of this study was to measure health related quality of life in Lebanese patients with certain chronic diseases using the EQ5D instrument and to associate this information with demographic data, socioeconomic status, health satisfaction and utility measures.

Ethics Approval:

This study was approved by the Lebanese American University Institutional Review Board.

Method:

A prospective cross-sectional study was conducted in six community pharmacies in Beirut region from October 2018 through January 2019. The study population consisted of patients of both genders above age of 18 years, visiting their community pharmacy to collect their prescribed medications for one of the following chronic conditions: heart failure, arrhythmia, and diabetes mellitus.

Procedure and survey: Data collection was performed by fifth year pharmacy students, enrolled at the Lebanese American University School of pharmacy, assigned at a community pharmacy as part of their required training. Every two students were supervised by one preceptor from the school in addition to the adjunct preceptor at each of the five sites. Students approached around 160 potential participants during their visit to the pharmacy to initiate filling out the survey questionnaire during half of their time at the site four days a week over three months period. A total of 103 participants accepted to voluntarily and anonymously fill the predesigned survey which included questions that mostly capture health related quality of life, and information on health condition and satisfaction. The first part of the survey was to collect information on demographic data, socioeconomic status, medical management like duration of drug therapy, number of doctor's visits, number of hospitalizations, and satisfaction with overall health condition with current medical problem. The second part of the survey included the seven questions of the EuroQol 5 Dimension (EQ5D) standardized instrument for measuring generic health status and health related quality of life. Questions of the EQ5D validated tool address the physical and emotional domains, aiming to reveal important insight into the patient experience with a disease and its treatment.

Description of the EQ5D Instrument: The EQ5D 5 level index (5L) score was administered and consists of seven questions regarding five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each question five answer categories are possible; no problems, slight problems, moderate problems, severe problems or extreme problems. The outcome scores range from - 0.285 to 1.0, where 1.0 represents perfect HRQOL, using the UK tariff[15]. Outcomes for the EQ5D 5L could only be calculated for completed surveys.

Statistical analysis: SPSS v26 was used to conduct the statistical analysis once data was coded and entered. Sample socioeconomic characteristics, health condition, and medication used were summarized using frequency and percentage, whereas Satisfaction with treatment and ranking of current health were summarized using mean and standard deviation. EQ5D 5L items were presented as both percentages and means and standard deviations. Differences in EQ5D 5L score among the sample characteristics were tested using either the independent t test or the analysis of variance with bonferroni correction for pair-wise comparisons. Multivariate linear regression model was also created to test for independent effect of the covariates. All analyses were done at the 0.05 significance level.

Results:

Table 1 presents the socio-demographic characteristics of 102 respondents out of whom 54.5% were males and 45.5% were females. Among the total respondents, 4.9% were below the age of 34, 12.7% were aged between 35 and 49, 37.3% were aged between 50 and 64, 24.5% were aged between 65 and 74 and 20.6% were aged 75 and older. 77.8% of the respondents were living with their families. Most of the participants classified themselves as either middle-class (39.4%) or high-class (37.4%). About 65.7% have been receiving treatment for over a year, 44% made none or one visit to their physician within the previous year, and 67.6% have not been hospitalized in the past 12 months. About two-thirds of participants (65.7%) were diagnosed with one medical condition, 17.6% were diagnosed with two medical conditions and 16.7% were diagnosed with three or more medical conditions. The most common medical conditions were hypertension (37.3%), diabetes (32.4%), dyslipidemia (26.5%), and cardiovascular disease (CVD) (16.7%).

Table 1
Demographic characteristics of Participants

	N	%
Gender*		
Male	55	54.5%
Female	46	45.5%
Age		
34 and Below	5	4.9%
35–49	13	12.7%
50–64	38	37.3%
65–74	25	24.5%
75 +	21	20.6%
Living status		
Alone	22	22.2%
With Family	77	77.8%
Socio-economic status		
3–5 Low	23	23.2%
6–7 Middle	39	39.4%
8–10 High	37	37.4%
Current treatment duration		
< 3 months	9	8.8%
3–6 months	8	7.8%
7–12 months	18	17.6%
> 12months	67	65.7%
Visits to the doctors in past 12 months		
0–1	44	44%
2–3	38	38%
4 and more	18	18%

*1 missing for gender, 3 missing for living status, 3 missing for socioeconomic status, 2 missing for visits to the doctors in past 12 months

	N	%
Admissions to Hospital in past 12 months		
None	69	67.6%
Once	13	12.7%
Two and More	20	19.6%
Medical Conditions		
Hypertension	38	37.3%
Diabetes	33	32.4%
Dyslipidemia	27	26.5%
Cardiovascular	17	16.7%
Others	37	36.3%
Number of diagnosis		
1	67	65.7%
2	18	17.6%
3 and more	17	16.7%
*1 missing for gender, 3 missing for living status, 3 missing for socioeconomic status, 2 missing for visits to the doctors in past 12 months		

When asked to rank their current health status over a 10 point scale, participants gave an average of 6.8, and 7.4 for their current health over ten and for their satisfaction with their treatment, respectively

When asked about prescribed medications, 31.4% of the respondents were found to be on antidiabetic medications, more specifically 26.5% were on biguanides. Almost one-third (35.3%) were taking lipid-lowering medications (majority of which were Statins (34.3%). Beta blockers were reported to be taken by 27.5% of the sample, followed by angiotensin converting enzyme inhibitors/ angiotensin receptor blockers (24.5%), calcium channel blockers (23.5%), and diuretics (14.7%). Antiplatelets and anticoagulants were reported to be taken by 17.6% of the sample, proton pump inhibitors by 9.8%, and psychotropics by 9.8%. The number of medications per patient showed that the majority were prescribed monotherapy (42.2%) followed by dual or triple therapy (29.4%) (Table 2).

Table 2
Type and Prevalence of Medications Used by Participants

	N	%
Antidiabetics	32	31.4%
Biguanide	27	26.5%
Other antidiabetic*	23	22.5%
Antidyslipidemic	36	35.3%
Statin	35	34.3%
Other Antidyslipidemic*	6	5.9%
Beta Blocker	28	27.5%
ARB/ACEI*	25	24.5%
ARB	16	15.7%
ACEI	9	8.8%
Calcium Channel Blocker	24	23.5%
Antiplatelet/Coagulant	18	17.6%
Antiplatelet	16	15.7%
Anticoagulant	3	2.9%
Diuretic	15	14.7%
Proton Pump Inhibitor	10	9.8%
Psychotropics	10	9.8%
Others	31	30.4%
Number of Medications		
1	43	42.2%
2-3	30	29.4%
4-6	21	20.6%
7+	8	7.8%
*Other Antidiabetics include DPP4 = dipeptidyl peptidase 4 inhibitors, SGLT2 = sodium glucose cotransporter 2 inhibitors, GLP1 = glucagon-like peptide-1 agonists, Sulfonyurea, Insulin. Other Anti-Dyslipidemics = fibrates. Psychotropics include antipsychotic tricyclics, benzodiazepines, serotonins. ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker.		

The frequencies of item responses for each EQ5D 5L dimension are presented in Table 3. The mean utility score was 0.762 (SD 0.202). Moderate to incapacitating problems were reported by 20.5% of participants for mobility, 10.9% for self-care, and 20.6% for usual activities. Moderate to extreme pain/discomfort was reported by 36.3% of the sample, and moderate to extreme depression/anxiety was reported by 23.6%.

Table 3
Descriptive statistics for EQ5D Five Level Items and Scores

	N	%	Mean (SD)
Mobility			0.048 (0.058)
I have no problems	41	40.2%	
I have slight problems	40	39.2%	
I have moderate problems	15	14.7%	
I have severe problems	3	2.9%	
I am unable	3	2.9%	
Self-Care			0.021 (0.042)
I have no problems	74	72.5%	
I have slight problems	17	16.7%	
I have moderate problems	7	6.9%	
I have severe problems	2	2.0%	
I am unable	2	2.0%	
Usual Activities			0.033 (0.04)
I have no problems	50	49.0%	
I have slight problems	31	30.4%	
I have moderate problems	16	15.7%	
I have severe problems	5	4.9%	
Pain/Discomfort			0.07 (0.071)
I have no pain or discomfort	27	26.5%	
I have slight pain or discomfort	38	37.3%	
I have moderate pain or discomfort	29	28.4%	
I have severe pain or discomfort	7	6.9%	
I have extreme pain or discomfort	1	1.0%	
Anxiety/Depression			0.066 (0.073)
I am not anxious or depressed	40	39.2%	
I am slightly anxious or depressed	38	37.3%	

	N	%	Mean (SD)
I am moderately anxious or depressed	17	16.7%	
I am severely anxious or depressed	5	4.9%	
I am extremely anxious or depressed	2	2.0%	
EQ 5D 5L score			0.762 (0.202)

EQ5D 5L scores by socio-demographic variables, age and gender are summarized in Table 4. The bivariate analysis shows that males had significantly higher utility scores than women (mean 0.815 (SD 0.148) versus 0.697 (SD 0.240), $p = 0.003$). There were statistically significant differences in scores in terms of age groups (lowest score for age group 75+, $p < 0.001$), socio-economic status (lowest score for those self-identified as low SES, $p = 0.002$), doctors visit in the past year (lower score for those reporting 4 or more visits, $p = 0.014$) and hospital admissions over the past year (lower score for those reporting 2 or more admissions, $p < 0.001$), but not for the living status nor the duration of current treatment.

Table 4
Bivariate Analysis of EQ5D Five Level Scores by Sociodemographic Characteristics

	Mean	SD	P-value
Gender			
Male	0.815	0.148	
Female	0.697	0.240	0.003
Age groups			
Below 50 ^a	0.828	0.132	
50-64 ^a	0.804	0.155	
65-74 ^a	0.796	0.130	
75 + ^b	0.590	0.295	< .001
Living Status			
Alone	0.797	0.144	
With Family	0.748	0.218	0.328
Socio economic status			
3-5 Low ^a	0.631	0.222	
6-7 Middle ^b	0.796	0.174	
8-10 High ^b	0.799	0.194	0.002
Duration of current treatment			
< 3 months	0.729	0.121	
3-6 months	0.739	0.234	
7-12 months	0.746	0.180	
> 12months	0.774	0.215	0.880
Visits to the doctors in past 12 months			
0-1 ^a	0.823	0.145	
2-3 ^{ab}	0.736	0.209	
4 and more ^b	0.668	0.271	0.014

a, b superscripts indicate statistical significance between the groups using bonferroni correction

	Mean	SD	P-value
Hospital admissions in past 12 months			
None ^a	0.824	0.138	
Once ^b	0.670	0.266	
Two and More ^b	0.610	0.245	< .001
a, b superscripts indicate statistical significance between the groups using bonferroni correction			

As presented in Table 5, being diagnosed with hypertension and CVD along with the number of diagnosis were shown to have a statistically significant lower score on the EQ 5D 5L ($p = 0.019$, $p = 0.017$ and $p < 0.001$ respectively). Concerning drug class, only the class of Diuretics was shown to have a significant difference in EQ5D 5L scores with a p -value < 0.001 . The number of prescribed medications per respondent indicates a significant effect on the quality of life ($p = 0.002$).

Table 5
Bivariate Analysis of EQ5D Five Level Score by Medical Conditions and Medication

	Mean	SD	p-value
Medical Condition			
Hypertension			
Yes	0.702	0.250	
No	0.798	0.158	0.019
Diabetes			
Yes	0.753	0.270	
No	0.767	0.162	0.753
Dyslipidemia			
Yes	0.811	0.196	
No	0.745	0.203	0.144
Cardiovascular			
Yes	0.657	0.290	
No	0.783	0.174	0.017
Number of Diagnosis			
1 ^a	0.777	0.183	
2 ^a	0.772	0.144	
3 ^a	0.806	0.107	
4 or more ^b	0.333	0.459	< 0.001
Medications			
Antidiabetics			
Yes	0.770	0.256	
No	0.759	0.174	0.829
Antidyslipidemics			
Yes	0.775	0.239	

*angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)

a, b superscripts indicate statistical significance between the groups using bonferroni correction

	Mean	SD	p-value
No	0.755	0.180	0.629
Beta Blocker			
Yes	0.710	0.264	
No	0.782	0.171	0.111
ARB/ACEI*			
Yes	0.711	0.227	
No	0.779	0.192	0.149
Calcium Channel Blocker			
Yes	0.747	0.191	
No	0.767	0.206	0.677
Antiplatelet/Anticoagulant			
Yes	0.691	0.242	
No	0.778	0.190	0.097
Diuretic			
Yes	0.579	0.295	
No	0.794	0.164	< 0.001
Number of Medication			
1-2 ^a	0.791	0.179	
3-4 ^a	0.761	0.187	
5-6 ^a	0.785	0.113	
7 + ^b	0.509	0.353	0.002
*angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)			
a, b superscripts indicate statistical significance between the groups using bonferroni correction			

EQ5D 5L scores were positively correlated with the participants ranking of current health status ($r = 0.639$, $p < 0.001$) as well as with their satisfaction with his current treatment ($r = 0.465$, $p < 0.001$). Variables were simultaneously tested for their independent association with EQ5D 5L score using a multivariate linear regression model. Older age, having been hospitalized in the past 12 months, having hypertension, and using 7 or more medications, were all independent predictors of a lower EQ 5D 5L score, whereas a higher

score on treatment satisfaction was associated with a higher EQ5D 5L score. Patients 75 years of age or more, had on average 0.15 lower score on quality of life ($p < 0.001$). Patients that were hospitalized in the past 12 months had 0.111 lower score on average ($p = 0.001$), while those diagnosed with hypertension had an average 0.065 lower score ($p = 0.035$). Participants reporting taking 7 or more medications had an EQ score that was 0.282 lower than their counter parts ($p < 0.001$). Finally, for every unit increase treatment satisfaction the quality of life score increase by 0.036 unit ($p = 0.001$) (Table 6).

Table 6
Correlation of EQ5D with Selected Information (A Multivariate Linear regression)

Variable	Coefficient Beta	Standard Error	P-value
Age			
Below 75 (ref)	--		
75 and more	-0.153	0.036	< 0.001
Hospitalized in the past 12 months			
No (ref)	--		
Yes	-0.111	0.034	0.001
Hypertension			
No (ref)	--		
Yes	-0.065	0.030	0.035
Medications			
1 to 6 (ref)	--		
7 and more	-0.282	0.076	< 0.001
Satisfaction with Treatment (score)	0.036	0.011	0.001
Adjusted R ² = 50.0%			

Discussion:

To our knowledge, this is the first study to use EQ5D 5L UK value set to assess the patients' HRQOL with chronic disease in Lebanon. A recently published study highlighted negative impact of type II diabetes on the patients' quality of life in Middle Eastern countries[4]. In our study, patients with a history of heart disease and hypertension, had a negative impact on their quality of life compared to patients without heart disease or hypertension, similar to previous studies[16–18]. Furthermore, results showed a decreasing trend of the HRQOL of patients with dyslipidemia and diabetes mellitus. This negative correlation with the HRQOL was not statistically significant was probably due to the low number of participants. Evaluation of EQ5D in China for different chronic diseases including heart disease, diabetes

and hypertension demonstrated a stronger negative correlation of HRQOL with hypertension than with diabetes mellitus[17].

The number of comorbidities is another factor influencing the patient's quality of life. This study demonstrated an inverse correlation between HRQOL and the number of comorbidities. This inverse relationship has also been observed elsewhere in various chronic conditions such as dementia, psoriasis and cancer[19–22]. Furthermore, the number of prescribed medications equal or more to seven being prescribed 7 or more medication was negatively correlated with the HRQOL which is in line with previous findings in the literature[23]. In fact, the number of prescribed drugs may be considered as a proxy for general morbidity and another indicator of comorbid conditions that were not actively sought by patients[23].

Anti-hypertensive medications were the most frequently used s which is expected since hypertension was the most prevalent cardiovascular disease.

The HRQOL was affected by the sociodemographic characteristics. Female patients had poorer HRQOL compared to male patients. Many studies demonstrated gender differences in HRQOL among patients with chronic diseases such as coronary artery disease; for instance, Yinko et al found that after adjusting for disease characteristics and management, several factors were found to be significantly associated with HRQOL including femininity score, household responsibility and social support[24].

Elderly people were more represented in this sample due to the nature of the studied diseases. Increased age was associated with poorer HrQOL in both bivariate and multivariate linear regression. The coefficient for age was greater than that of the frequency of hospitalization and the presence of hypertension. These results should be interpreted with caution as a cut off of 75 years of age was considered for analysis meaning that only advanced age (> 75) is strongly and significantly correlated with poorer health related quality of life.

More patients live with their family than alone due to characteristics of the Middle Eastern culture. Most of the patients have Middle to high socio-economic status probably because the pharmacies are in areas where middle to high income people live (to validate). More than half of the patients were on their current treatment for more than 12 month which increases the internal validity of the study showing that we included patients with chronic diseases. Majority of patients had more than two consultations per year, reflecting the rate of visits of patients who have chronic diseases. Having middle to high socio-economic status, these patients had more access to their health care professionals.

More patients lived with their family than alone owing to the Middle Eastern culture and social consideration. Most of the patients reported middle to high socio-economic status which may reflect the location of these pharmacies. Patients with higher socioeconomic status had statistically significantly better HRQOL. Previous studies demonstrated similar association between level of income, education, social class and HRQOL[25, 26].

More than half of the patients were on their current treatment for more than 12 months which could be considered a validation of the targeted population of those with chronic diseases. The majority of patients did more than two physician consultations per year, which would reflect the rate of visits of patients with chronic diseases, their access to healthcare professionals, and reported socioeconomic status[25, 26].

The frequency of physician and or hospital visits can be considered as surrogate markers of the severity of the disease and comorbidities, which explains the positive correlation between these two factors and the HRQOL. The study results confirm previous study findings in various patient groups showing a link between healthcare resource utilization and HRQOL. In addition, EQ5D was found to be an accurate measure that predicts mortality, emergency department utilization and hospital discharge rates[27].

Furthermore, the positive correlation of the treatment satisfaction with HRQOL, further consolidates the results of a study done in Lebanon by Khabaz et al that showed positive associated between increased adherence to treatment, a higher global satisfaction and an increase in quality of life[28].

As for the EQ5D descriptive part, this study demonstrated that self-care was the least affected dimension with 72.5% of the people reporting having no problems with self-care. Although Zhang Li et al reported that hypertension was related to lower scores in mobility, self-care and usual activity, our findings might be partly explained by the fact that the survey was done at community pharmacies where patients were filling their prescriptions in person[16, 18]. Similar to a previous study, the score in the domain of pain/discomfort among individuals with cardiovascular disease was the most affected dimension[29]. In fact, Zang li et al reported that hypertensive individuals with body pain/discomfort might have a poorer HRQOL than the general population[18].

The main strength of this study is that it is the first and only study to measure the EQ5D by health utility index scores based on UK Tariff, which reflects EQ5D utility index scores among patients with chronic diseases in Lebanon.

The study limitations include the health utility index which could be influenced by the choice of value set used to convert self-classification scores. Also, patient recruitment was limited to one geographic area (capital city) and may have limited the subgroup analysis of EQ5D per disease. EQ5D and socioeconomic status were self-reported which lead to potential subjective bias. In additions, a sampling bias may exist because only patients who presented personally to the pharmacy were included so generally, they might have higher mobility and thus better quality of life. In the absence of a health utility index specific to Lebanon, EQ5D UK value set was used.

Conclusion:

HRQOL as measured by the EQ5D in this study was affected in patients with cardiovascular diseases. Male gender, advanced age, low socio-economic status, frequent hospital and doctor visits were important risk factors for a poor HRQOL. This study provided a model to pinpoint the potential

determinants of poor HRQOL in cardiac disease or diabetic patients enabling healthcare authorities to better detect the individuals at risk and plan their disease management and reimbursement coverage.

Declarations

Authors' contribution:

All authors contributed to the study conception and design. Material preparation and data collection were performed by Soumana C. Nasser, Aline Issa, and Bassima Hazimeh. Data analysis and first draft were performed by Hani Dimassi, Soumana C. Nasser, Sandrine Sarine Adrian, and Aline Issa. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

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