BETTER UNDERSTANDING OF HEALTH RELATED QUALITY OF LIFE IN THALASSEMIA PATIENTS TREATED BY IRON CHELATION THERAPY IN THE UNITED ARAB EMIRATES.

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Abstract:

β-thalassemia constitutes a major public health problem in the UAE and shows one of the highest carrier frequencies of β-thalassemia in the Gulf region. In spite of the advances in thalassemia treatment and increased survival rates, patients still suffer disease complications and significant burden from chronic treatment with transfusions and chelation. Furthermore, it is rather harder for them to face life challenges. Hence, the preservation of good quality of life is one of the major targets in clinical management of thalassemia patients which was assessed and highlighted in different studies. It is believed that these assessments provide complementary clinical information to help the hematologists in the holistic evaluation of the patient's health status.

Methods: A cross-sectional study was conducted among children and adolescents with thalassemia who received treatment in Saqr Hospital in UAE. Quality of life assessment was performed using the Quality of Life SF-36 questionnaire. The other instrument was a clinical record form including the demographics of the patients and clinical information about the disease history and lab findings pertaining to blood transfusion, blood indexes and medications. All patients signed a consent form prior to participating in the study. The results were compared to similar study done in the same center three years earlier.

Results: Out of 25 patients recruited, more patients expressed better health than one year ago in our study (56%) than the previous study (36%). Physical Functioning was nearly the same in both studies while Role-Physical, Body Pain and General Health, Vitality, Social functioning, Role-emotional, Mental Health, and mental composite summary were higher in the current study. The average serum ferritin of the patients was 1473.358 ng/mL.

Conclusion: Quality of life in thalassemic patients in our study done in 2014 showed improvement when compared to the results obtained in the same center three years ago. The domains mostly affected were the role-physical and role-emotional. This improvement in the quality of the patient life can be explained by changing parenteral to oral iron chelation therapy and the continuous health education programs. Quality of life assessment studies are warranted to increase the understanding of the thalassemia impact on the patients and to provide the necessary patient and family support.

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Abbreviations and definitions

ANOVA	Analysis of Variance
BP	Body Pain
CBCL	Child Behavior Check List
DFE	Desferoxamine
DFO	Deferoxamine
DoH	Declaration of Helsinki
EPIC study	Iron Chelation with Exjade study
G6PD	Glucose-6-phosphate dehydrogenase
GH	General Health
Hb	Hemoglobin
HEED	Health Economic Evaluation Database
HLA	Human Leucocytic Antigen
HRQOL	Health Related Quality of Life
ICT	Iron Chelation Therapy
KW	Kruskal-Wallis test
MCS	The mental composite scores
MDS	Myelodysplasias
MH	Mental Health
MOH	Ministry Of Health
MOS	Medical Outcomes Study
MRI	Magnetic Resonant Imaging
PCS	The physical composite scores

PedsQLTM SCD	Sickle Cell Disease Module for pediatric patients with sickle cell disease
PF	Physical Functioning
PRO	Patient-Reported Outcome
QOL	The Quality of Life
RAKHMSU	Ras Al Khaimah Medical And Health Sciences University
RE	Role Emotional
RES	Reticulo-Endothelial Systems
RP	Role Physical
SCD	sickle cell disease
SCPBI-Y	Sickle Cell Disease Pain Burden Interview-Youth
SD	Standard Deviation
SF	Social Functioning
SF-36	Short-Form Health Survey (Quality of Life questionnaire)
SICT	satisfaction with iron chelation therapy
SPSS	Statistical Package for the Social Sciences
STQOLI	self-administered Specific Thalassemia Quality of Life
UAE	United Arab Emirates
VT	Vitality

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1. Introduction and background:

1.1. Thalassemia

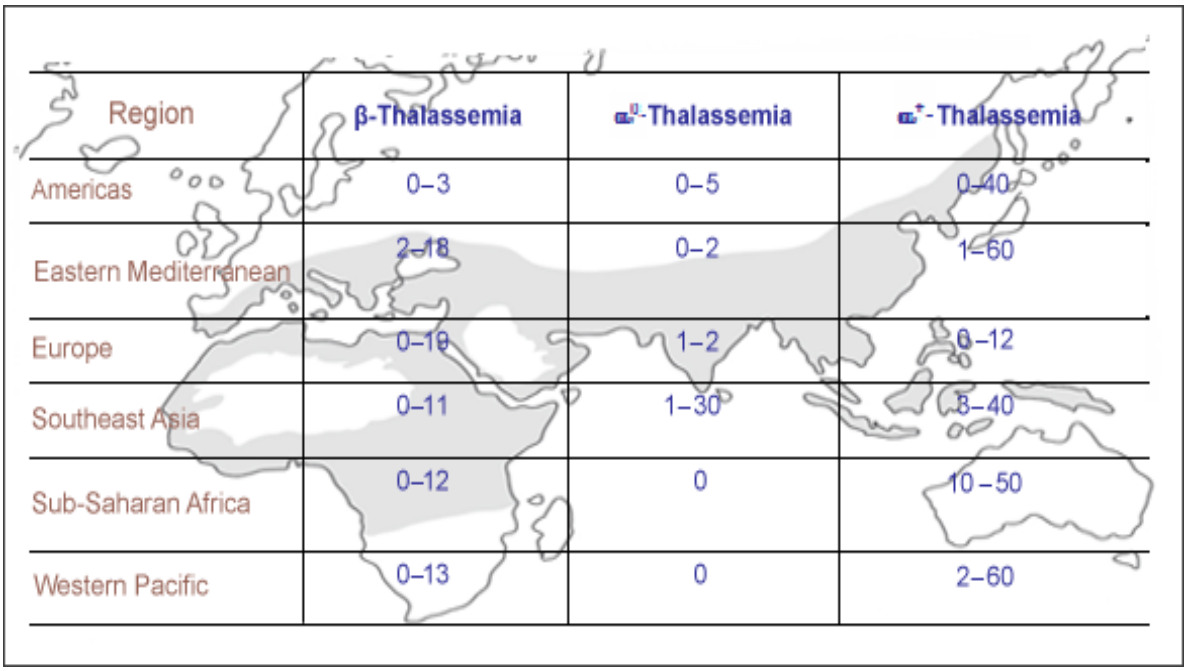
Normal hemoglobin A consists of two α and two β chains. The globin gene clusters are present on chromosome 16 while the β gene clusters are present on chromosome 11. Thalassemias are autosomal recessive disorders (1). In Beta thalassemia, beta globin chain synthesis is decreased resulting in an excess of alpha chains. This leads to increased synthesis of the hemoglobins without beta chains [e.g. Hb-F (alpha2 gamma2), Hb-A2 (alpha2 delta2)]. Left over free alpha chains form tetramers (alpha4), which are very insoluble and precipitate in red cells leading to increased fragility and early red cell death (2).

The main symptom of beta thalassemia major is severe anemia due to ineffective erythropoeisis, haemolysis and hypersplenism. Extramedullary erythrocyte precursor's destruction instigates a decrease in erythrocyte release into the blood stream. Hemolytic activity in the reticulo-endothelial systems (RES) increases due to the destruction of inclusion bodies containing mature erythrocytes, leading to hyperplasia of the RES, erythroid system, and extramedullary hemopoeisis. Extramedullary hemopoeisis occurs in the liver and spleen, initiating hepatomegaly and splenomegaly(3).

1.2. Epidemiology of thalassemia:

Thalassemia is a growing global public health problem with an estimated 900,000 births of clinically significant thalassemia disorders expected to occur in the next 20 years (4). Men and women are equally affected by thalassemia. The prevalence of thalassemia is 4.4 of every 10,000 live births. The prevalence of globin variant in the world population

is 5%. However, the prevalence of α- or β-thalassemia trait in the world population is 1.7% (Figure1). Globally, an estimated 15 million people have thalassemia. Thalassemia trait is more prevalent affecting 5-30% of people from the following ethnic groups:



Region	β-Thalassemia	α^0-Thalassemia	α^+-Thalassemia
Americas	0–3	0–5	0–40
Eastern Mediterranean	2–18	0–2	1–60
Europe	0–10	1–2	0–12
Southeast Asia	0–11	1–30	3–40
Sub-Saharan Africa	0–12	0	10–50
Western Pacific	0–13	0	2–60

Figure1: Epidemiology of thalassemia: carrier frequencies of thalassemia alleles (%) (5)

1. Alpha thalassemia is more common in: African, Middle Eastern, East Indian, Southeast Asian (Vietnamese, Laotian, Thai, Singaporean, Filipino, Cambodian, Malaysian, Burmese and Indonesian), Chinese and Occasionally Mediterranean (Italian and Greek). The most severe form of alpha thalassemia causes fetal or newborn death.
2. Beta thalassemia is more common in: Mediterranean (Italian and Greek), Iranian, African, Southeast Asian and Chinese.
3. E Beta thalassemia is more common in Southeast Asian (Cambodian, Vietnamese and Thai).

4. Sickle Beta Thalassemia is more common in Mediterranean (Italian, Greek and Turk) people.

β-thalassemia and malaria: The prevalence of β-thalassemia is highest in areas where malaria is (or was) endemic (Figure 2). Similar to β-thalassemia, α-thalassemia is prevalent in tropical and subtropical regions, where malaria was or still is endemic. It is thought that carriers of hemoglobinopathies have a degree of protection against malaria, although the mechanism underlying this protection is unknown.

Figure 2: Distribution of Non Transfusion Dependent Thalassemia (6)

According to the previous figures (1 and 2) and the ethnic distribution, it can be inferred that thalassemia represents a serious public health problem throughout the Mediterranean region, the Middle East and the Indian subcontinent, as well as in

Southeast Asia(7). United Arab Emirates (UAE) is one of the countries falling under the high risk regions where surveys have shown that the UAE exhibits one of the highest carrier frequencies of β-thalassemia in the Gulf region. This was detected by conducting DNA studies on over 400 consecutive UAE National newborns and nearly 2000 adult college students and 800 randomly selected Emiratis who demonstrated that the frequency of β-globin gene defect including the β-thal, βS gene and abnormal hemoglobins is estimated at 8.5%, which is one of the highest in the Gulf Region. During 1989-2004, more than 850 patients have been registered at the Dubai Genetics and Thalassemia center(8).

1.3. Thalassemia treatment and complications:

Although medical advances in the treatment of thalassemia have led to increased survival rates, patients still suffer disease complications. It was found that the life expectancy of thalassemic patients has dramatically increased to reach into 4^{th} and 5^{th} decades of life with the combination of regular blood transfusions and chelation therapy. However, the frequent blood transfusion has also led to iron overload with many complications including endocrinopathies, behavioral and neurotic problems, growth failure, cardiovascular problems, liver disease, gonadal dysfunction and delayed puberty(9, 10). It was also found that thalassemic children are1.6-fold higher than the healthy children concerning behavioral abnormality (11).

The detrimental effect of iron overload requires Iron Chelation Therapy (ICT) in order to reduce the excess iron load that is not eliminated properly. Desferoxamine (DFE), a parenteral drug used widely as ICT, has been employed in the treatment of beta thalassemia for nearly forty years and has shown to be effective in reducing the hepatic

and extra-hepatic adverse effects, particularly myocardial toxicity. Oral chelators such as Deferasirox are available also yet are much more expensive than the traditional ICT's(12).

The effect of thalassemia, its complications and chronic treatment options like transfusion and chelation can extend further to impact the patient's quality of life adversely (13, 14). It is important to assess the impact of this chronic disease on a patient's everyday life, thus a scale was used for that purpose; the "Health Related Quality of Life" (HRQOL). HRQOL refers to the patient's perception of their physical and mental health and it helps to compare different groups of patients and measure the effect of an intervention(15).

The Quality of Life (QOL) of individuals with thalassemia major is influenced by many factors such as the impact of the diagnosis and treatment, having a chronic condition, appearance, treatment components like frequent hospital visits for transfusion, nightly subcutaneous infusions, delayed or absent sexual development, complications of the disease and therapeutic interventions and uncertainties about the future (16). Various studies have discussed the social, cultural and educational difficulties faced by thalassemia patients. The patients QOL is mainly disturbed in the domains of education and sports where most thalassemics were not satisfied with their body image. Furthermore, high level of anxiety was expressed about their future health and education being dependent largely on their parents for financial and emotional support (17).

The thesis is structured as a monograph. Chapter two discusses the relevant literature review about the main topic. Chapter three covers the methodology used according to

the theoretical basis and the practical implementation of data collection and data analyses along with ethical considerations. The results obtained are presented in chapter four. In chapter five, the results are discussed as well as methodological strengths and limitations. Finally, the thesis ends up with a conclusion and recommendation for practice and future research.

2. Literature review:

Our current study is a follow up study preceded by a similar study done in 2011. To review the relevant literature Pub med, Medline and google scholar databases were searched by using these keywords; Quality of life, thalassemia major, SF-36, thalassemia, quality of life- instruments – validation, thalassemia - quality of life - iron chelation. The search result of relevant literature are considered and presented in this chapter. The rationale and research objectives are stated at the end.

In the beginning, it is worthy to mention that the therapeutic options for the treatment of thalassemia had resulted in the prolongation of survival rates. However, the continuous need for frequent blood transfusions and iron chelation therapy added more psychological and social impact on these patients. This would affect their quality of life and represents a crucial aspect of the patient's suffering that should not be neglected throughout the process of disease management. Several studies have been investigating instruments to assess the QOL in thalassemic patients to help in a sound assessment of the therapeutic benefit both physically and mentally.

2.1. Quality of life assessment instruments:

The health-related quality of life (HRQOL) has been widely used in the assessment of the quality of life in general and in patients with chronic diseases in specific. It has evolved since the 1980s to include health aspects; either physical or mental. The short form (SF-36) measures, which are part of the HRQOL, are now used by the Health care authorities in the United States of America (USA) to help evaluate the quality of care in managed care plans and other health care applications. The questionnaire underwent

extensive validation in the early 1990s by researchers and health care and prevention programs to consider it as a reliable set of measures in further studies (18).

Other researchers tried to adopt new instruments for the same purpose as in a study done in USA and UK to evaluate the reliability and validity of a new instrument used to assess satisfaction with iron chelation therapy (SICT) (19). The results showed that SICT was reliable and valid and it can be used in clinical trials.

In addition, an instrument was developed and validated in the form of interview which was found to be brief, clinically relevant, multidimensional to assess pain burden among children and adolescents with sickle cell disease (SCD). It was called “Sickle Cell Disease Pain Burden Interview-Youth” (SCPBI-Y). SCPBI-Y interview was found also to be useful in different clinical settings in children and adolescents (20).

PedsQLTM is another assessment tool studied in a qualitative study to develop the items and support the content validity. It stands for the Sickle Cell Disease Module for pediatric patients with sickle cell disease (SCD). The qualitative research was done on several phases in the form of Individual cognitive interviews. The interviews used both think aloud and cognitive debriefing techniques to assess the different items of the module. Interviews were conducted with patients and parents and the opinions of experts were put in consideration when constructing the module. It comprises six domains, consisting of 48 items to measure Pain Intensity/Location (9 items), Pain Interference (11 items), Worry (7 items), Emotions (3 items), Disease Symptoms/Treatment (12 items), and Communication (6 items).

The validity of PedsQLTM SCD was confirmed by several researches through field work in different sites in the world (21). Henceforth, the PedsQLTM SCD Module was accepted as a research instrument and it can be used in the assessment of SCD-specific health-related quality of life in clinical research and practice especially if combined with the PedsQLTM Multidimensional Fatigue Scale (22).

Similarly, an Iranian experimental study was done to discuss the effect of family-centered empowerment model on quality of life of school-aged children 6-12 years with thalassemia major. The Data collected were demographic and general quality of life questionnaires in children, these data covered physical, emotional and social aspects in addition to school functions. The questionnaires were used after determining the content validity and reliability by internal correlation method, quality of life was measured 1.5 months after the intervention. The average quality of life of thalassemic children after the intervention was significantly higher than before the intervention. Yet the questionnaire was not repeated in other studies to evaluate its effectiveness (23).

Considering the adult patients, Greek researchers carried out a study to develop a self-administered Specific Thalassemia Quality of Life Instrument (STQOLI) for adult patients according to psychometric measures. To develop (STQOLI), first, a qualitative study was done to generate items and identify domains using the critical analysis incident technique and a literature review, this qualitative study involved both patients and experts, then quantitative validation was carried out to select items, identify dimensions, and measure reliability and internal and concurrent validity, finally the questionnaire had 41 items comprising four main domains and one global item about general health. This instrument shows validity for HRQOL for patients with thalassemia

but still more research is needed to understand more about the universal properties of the questionnaire (24).

However, the Quality of Life SF-36 questionnaire is still considered more advanced instrument covering different aspects of QOL, used universally and can be applied for different age groups.

2.2. Thalassemia and Quality of life:

The literature showed studies about variable aspects of the disease progress in the patient's life ranging from assessing the impact of the disease *per se*, passing through the patient perception with regard to social and mental effects, ending with the complications or benefits of therapeutic measures and future solutions to find less invasive or even permanent remedies.

A study in India concluded that thalassemia can be considered nationally as a disability necessitating the involvement of different authorities as it was found that the disease is extremely stressful, and patients face a variety of physical, psychological and social problems. The findings also showed that cultural and educational backgrounds play a major role in illness experiences (25).

Not far from the previous study, a cross-sectional study assessed the quality of life (QOL) among thalassaemic children aged 4 to 12 years during the year 2007-08 in Pakistan, showed that parents were highly concerned about QOL aspects in their affected children. However, this study covered only thalassemic children; it did not involve adults (26).

Another study showed that the QOL of Thai children with thalassemia was significantly affected by the patient's age, age at onset of anaemia and age at first transfusion, pre-transfusion haemoglobin (Hb) level, receiving a blood transfusion during the previous three months and disease severity. It was found also that iron chelation therapy had negative effect of school functioning subscale (27). However, the study involved only sick children without determining the severity of the disease and the PedsQL™ 4.0 Generic Core Scale was used, limiting the study to children age only.

Moving to the Middle East, the SF-36' questionnaire was used to assess the QOL in patients in Saudi Arabia but it was on sickle cell disease (SCD). It showed obvious deterioration of QOL especially in role physical, general health and bodily pain domains irrespective of the gender. Notably, females with SCD showed more deterioration in emotional wellbeing. Worse deterioration was seen in patients with disease complications in the physical, general health and emotional wellbeing domains. The HRQOL scores were negatively affected by advanced age, female gender, rural areas residency, low socioeconomic status, presence of disease complications, multiple hospital admissions as revealed by multivariate regression analysis. The findings augmented the researchers' recommendation to emphasize and increase the public awareness about the national program for the premarital survey to screen for hematological diseases like SCD and thalassemia which is carried out in Saudi Arabia (28). It is worthy to mention that these findings are comparable to the factors which affect the QOL of thalassemic patients seen in other studies.

Similarly, school functioning and the physical functioning domains in the HRQOL and the Pediatric Quality of Life Inventory assessment showed the lowest mean score when

applied to thalassemic children in Jordan. They were related also to the socio-demographic and clinical data and a comparison was conducted with healthy children to verify the results (29).

In South America, the sociodemographic characters and the effect of the disease on the quality of life of SCD Brazilian adult patients were investigated by using SF-36 questionnaire. The results showed that the disease decreased the working capacity of individuals with low incomes and the resultant inaccessibility to healthcare services causing noticeable impairment of QOL(30).

Far away from their countries of origin, the thalassemic immigrants from Southeast Asian and Asian Indian origin were surveyed in the USA, namely those who were affected by thalassemia major and living in an urban area. The study discussed the sociocultural and socioeconomic problems suffered by them and it was found that the emotional and social aspects were maximally disturbed especially for the thalassemic children and their parents. This painful effect was found to be exaggerated by the disease severity and certain cultural believes, upon which the researchers recommended to do more investigations to develop initiatives to improve their QOL(31).

2.3. Thalassemia treatment and its impact:

Regarding the effects of the therapeutic interventions of thalassemia on the patients' QOL, several studies can be found to assess the impact of iron overload and iron chelation therapy and some researches went beyond that to study possible permanent treatment modalities which seem to be promising to provide better QOL.

Deferoxamine (DFO), most commonly delivered by continuous subcutaneous infusion over 8 to 12 hours a day, is the oldest available form of ICT used by patients with transfusion-dependent disorders. Prior research, albeit in small sample sizes, has indicated significant deficits in health related quality of life (HRQOL) among patients receiving DFO for the treatment of transfusion-dependent iron overload, compared to values from age-matched normative populations (32,33). In particular, the time-consuming nature of DFO regimens and side effects associated with this form of ICT (including local site reactions) (34-36) can have a detrimental impact on numerous facets of patients' lives; including work, social activities, sex life, sleep and emotional well-being (37). As a result, patient satisfaction with DFO treatment regimens was low and suboptimal adherence was common among patients (32, 33). Improvements in ICT administration convenience and tolerability are expected to improve patient's satisfaction with ICT and HRQOL, thus promoting adherence to ICT regimens and potentially reducing iron overload-related morbidity/mortality and associated healthcare costs (38, 39).

The other ICT, Deferasirox (Exjade), was first approved in 2005 and nowadays is the most widely prescribed for patients as it is orally administered (40). Deferasirox has been shown to be effective and generally well-tolerated for the treatment of iron overload in β-thalassemia and Myelodysplastic syndrome patients (41, 42). Findings from clinical trials comparing outcomes in patients with iron overload treated using deferasirox or DFO have also suggested the superiority of deferasirox in terms of treatment satisfaction and adherence (43, 44). However, additional research using validated patient-reported outcome (PRO) measures is needed in order to better

understand the added benefits of deferasirox over DFO in improving HRQOL and treatment satisfaction, adherence, and persistence among patients with transfusion-dependent iron overload (41, 42).

The superiority of oral chelators over injectable ICT was also proved in a cross-sectional study in Kerman city in Iran where the QOL was better in the former ICT in a group of patients suffering from thalassemia major and intermedia (45). The study was meant mainly for children and did not investigate the benefit in adult patients.

Furthermore and regardless of the ICT medication used, it was found that delayed start of iron chelation therapy had negative effect on HRQOL thalassemia children and their parents originally coming from countries of the Middle East. The study which was conducted in Italy used the Pediatric Quality of Life Inventory (PedsQL) 4.0 as an instrument in a cross-sectional study from November 2007 to August 2008. The Questionnaire was completed by all patients and their parents with lower scores presented by the parents (46).

Yet, more research is needed to study the factors associated with HRQOL in children and adolescents with thalassemia to provide better understanding of these factors and hence, more suitable clinical, counseling, and social support programs or proactive care assistance can be offered to enhance treatment outcomes (44).

More advances in the treatment of thalassemia were suggested by an Italian study stating that the prognosis for thalassemia major patients became "open-ended". The advances upon which the researchers built their recommendations are advances in red cell transfusion and the introduction of new ICT. More progresses are expected as well in the management of thalassemia with the possibility of bone marrow transplantation

using HLA-matched unrelated donors, gene therapy and improvement in iron chelation. This would improve survival and quality of life. The study recommended also that Western countries and economic organizations should spend more efforts to deliver high standard of management of thalassemia everywhere in the world (47). This will open the scope for future clinical studies to discuss the effect of the newer agents and modalities in improving the quality of life and life expectancy of thalassemia patients (48).

2.4. Research objectives and rationale:

The research work was done in response to the growing needs to assess the quality of life of this group of patients and to attain the benefits of the early detection of social and physical disturbances caused by thalassemia and its treatment. The main objectives were to study the impact of thalassemia disease on the physical and psychological activity of thalassemia patients, and to study the different clinical and therapeutic factors such as rate of blood transfusion, chelation therapy on physical and psychological well-being of those patients. In addition, it was projected to compare the patients' perception about the progress of the disease and QOL on two different occasions.

3. Methodology:

In this chapter, the methodological design of our study is deliberated but this is preceded by a short account on the different qualitative and quantitative research methodologies. Then the cross sectional design, sample selection, location and population of this study are discussed, followed by data collection and SF-36 questionnaire discussion. Lastly, the ethical considerations and data handling were elaborated.

Research methodology can be qualitative or quantitative. The research question in qualitative type is to know why something is a problem or how it is perceived as a problem, and the participants views about the problem.(49) Hence, qualitative research is descriptive and interpretative, and seeks to understand the meaning of problem experiences of the participants.(50)

On the other hand, Quantitative research methods are used to answer questions on quantifying size and distribution of a disease and to study the associations of a disease and another dependent variable.(49)

Epidemiology studies are quantitative researches developed to investigate how an exposure affects a certain population focusing on factors influencing or determining the distribution of a disease.(51) In other words, the objectives of epidemiology studies are to identify etiology and influencing risk factors, the extent of the disease or the health status in a population, the natural history and prognosis of the disease, to evaluate interventions, and to provide the foundation for developing public health policies.(52)

According to the design, the epidemiological studies can be divided into observational (Non-interventional) and experimental (interventional). Observational studies include

exploratory, descriptive, analytical, ecological, cross sectional, case control and cohort studies. Experimental studies are interventional and include randomized controlled trials, cluster randomized controlled trials, field trials, and community trials.(49, 52)

3.1. Study design:

Our study was a cross sectional study conducted among children and adolescents with thalassemia who received treatment at Saqr hospital, Ras Al Khaimah (RAK) – UAE. The cross sectional study design suits this study as this design is commonly used to describe the burden of the disease in the community and its distribution. It can be repeated to measure change in a population through data collection by questionnaire predominantly or by structured interview on more than one case at a single point of time with the possibility of detecting patterns of association between the collected variables. Furthermore, the cross sectional studies can be completed within short time with limited resources.

Moreover, it allows collecting large amounts of data from a large number of people on wide variety of subjects, so the data can be used by researchers from various disciplines. Also cross-sectional research works well for exploratory studies to test a research topic prior to large scale studies. To do a cross sectional study, it is also feasible to do within the scope of a master thesis both regarding the obvious time constraints, and the limited resources available. However, the cross- sectional method can only reveal associations, no causative links.

3.2. Study instrument: Quality of life (QOL), (SF-36 questionnaire)

In our study, quality of life assessment was performed using the Quality of Life SF-36 questionnaire, the standard Forward-Backward procedure was applied to translate the SF-36 questionnaire from English to Arabic by a bilingual individual with some cultural adaptation. In addition to the Quality of Life SF-36 questionnaire, the other instrument was a clinical record form, this form consisted of questions concerning demographics of the patients (e.g., gender, age, etc.), and clinical information (e.g., onset of anemia, diagnosis, age at first transfusion, history of blood transfusion, hemoglobin (Hb) levels and other laboratory reports, complications, serum ferritin level, iron chelation treatment, etc.).

3.3. Sample selection:

3.3.1. Inclusion criteria:

1- Patients diagnosed with thalassemia.
2- Patients above 5 years of age.

3.3.2. Exclusion criteria:

1- Patients with severe clinical condition which may limit their ability to participate in the study.
2- Patients unwilling to participate in the study

3.4. Location and population:

Participants were recruited from Saqr Hospital in RAK Emirate in the UAE. We recruited patients above 5 years old as they can express their feelings while children below 5 years cannot. Our participants are residents of RAK. The RAK Medical Zone oversees a number of hospitals and public medical centres as well as a range of specialized clinics

and pharmacies all over RAK. The most important health facilities in RAK are: Saqr Hospital, Obaidullah Hospital, Shaam Hospital, RAK Preventive Medical Center, Dental Center, RAK Rehabilitation Centre for Disabled with special needs and RAK centre for special needs.

Our research was run by Ras Al Khaimah Medical and Health Sciences University (RAKHMSU).

Figure 3: Saqr Hospital in RAK- UAE

Figure 4: Ras Al Khaimah Medical and Health Sciences University- RAK- UAE

3.4.1. Pre recruitment and recruitment:

Thalassemia patients were recruited while attending the clinic for routine follow up. In addition we used a social network to arrange appointments with thalassemia patients to discuss about our research project.

3.4.2. Sample size

We were intending to recruit all thalassemia patients who attended their clinic during the study, but only twenty five participants were possible to be recruited in the study period.

3.5. Data collection:

3.5.1. The procedure

All eligible patients and their parents were approached as they came in for routine follow-ups during the data collection period in Saqr hospital in Ras Alkhaimah. The SF 36 Questionnaire was pretested in the former study done in 2011. Serum ferritin levels were collected from patient files.

3.5.2. Questionnaire

The SF-36 questionnaire was chosen for its capability to evaluate both the physical and psychological components of quality of life. The SF-36 questionnaire assesses eight dimensions of health related quality of life, which relate to the physical and mental components of the individual's health perception. (Figure 5)

Specifically, the domains 'physical functioning'(10 items) , 'role-physical' which means role limitation due to physical health problems(4 items), 'bodily pain'(2 items), and 'general health'(5 items) are more related to the physical component, whereas the domains 'vitality/energy'(4 items), 'social functioning'(2 items), 'role-emotional' which means role limitations due to emotional problems (3 items), and general 'mental health'(5 items) are more related to the psychological component. Possible scores for each domain range from 0 (corresponding to the worst possible state) to 100 (corresponding to the best possible state). These eight domains can be grouped into two summary scores: the 'physical component summary' (PCS) evaluates the patients' perception of limitations or disabilities in self-care, physical, social and role activities, the presence of bodily pain and fatigue. The 'mental component summary' (MCS) score evaluates the feelings of psychological distress, social and role disability because of emotional problems.

The scales (Vitality, General Health, and Social Functioning) can be considered either physical or mental components. It is better to use the two summary measures than using the eight scales in statistical analysis of the SF-36 as it reduces the number of statistical comparison tests. In addition, the two summary measures discriminate between physical and mental health outcomes, cross-sectional and longitudinal studies

confirmed these advantages of the two summary measures. Scales of the physical component are most responsive to treatments that affect physical morbidity, while scales of the mental component respond most to therapies that act on mental health.

The SF-36 includes only eight of 40 health concepts in the MOS (Medical Outcomes Study) study; in addition the SF-36 measures each concept with a short-form scale. The content validity of the SF-36 was compared to its corresponding content validity of other commonly used generic health surveys (56). Comparisons show that the SF-36 contains eight of the most frequently used health concepts.

However, there are several concepts included in widely-used surveys but not included in the SF-36. Of these concepts are: cognitive functioning, family functioning, health distress, sleep adequacy, sexual functioning, recreation/hobbies, self-esteem, eating, spirituality, communication, and symptoms/problems that are specific to one condition. The concept of symptoms and problems that are specific to a particular condition was excluded from the SF-36 because the SF-36 is a generic measure.

SF-36 user's manuals contain tables of correlations between the eight scales and the two summary measures and 32 measures of other general concepts (52, 53) and 19 specific symptoms. This correlation considers the concepts not included in the SF-36.

Items		Scales	Summary measures
3a	Vigorous activity	Physical functioning (PF)	Physical Health (PCS)
3b	Moderate activity		
3c	Lift, carry grocery		
3d	Climb several flights		
3e	Climb one flight		
3f	Bend, kneel		
3g	Walk mile		
3h	Walk several blocks		
3i	Walk one block		
3j	Bathe, dress		
4a	Cut down time	Role-Physical (RP)	
4b	Accomplished less		
4c	Limited in kind		
4d	Had difficulty		
7	Pain magnitude	Bodily Pain (BP)	
8	Pain –interfere		
1	EVGFP rating	General Health (GH)	
11a	Sock easier		
11b	As healthy		
11c	Health to get worse		
11d	Health excellent		
9a	Pep/life	Vitality (VT)	Mental Health (MCS)
9e	Energy		
9g	Worn out		
9i	Tired		
6	Social extent	Social Functioning (SF)	
10	Social time		
5a	Cut down time	Role-Emotional (RE)	
5b	Accomplished less		
5c	Not careful		
9b	Nervous	Mental Health (MH)	
9c	Down in dumps		
9d	Peaceful		
9f	Blue/sad		
9h	Happy		

Figure 5: SF-36 aspects (53-55)

It was found that SF-36 scales correlate (r = 0.40 or greater) with most of the excluded general health concepts in addition to the severity and frequency of many specific symptoms and problems. However, the correlation was not the same in sexual functioning that correlates weakly with SF-36 scales. So, sexual functioning was recommended to be included in the questionnaires that have space for supplementing the SF-36.

The studies done in the United Kingdom, United States, and Sweden showed that the scales used in the SF-36 except General Health could explain only about two-thirds of the variance in individual evaluations of current health status(58).

In comparison with other published measures, SF-36 scales have been performing well in most tests published till now. The SF-36 was compared with 225 other measures(59).

Comparing short-form versions of SF-36 with full-length versions, it was found that SF-36 scales perform with about 80–90% empirical validity in studies involving physical and mental health criteria (60).

However, this disadvantage of the SF-36 can be balanced by the fact that some long-form measures have 5–10 times greater burden respondent. So, the SF-36 is considered a practical alternative to longer measures. In addition, eight scales and two summary scales cover almost all differences in physical and mental health status in comparisons between different group levels (56, 57, 61). Moreover, the SF-36 has performed equally as well as the longer non-MOS measures, such as the Sickness Impact Profile in detecting average group differences or changes over

time (61,62). Compared to longer MOS measures, using SF-36 leads to reduction in the statistical power of hypothesis testing. This is to be considered in planning clinical trials and other studies. Each scale has its own validity which is completely different from the validity of the other scales. This was shown in the results of factor analytic studies of their construct validity (Figure 6) (57,63,64). A similar trend has been shown for the two summary measures.

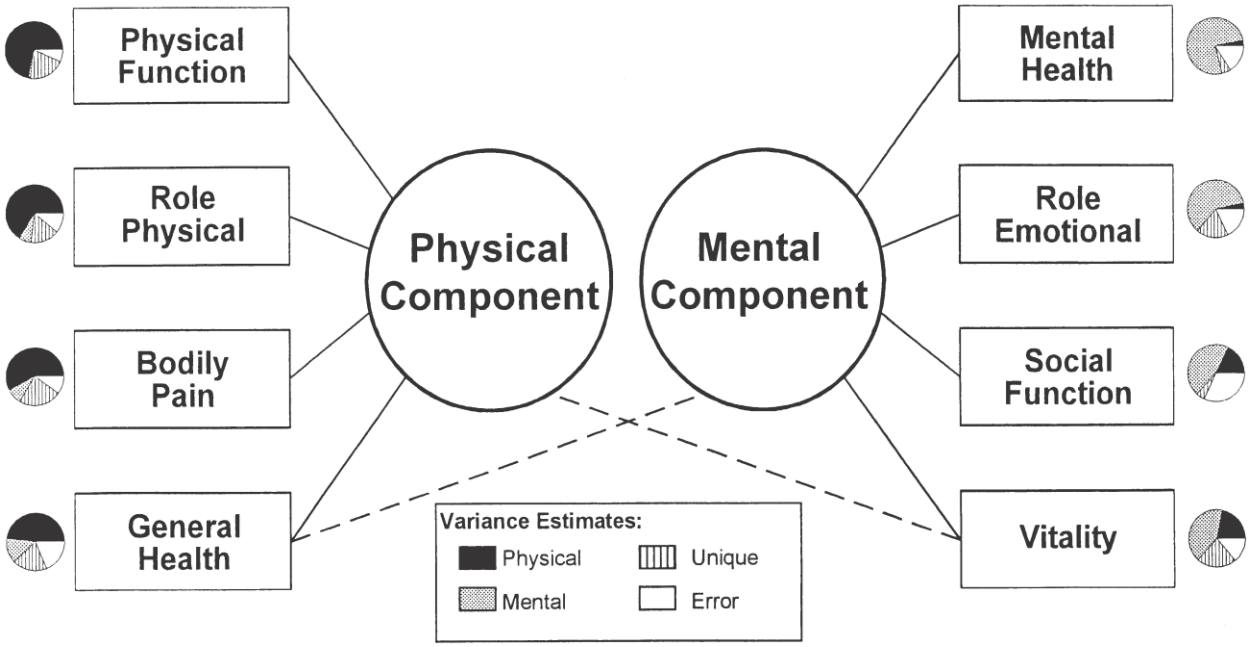


Figure 6: Construct validation of the SF-36 two-component model (57).

In both cross-sectional and longitudinal tests, the Mental Health, Role-Emotional and Social Functioning scales and the MCS summary measures were the most valid mental health measures. Similarly, The Physical Functioning, Role-Physical, and Bodily Pain scales and the PCS were found to be the most valid physical

health measures. Specific Criteria used in the validation of the SF-36 in known-groups include clinical indicators of diagnosis and severity of depression, heart disease, and other conditions. These criteria are documented in previous reviewed publications and in the two user's manuals (56,57,63-65).

To screen for psychiatric disorders, the Mental Health scale and the MCS summary measure were used (57,66). For example, on using a score of 42 as a cutoff, the sensitivity of the MCS was 74% and its specificity was 81% in detecting patients diagnosed with depressive disorder (57).

Clinical studies have shown the three scales with the most physical factor content (Physical Functioning, Role-Physical, and Bodily Pain) in (Figure 6) are most responsive to the benefits of knee replacement (68) , hip replacement (61,68), and heart valve surgery (69). On the other side, factor analytic studies showed that the three scales (Mental Health, Role-Emotional, and Social Functioning) with the most mental factor content were most responsive in comparing patients before and after recovery from depression (64); change in the severity of depression (70); as well as drug treatment and interpersonal therapy for depression(71). Moreover, nearly 100 studies showed that the SF-36 can be used in studying the benefits of other treatments as well (59).

SF-36 scales and summary measures were found to be linked to utilization of health care services (57), the clinical course of depression (70,72), loss of job within 1year, and 5-year survival (57) as shown from the results of Predictive validity studies.

Studies demonstrated the interpretation value of general and specific population norms for the SF-36. General population normative data for the SF-36 has been collected in the United States (56,57,73) and in 12 other countries (74).This interpretation value has been demonstrated also for the Sickness Impact Profile (75) ,the MOS SF-20 (76,77) and other measures.

At the beginning, some studies were done to validate scale scores (78). In addition, SF-36 scales have been increasingly accepted as valid health measures to document disease burden. Moreover, the advantage of a generic survey (such as the SF-36) in estimating disease was discussed in a group of articles about more than 130 diseases and conditions. Some diseases were more frequently studied as arthritis, back pain, depression, diabetes, and hypertension (79). Measurement was standardized across studies to be useful in comparing “well” and “sick” populations.

The first IQOLA(The International Quality of Life Assessment) Project meeting was held in September 1991 in Paris to discuss the basic project policies and procedures. Permission was given for other academic researchers to use the IQOLA Project translations while they were in development and testing after signing user’s agreement before completion and testing of these translations. Attendants in the first IQOLA Project meeting made the translations available for free for all users after publication.

In 1992-1993, more countries joined the project including Denmark and Norway. IQOLA research procedures were revised subsequently. Between 1993 and 1998, SF-36 was widely spread all over the world.

The IQOLA Project followed a three-stage research protocol for translating and testing the SF-36.The first stage was translation following a standard process which produced a survey form. The second stage was formal psychometric tests of the assumptions underlying item scoring with scale construction which lead to scoring algorithms. The third stage was validations and norming and the equivalence of interpretations across countries (80,81).

The three stages IQOLA project produced questionnaires for data collection and scoring algorithms used for standardized comparisons. Lastly, the project ended with validation and norming studies for interpretation.

3.5.3. Dependent variables:

Are the scores of different components of the questionnaire; PF, RP, RE, BP, GH, VT, SF, MH, MCS and PCS in a scale (0–100 General Health Rating Index); these are numerical variables.

3.5.4. Independent variables:

Are categorical variables; Designations of thalassemia patients according to Quality of life scores, Age group, Effect of gender, splenectomy, rates of blood transfusion and levels of education on HRQOL.

3.6. Data analysis

The questionnaires were filled and collected from participants, the data were introduced in an excel file, and then a web site (www.SF-36.org/Demos) was used to change the scale from the scale in the SF-36 questionnaire to another scale (0–100 General Health Rating Index). The results from this website were introduced into an excel file again.

SPSS program was used for analysis of the current study findings and to compare the mean differences in the different components of the questionnaire; PF, RP, RE, BP, GH, VT, SF, MH, MCS and PCS with a previous study conducted in the same center with identical specifications. Independent t-tests and ANOVA were used for the inferential statistics. Analysis of variance (ANOVA) was followed by a posthoc test to check if the categories differ significantly.

3.7. Ethical consideration and research clearance:

3.7.1. Ethical considerations (82-90):

The study protocol was sent to Dubai Health Authority-UAE (the central committee) for judgment and approval of the Research and to Ethics Committee in RAK Medical and Health Sciences University (the regional committee). See appendix (1) for details.

Our main ethical concern is taking informed consent from participants. At the beginning of the interview; all respondents were informed about the objectives of the study and were assured that all responses will remain confidential. In addition, a written consent was signed from the patients if they were above 18 years and from the parents, if they were less than 18 years old prior to the use of the questionnaire.

3.7.2. Ethical clearance

The Research and Ethics Committee clearance at RAKMHSU was obtained for a prior study in 2011 and ethical clearance for the current study followed the same specifications but for a different research team and was obtained in February 2015. See appendix (2) for the details.

3.8. Data handling:

Questionnaires were collected and analyzed**.** The data were saved in a hard copy. Confidentiality of patients' details was maintained and the research team only had access to them.

4. Results:

In this chapter the results of data analyses will be presented. First, socioeconomic and demographic characteristics of the sample, followed by personal opinion on health status, then quality of life scores with mean comparison of QOL between 2011 and 2014 studies. The main sections of this chapter are ordered in a way to answer the research objectives and questions.

4.1. Socioeconomic and demographic characteristics of the sample:

The total number of eligible patients was 25. Twenty three of them had thalassemia major only while two were diagnosed with thalassemia major and sickle cell anemia as shown in Table 1. Fourteen participants were males with a mean age of 16.7 years and 11 were females with a mean age of 18.7 years. Half of the participants (52%) had received secondary education. Thalassemia was diagnosed in the first 3 years of life in the majority of the participants (72%) while 40% were diagnosed in their first year of life.

Seventy six percent (76%) of the participants were from families with consanguineous marriage while 24% had unrelated parents. The majority of participants (76%) had siblings with thalassemia while only 24% had no thalassemic siblings. Twenty two patients (88%) have family history of thalassemia.

Concerning the association between thalassemia and the family history of other blood disease, only 20% of participants had positive family history of blood disease other than thalassemia while the majority (80%) had negative family history. Only 6.7% had sickle cell anemia in addition to thalassemia major while others had thalassemia major only.

Majority of participants (72%) received blood transfusion at a rate of 12-24/year while fewer participants (20%) were on blood transfusion at a rate < 12/year. Only one patient received blood transfusion at a rate > 24/year and the same is found for “no blood transfusion”.

All participants needed to get chelation with Desferroxamine at a rate ≤5/month. Out of the 25 participants, 9 (36%) were splenectomized while 16 (64%) were not splenectomized.

Splenectomy was effective in reducing blood transfusion in only 12% of splenectomized patients while it did not reduce the rate of blood transfusion in 88% of splenectomized participants. The average serum ferritin of the patients was 1473.358 ng/mL.

Table 1: Socio-demographic characteristics of the participants and their quality of life domains

	Males	Females	Total: n (%)
Number (%)	14 (56)	11 (44)	25 (100)
Age: (Mean± SD)	16.7 ± 8.43	18.7 ± 8.49	
Age group {n (%)}: < 17 Years	7 (28)	5 (20)	12 (48)
17 – 24 Years	5 (20)	3 (12)	8 (32)
≥ 25 Years	2 (8)	3 (12)	5 (20)
Physical Functioning (PF)	74.3 ± 14.4	71.8 ± 16.2	
Role Physical (RP)	67.9 ± 31.7	59.1 ± 35.8	
Body Pain (BP)	64.5 ± 33.3	62.3 ± 22.3	
General Health (GH)	62.1 ± 12.7	69.9 ± 20.2	
Vitality (VT)	63.9 ± 19.03	63.2 ± 22.8	
Social Function (SF)	75.00 ± 27.95	78.6 ± 22.49	
Mental Health (MH)	64.9 ± 18.3	72.00 ± 15.39	
The physical composite scores (PCS)	6.14 ± 9.1	41.2 ± 11.13	
The mental composite scores (MCS)	46.4 ± 8.35	49.8 ± 8.8	
Hemoglobin (Hg)	8.5 ± 1.3	7.7 ± 1.78	
Education: Not educated	1	1	2 (8)
Primary	5	4	9 (36)
Secondary	8	5	13 (52)
Age at which thalassemia was diagnosed			
≤ 1 year	6	4	10 (40)
1 – 3 years	4	4	8 (32)
3-5 years	2	3	5 (20)
>5	2		2 (8)
Parents consanguinity: Yes / No	9 / 5	10 / 1	19 (76) / 6 (24)
Siblings status of thalassemia: Yes / No	13 / 1	6 / 5	19 (76) / 6 (24)
Family history of thalassemia: Yes / No	14 / 0	8 / 3	22 (88) / 3 (12)
Types of thalassemia			
Thalassemia major	13	10	23 (92)
Thalassemia major + Sickle cell anemia	1	1	2 (8)
Rate of blood transfusion/ year			
< 12	3	2	5 (20)
12-24	11	7	18 (76)
Times of chelation/ month: ≤5			25 (100)
Splenectomy: Yes / No	4 / 10	5 / 6	9 (36) / 16 (64)
Effectiveness of splenectomy in reducing blood transfusion:			
Yes / No	2 / 12	1 / 10	3 (12) / 22 (88)

- One male and one female did not go to school at all, whereas one female has higher education.
- Only one girl has not been given blood transfusion yearly, while one female was given more than 24 times.
- Other blood diseases can be inherited in families with Thalassemia as sickle cell anemia,G6PD deficiency anemia and hemophilia was found in 5 (20%) only.

4.2. Personal opinion on health status

4.2.1. Frequency of personal opinion on health in general:

Twenty eight percent (28%) of the patients thought that their general health was good, 32% thought it was very good and a further 16% said it was excellent (Table 2).

4.2.2. Proportion of patients in each category of personal opinion on health status compared to one year ago:

Compared to one year ago, 20% said that their health now was similar to one year ago while 56% thought it was much better than one year ago(Table 3).

Table 2: Frequency of personal opinion on health in general

Personal opinion	**n (%)**
Poor	1 (4)
Fair	5 (20)
Good	7 (28)
Very good	8 (32)
Excellent	4 (16)

Table 3: Proportion of patients in each category of personal opinion on health status compared to one year ago

Personal Opinion	**n (%)**
Somewhat worse now than one year ago	1 (4)
About the same	5 (20)
Somewhat better now than one year ago	5 (20)
Much better now than one year ago	14 (56)

4.3. Quality of life scores

Scores on quality of life ranging from 0 to 100 were obtained and categorized on an ordinal scale from weak to excellent. For example, a score between 80 and 100 indicates excellent of quality of life for each of the 8 indices. The distribution of the proportion of patients with an excellent score were as follows; 7 patients (28%) for physical functioning, 8 (32%) for Role-physical, 7 (28%) for bodily pains, 5 (20%) for general health, 5 (20%) for vitality, 7 (28%) for social functioning, 13 (52%) for role-emotional, and 3 (12%) for mental health (Table 4).

4.3.1. Designations of thalassemia patients according to Quality of life scores

Table 4: Designations of thalassemia patients according to Quality of life scores (Current study 2014)

Score	PF	RP	BP	GH	V	SF	RE	MH
Excellent	7(28%)	8(32%)	7(28%)	5(20%)	5(20%)	7(28%)	13(52%)	3(12%)
Very good	13(52%)	6(24%)	7(28%)	13(52%)	9(36%)	4(16%)	-	14(56%)
Good	5(20%)	5(20%)	6(24%)	4(16%)	8(32%)	4(16%)	-	6(24%)
Bad	-	4(16%)	3(12%)	3(12%)	3(12%)	1(4%)	-	2(8%)
Weak	-	2(8%)	2(8%)	-	-	-	4(16%)	-

4.3.2. Mean comparison of quality of life between 2011 and 2014 studies:

A comparison of quality of life between patients in the former study of 2011 and the current 2014 study showed significant difference in all the domains except physical functioning and vitality, with the highest mean difference of -54.0 observed in the role-physical (Table 5). The differences were significant for Role-Physical, Body Pain, General Health, Social functioning, Role-emotional, Mental Health and Mental composite summary (p value<0.05). In addition, there was a significant difference in mental composite summary while the physical composite summary showed insignificant difference (Table 5).

Table 5: Mean and SD of SF-36 domain and summary scores among thalassemia patients in former study (2011) compared with current study (2014)

	Former study 2011 (Mean ± SD)	Current study 2014 (Mean ± SD)	Difference	P-value
Physical Functioning	74.2 ± 13.28	73.20 ± 14.92	1,000	0,80
Role-Physical	10 ± 28	64.00 ± 33.14	-54,000	**< 0.01**
Body Pain	45.6 ± 16	63.52 ± 28.43	-17,920	**0.01**
General Health	46.92 ± 24.37	65.56 ± 16.55	-18,640	**< 0.01**
Vitality	53.2 ± 20.35	63.60 ± 20.34	-10,400	0,08
Social functioning	53 ± 20.19	76.56 ± 24.95	-23,56250	**0,002**
Role-emotional	34.66 ± 46.6	76.47 ± 43.72	-41,80659	**0,01**
Mental Health	48.32 ± 16.7	68.00 ± 17.13	-19,68000	**< 0.01**
Physical composite summary	39.49 ± 5.9	43.97 ± 10.15	-4,21800	0,08
Mental composite summary	37.22 ± 10.5	47.90 ± 8.56	-10,68400	**< 0.01**

4.3.3. Age group differences in the differnt apsects of the questionare.

Physical Functioning, Role-Physical, Vitality, Role-emotional ,Physical composite summary and Mental composite summary mean scores were highest in the age group < 17 years compared to the other age groups as shown in Table 6. However, Body Pain, General Health and Mental Health mean scores were highest in the age group ≥ 25 years compared with the other age groups. Social functioning was highest in age group ≥ 25 but equal in the age groups < 17 years and 17 – 24 years (Table-6).

Table 6: Age group differences in the differnt apsects of the questionare.

	< 17 Years Mean ± SD	**17 – 24 Years Mean ± SD**	**≥ 25 Years Mean ± SD**
Physical Functioning	77.92 ± 14.22	65.63 ± 14.75	74,00 ±14.75
Role-Physical	66.67 ± 26.83	59.38 ± 35.20	65.00 ± 48.73
Body Pain	67.75 ± 28.16	52.50 ± 29.74	71.00 ± 27.50
General Health	65.33 ± 17.42	63.38 ± 18.97	69.60 ± 12.20
Vitality	70.83 ± 19.29	51.25 ± 18.66	66.00 ±19.49
Social functioning	75.00 ± 29.88	75.00 ± 20.41	81.25 ± 23.94
Role-emotional	87.50 ± 35.36	60.00 ± 54.77	75.00 ± 50.00
Mental Health	70.00 ± 16.40	61.50 ± 18.88	73.60 ± 16.15
Physical composite summary	43.76 ± 11.23	42.93 ± 9.14	46.14 ± 10.79
Mental composite summary	49.12 ± 9.92	44.59 ± 6.82	50.00 ± 7.37

4.3.4. Effect of gender, splenectomy, blood transfusion and education on HRQOL

No statistically significant differences were found between males and females in HRQOL as shown in Table 7.

Table 7: Comparison between males and females in HRQOL score using the independent T-test

Test variable	Males Mean ± SD	Females Mean ± SD	Mean difference	P-value
Physical Functioning	74.3 ± 14.4	71.8 ± 16.2	2.5	0.69
Role-Physical	67.9 ± 31.9	59.1 ± 35.8	8.8	0.52
Body Pain	64.5 ± 33.3	62.3 ± 22.3	2.2	0.85
General Health	62.1 ± 12.7	69.9 ± 20.2	-7.7	0.25
Vitality	63.9 ± 19.0	63.2 ± 22.8	0.75	0.93
Social functioning	75 ± 28.0	78.6 ± 22.5	-3.6	0.79
Role-emotional	66.7 ± 50.0	87.5 ± 35.4	-20.8	0.34
Mental Health	64.9 ± 18.3	72.0 ± 15.4	-7.1	0.31
Physical composite summary	46.1 ± 9.1	41.2 ± 11.1	4.9	0.23
Mental composite summary	46.4 ± 8.4	49.8 ± 8.8	-3.4	0.33

HRQOL scores were also not significantly different between patients with splenectomy and those without (table 8).

Table 8: Comparison between patients with splenectomy and those without in HRQOL score using the independent T-test

Test variable	Splenectomy Mean ± SD	No splenectomy Mean ± SD	Mean difference	P-value
Physical Functioning	69.4 ± 17.8	75.3 ± 13.2	5.9	0.36
Role-Physical	55.6 ± 41.0	68.8 ± 28.1	13.2	0.35
Body Pain	55.7 ± 32.2	67.9 ± 26.2	12.3	0.31
General Health	71.0 ± 17.8	62.5 ± 15.5	-8.5	0.23
Vitality	59.4 ± 24.4	65.9 ± 18.1	6.5	0.46
Social functioning	80.0 ± 20.9	75.5 ± 27.4	-5.0	0.72
Role-emotional	66.7 ± 51.6	81.8 ± 40.5	15.2	0.51
Mental Health	69.3 ± 21.9	67.3 ± 14.5	-2.1	0.78
Physical composite summary	43.2 ± 10.5	44.4 ± 10.3	1.1	0.80
MCS Mental composite summary	48.7 ± 9.0	47.5 ± 8.6	-1.2	0.75

Patients with less blood transfusion (<12/year) had better quality of life in 7 out of the eight SF-36 domains in comparison with patients with more blood transfusion. However, the only difference that was significant statistically is general health (table 9).

Table 9: ANOVA (KW test) table showing mean differences between different rates of blood transfusion on HRQOL

Test variable	Rate of transfusion				P-value
	0**	1	2	3**	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Physical Functioning	90.0	63 ± 17.5	76.1 ± 12.9	55.0	0.12
Role-Physical	75.0	65.0 ± 33.5	61.1 ± 34.5	100.0	0.72
Body Pain	100.0	49.4 ± 32.7	66.1 ± 27.2	52.0	0.38
General Health	90.0	49.8 ± 13.8	68.8 ± 14.9	62.0	0.05
Vitality	80.0	53.0 ± 23.6	66.4 ± 19.6	50.0	0.45
Social functioning	100.0	75.0 ± 35.4	75.0 ± 22.4	-	0.66
Role-emotional	100.0	100.0 ± 0.0	66.7 ± 49.2	100.0	0.60
Mental Health	92.0	64.0 ± 14.1	67.1 ± 17.9	80.0	0.45
Physical composite summary	52.9	39.4 ± 11.1	44.9 ± 10.2	40.0	0.58
Mental composite summary	59.7	47.5 ± 8.0	47.1 ± 8.8	53.4	0.50

**Only one patient in this group

As shown in Table 10, patients with higher educational level (secondary school or more) had better quality of life in comparison with those who had lower educational level. This occurs in all the domains except in vitality, where the quality of life was higher in primary school holder than the higher degrees. However, there was insignificant difference between the quality of life and educational level in any of the domain scores or the summary scores (all *p* values are >0.05).

Table 10: ANOVA table showing mean differences between different levels of education on HRQOL

Test variable	Level of Education				P-value
	Not in school	Primary	Secondary	More**	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Physical Functioning	72.5±10.6	73.9±17.3	71.9 ± 14.9	85.0	0.88
Role-Physical	75.0±35.4	55.6±34.9	65.4 ± 33.1	100.0	0.60
Body Pain	51.5±0.7	65.3±33.8	64.2 ± 28.7	62.0	0.95
General Health	57.5±10.6	67.7±17.2	63.5 ± 16.5	90.0	0.41
Vitality	67.5±3.5	71.7±21.7	56.2 ± 19.5	80.0	0.29
Social functioning	62.5±53.0	85.0±22.4	75.0 ± 23.1	75.0	0.78
Role-emotional	100.0	75.0±46.3	71.4 ± 48.8	100.0	0.90
Mental Health	78.0±2.8	60.9±23.6	71.1 ± 12.1	72.0	0.46
Physical composite summary	41.7±2.3	42.5±12.5	44.7 ± 9.6	52.0	0.83
Mental composite summary	51.9±10.0	46.8±12.0	47.7 ± 6.1	52.0	0.85

**Only one patient in this group

5. Discussion:

The aim of this study was to study the impact of the diseases on the physical and psychological activity of thalassemia patients and to study the different clinical and therapeutic factors such as rate of blood transfusion and chelation therapy on physical and psychological well-being of those patients.

5.1. Results of QOL:

The highest domain score in the current study was in physical functioning (73.20 ± 14.92) which was nearly the same in the former study (74.2± 13.28). Dahlui *et al*, (2009) (2012) and Safizadeh *et al*, explained the high physical functioning score by saying that these patients had low expectations of physical performance because they have been living with the disease for long time without the burden of work (45,91).

The lowest domain scores in our current study were in Role-Physical (64.00 ± 33.14), Body Pain (63.52 ± 28.43), Vitality (63.60 ± 20.34) and General Health (65.56 ± 16.55). In the former study, the lowest domain score was in Role-Physical (10 ± 28). Safizadeh *et al* (2012) found lowest scores in the general health and role-physical domains (45).

In the current study, Physical Functioning, Role-Physical, Vitality, Role- emotional, Physical composite summary and Mental composite summary were the best in age group < 17 years followed by age group ≥ 25 years followed by age group 17 – 24 years. However, Body Pain, General Health and Mental Health were highest in age group ≥ 25 years followed by < 17 years followed by 17 – 24 years. Social functioning was highest in age group ≥ 25 while it was equal in groups < 17 years and 17 – 24 years. However, in the former study, the quality of life was better in the age group (17-24 years) compared to elder and younger age groups.

The female participants had higher domain scores in GH, SF, MH and RE while RP score was higher in males than in females. However, the male participants had slightly higher domain scores in PF, BP and VT.

The differences in the domains were insignificant as shown by *p* values >0.05. Safizadeh *et al* (2012) found that female participants had a higher score in all domains except for BP, when compared to the male participants(45) . Males have many stresses and challenges in their life as sponsoring their families and job stresses.

Patients with higher educational level (secondary school or more) in this study had better quality of life in comparison with those who had lower educational level. This occurs in all the domains except in vitality, where the quality of life was higher in primary school holder than the higher degrees. However, there was insignificant difference between the quality of life and educational level in any of the domain scores or the summary scores (all *p* values are >0.05). The Ministry Of Health in the UAE has been providing massive health education campaigns for thalassemic patients with different education levels. Health education helps to increase awareness about the disease which improves the quality of life. In addition, health educators explain to the patients how thalassemia is inherited through the family which decreases the occurrence of new cases (92). One of the main tests included in the premarital examination in the UAE is a test for thalassemia. This examination is mandatory before marriage; premarital examination includes counseling the married couple about thalassemia.

Furthermore, patients with less blood transfusion (<12/year) had better quality of life in 7 out of the eight SF-36 domains in comparison with patients with more blood transfusion. However, the only difference that was significant statistically is general health. There

was only one patient receiving blood transfusion ≥24 times/year and one patient without blood transfusion that was not enough to study the effect of the rate of blood transfusion on the health related quality of life. It was found that patients who need more transfusion are those who had more severe disease with more complications in addition to the burden and complications of blood transfusion itself (93); this can explain the difference in the quality of life with different rates of blood transfusions.

In the previous study on the same population, more than (50%) were receiving blood transfusion ≥24 times/year while fewer patients (24%) were receiving blood transfusion <12 times per year while in our study, the Majority of participants (76%) received blood transfusion at a rate of 12-24/year while fewer participants (20%) were on blood transfusion at a rate < 12/year. Only a small proportion of the participants (4%) received blood transfusion at a rate > 24/year while a similar proportion (4%) did not receive blood transfusion.

Oral iron chelation became available to all patients who became more compliant with regular administration of their iron chelation; this helped to improve HRQOL of our patients more than those of the previous study.

The average serum ferritin of the patients was 1473.358 ng/mL, which is a little bit higher than the average serum ferritin level in the first study.

This can be explained by knowing that serum ferritin is not the most reliable test as it is an acute phase protein that does not exactly reflect the status of hemochromatosis. A more reliable test is MRI showing iron deposition in different body organs (94) which was not available and is not done routinely for those patients. Besides MRI cannot be used for children under 10 years because they cannot react to MRI machine. The other

point to explain the serum ferritin difference in spite of better result with regards to QOL aspects is that it was difficult to recruit exactly the same patients in the study done in 2011, yet it was possible to recruit the same number; 25 patients. This was because one of the patients in the first study died and other participant left UAE to his mother country, Jordan.

If we compare these results to the results of the study done in the same center three years earlier, we will find that in the previous study (53%) were in general, in a good health. Compared to one year ago, in the former study, (48%) said that their health now is the same as compared to previous year, while (36%) said it is now much better than one year ago which may reflect the improved patients perception about their health with the progress of treatment policy followed in Saqr Hospital.

5.2. Strengths and Limitation of methodology:

The following sections will provide a discussion of the methodological weaknesses and strengths in the research done with an account on validity and reliability of the research.

5.2.1. Strengths of SF-36:

It can measure the health status in different groups and different diseases and even give us the ability to compare between them. In addition, it can be used for follow up the patients during their chronic diseases and see the impact of the disease, its complications and management on the quality of life. Moreover, the SF-36 takes short time to administer with good to excellent reliability and validity and it can be used to produce more detailed questionnaires for more precise and more specific measures. It

can be said that this questionnaire evaluates both the physical and psychological components of quality of life of our patients. Lastly, the translation of the questionnaire and the interviews were carried by researchers talking the same language of the patients; Arabic. This helped clearly to reduce the misunderstanding or ambiguity of responses.

5.2.2. Limitations of SF-36:

First of all, without a control group it is not possible to know whether changes in self-rated functioning and well-being would have occurred in individuals without the same condition. In addition, the SF-36 is a generic measure and may not adequately capture all areas of functioning and well-being that are relevant to people with thalassemia; optimally, a disease-specific instrument should be used alongside it. Concerning analysis, the correlational design of the analyses leaves the potential for other unmeasured factors to contribute to, or confound, the observed relationships. Moreover, because the measurement of quality of life is new and without the presence of specific guidelines, there are some difficulties in the interpretation of the results. Finally, SF-36 reflects the patients' perception to their health, which might not reflect the real clinical situation. In our study, the small sample size was not enough to give in depth as if it was a large sample size.

5.2.3. Reliability

Reliability and validity are two concepts that are important for defining and measuring bias and distortion. Reliability is the degree to which a measurement technique can be depended upon to secure consistent results upon repeated application making it one of the most important elements of test quality. The minimum standard of reliability

which is recommended for measures used in group comparisons is 0.70(95). In previous published studies, reliability for the same test frequently exceeded 0.80 in most of them (96).

To reduce systematic variations all interviews were conducted by the same researcher. We tried to reduce Observer variations by asking the same questions to all respondents, and by using a standard questionnaire SF-36. However, questions often needed to be rephrased or central concepts explained, so that the respondent understood the meaning.

5.2.4. Validity

Validity refers to the degree in which our test or other measuring device is truly measuring what we intended it to measure or, in other terms, the accuracy of an assessment. It is the most important measure of the quality of a test as it is concerned with the meaning and interpretations of scores. The SF-36 is used in different applications, so its validity was proven.

The two aspects of validity; internal and external validity, were considered here.

The internal validity which shows how accurately the data and the conclusions drawn from the data represent what really happened was assured by translating the SF-36 questionnaire into Arabic to fit the patients who speak Arabic. In addition the interviewer, as mentioned before, speaks the same language. Moreover, the same questionnaire with the same context was used for the study group in 2011. However, there was unavoidable **bias** in the data gathering represented as follows. First, the selection bias; as It was intended to recruit all attendants to thalassemia clinic (60

patients registered), but we could recruit only 25 patients, this cannot exclude selection bias. Second, the information bias where selection was not randomized and participant individuals differ in their ability to express their feelings, this might cause information bias. Confounding bias was inevitable also as the answers of the participants might be affected by other confounding factors as psychosocial status and mood condition, this could cause confounding bias.

The external validity shows how accurately the data and the conclusions from the data can be generalized to the larger population. Surely, the work done in our study can be repeated in thalassemic patients throughout UAE and abroad as explained in the following account.

Thalassemia patients are followed up in different thalassemia centers all over the UAE. In addition the ministry of health (MOH) in the UAE provides patients with oral iron chelation therapy for all patients in all thalassemia centers following the international standards. Moreover, the Ministry Of Health implements continuous health education programs and premarital examination program all over the UAE. So, our study can be replicated in different places in the UAE. The SF-36 is used in different applications, so various types of validity are relevant as content, concurrent, construct, criterion, and predictive validity. (97)

However, the small sample size makes it difficult to represent the total population of the United Arab Emirates.

6. Conclusion

Quality of life in thalassemic patients was higher in the second study done in 2014 than in the first study done in 2011. The domains mostly affected were the role-physical and role-emotional. Thalassemia disease limits the physical and emotional ability of the patients, this change can be explained by several factors, first of all the availability of the oral iron chelating medicine, so all patients became more compliant with their iron chelating therapy. In addition, health education programs increased the awareness about thalassemia among patients and their families and the patients became more involved in social networks.

7. Recommendations and implications

This study has implication for both practice and future areas of research. We recommend that all patients with thalassemia should regularly undergo assessment of the quality of life. There is a knowledge gap in this area of research which requires repeated and continuous research to explore more about HRQOL in thalassemia patients, thus we can plan intervention programs that focus on the affected domains. In addition, intervention programs should include support of the patients and their families especially the psychological support to avoid mental disorders. (98-100)

Lastly, we recommend repeating our study every other year and on a wider scale recruiting more thalassemia patients. In thalassemia center in Dubai (http://www.thalassemia-dubai.com/default.aspx), there are about 850 thalassemia patients registered for treatment and follow up. This is a good place to recruit much more patients.

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Appendixes

Appendix 1: Ethical approval (Research and ethics committee RAKMHSU)

RAK Medical & Health Sciences University
(Member of RAK Human Development Foundation)

( )

INTERNAL COMMUNICATION NOTE

24.01.2012

From	To
Dr. R.S.P. Rao Chairperson Research and Ethics committee RAKMHSU	Dr.Ibrahim Y Hachim Lecturer Dept of Pathology RAKCOMS

Dear Dr. Ibrahim

Sub:- -Approval of the research proposal –reg

The research proposal entitled "**Prevalence, Types and Quality of life of Thalassemia patients in R.A.K** "has been approved by the Research and Ethics Committee.

Yours sincerely.,

R.S. Thaneendrao

Dr.R.S.P.Rao,
Chairperson
Research & Ethics Committee
RAKMHSU

Copy to
1. Dean RAKCOMS
2. Chairperson , Dept of Pathology, RAKCOMS

Appendix 2: Consent regulations in the Health Authorities in the UAE and the researchers comments on its clauses**.**

CONSENT FORM ABOVE 18 YEARS OF AGE:

Concerning the process of obtaining informed consent the CIOMS guidelines emphasize that the sponsors and the investigators have the obligation to:

- refrain from unjustified deception, undue influence, or intimidation.

- seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;

- As a general rule, obtain from each prospective subject a signed form as evidence of informed consent.

– Investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee.

The normal procedure today is that consent is sought after the trial person has been given an oral orientation and received written information about the project.

ICH GCP E6; section 4.8-4.8.14

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

The standard Forward-Backward procedure was applied to translate the SF-36 questionnaire from English to Arabic by a bilingual individual with some cultural adaptation, this is to make it easy and understandable for participants.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research.

b) The purpose of the trial.

In the general information part of the consent form, we explained everything about the study and gave enough time and chance for any question to be answered, in addition, we explain the

purpose of the study.

Part of the consent form states:

As part of the research we are asking thalassemic patients to fill in questionnaires so that we can learn more about the physical and mental impact of thalassemia and its management on the quality of life in more detail.

If you agree, you will be asked to complete a questionnaire; the questionnaire will be explained to you by the researcher who will answer any questions you have about how to fill it in.

The questionnaire has been carefully developed; it contains questions about a range of physical symptoms and activities, your emotional wellbeing and other aspects of your everyday life. There are no 'right' or 'wrong' answers – we simply want to find out your personal perception of your physical and mental activities.

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

We explained to participants that there is limited research examining the factors associated with HRQOL in children and adolescents with thalassemia, information from this study will help us for better understanding of these factors, and as a result to develop more suitable clinical, counseling, and social support programs to enhance treatment outcomes, especially in terms of HRQOL of these patients, in addition, at-risk groups of children and adolescents could be identified as candidates for proactive care assistance. Given the insufficient research in this area, this study aims to focus on patient perspective.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

It is clear in the consent form that there is no money incentive for participating in the study as shown in the next statement in the consent form:

□ *also understand that I will not receive money for participation in this study.*

l) The anticipated expenses, if any, to the subject for participating in the trial.

The consent form states:

□ *I understand that I will not be charged additional expenses for my participation in this study.*

M) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Part of the consent form states:

 I understand that I am free to withdraw my consent to participate in this study, i may withdraw consent at any time and this decision will not adversely affect my care.

N) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

O) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

The names of participants will be omitted from the questionnaire papers.

This is shown in our consent form which states:

 All data obtained from this research will remain confidential and will only be used for research purposes, the confidentiality of this document and all records from this research will be protected to the extent provided by law. Neither my name nor any other family member's name will be used in any report.

UNDER 18 YEARS OF AGE :

Written consent was required from patients if they were above 18 years and from the patient's parents, if they were less than 18 years old prior to the use of the questionnaire.

ICH GCP E6; section 4.8-4.8.14

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

This was done as an introductory general information part of the informed consent form.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

Part of our informed consent form says:

 My signature below indicates that I have read all the above information, received answers

concerning areas I do not understand, and I am willingly giving my consent for my child to participate in this program.

□ *On signing this form, I will receive a copy.*

In the information part of our questionnaire, we explain in details about the questions and will give chance to any question or explanation from the participant.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

In our study there is foreseeable risk.

c) The negative impact on the subject's well-being is minimized and low.

There is minimal effect on our participants.

d) The trial is not prohibited by law.

It is a questionnaire about life style of thalassemia patients which is not prohibited by law in UAE.

e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

In our study 4.8.7,4.8.8, 4.8.14 are fulfilled as shown in the consent form for participants under 18years age.

The DoH states that

"For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons."

Thalassemia is a hereditary genetic disease starting from child birth till the end of life. So we cannot ignore the group of participants under 18 years as they are one of the two categories of participants.

"When a subject deemed legally incompetent, such as a minor child, is able to give assent to

decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative."

In our questionnaire, we took assent of participants below 18 years age.

Confidentiality:

When data are used for research purposes, the participant's names are omitted to keep privacy.

The Helsinki declaration paragraph 21 states that researchers have to protect the integrity of the trial person: Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Confidential personal information should be treated in a way to avoid breaking confidentiality.

The 1991 international guidelines for ethical review of epidemiological studies states that research may involve collecting and storing data relating to individuals and groups, and such data, if disclosed to third parties, may cause harm or distress. Consequently, investigators should make arrangements for protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, anonymizing data or by other means.

A part of the informed consent form says*:*

 All data obtained from this research will remain confidential and will only be used for research purposes. The confidentiality of this document and all records from this research will be protected to the extent provided by law. Neither my child's name nor any other family member's name will be used in any report.

Appendix 3: Comprehensive results of the study

Variable	Males	Females	Total (%)
N	14	11	25
Education			
Not at school	1	1	2
Primary	5	4	9
Secondary	8	5	13
More	-	1	1
Age at which thalassemia was diagnosed			
< 1 year	6	4	10
1 – 3 years	4	4	8
4 – 5 years	2	3	5
> 5 years	2		2
Consanguineous marriage of parents			
No	5	1	6
Yes	9	10	19
Siblings status of thalassemia			
No	1	5	6
Yes	13	6	19
Family history of thalassemia			
No		3	3
Yes	14	8	22
Family history of any other blood disease Like(sickle cell anemia,G6PD deficiency anemia, hemophilia)			
No	11	9	20

Yes	3	2	5
Rate of blood transfusion/year			
0		1	1
<12	3	2	5
12-24	11	7	18
>24		1	1
Splenectomy(removal of the spleen)			
No	10	6	16
Yes	4	5	9
Effectiveness of splenectomy in reducing blood transfusion			
No	12	10	22
Yes	2	1	3
In general, would you say your health is			
Poor	1		1
Fair	3	2	5
Good	3	4	7
Very good	5	3	8
Excellent	2	2	4
Compared to one year ago, how would you rate your health in general now			
Somewhat worse now than one year ago	1		1
About the same	3	2	5
Somewhat better now than one year ago	2	3	5
Much better now than one year ago	8	6	14
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?			
No, Not Limited At All	2	2	4

Yes, Limited A Little	10	6	16
Yes, Limited A Lot	2	3	5
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?			
No, Not Limited At All	9	6	15
Yes, Limited A Little	5	4	9
Yes, Limited A Lot		1	1
Lifting or carrying groceries?			
No, Not Limited At All	6	7	13
Yes, Limited A Little	7	4	11
Yes, Limited A Lot	1		1
Climbing several flights of stairs?			
No, Not Limited At All	3	4	7
Yes, Limited A Little	7	4	11
Yes, Limited A Lot	4	3	7
Climbing one flight of stairs?			
No, Not Limited At All	12	10	22
Yes, Limited A Little	2	1	3
Bending, kneeing or stooping?			
No, Not Limited At All	9	5	14
Yes, Limited A Little	3	5	8
Yes, Limited A Lot	2	1	3
Walking more than a mile?			
No, Not Limited At All	4	2	6
Yes, Limited A Little	6	4	10
Yes, Limited A Lot	4	5	9
Walking several blocks?			

No, Not Limited At All	9	6	15
Yes, Limited A Little	4	4	8
Yes, Limited A Lot	1	1	2
Walking one block?			
No, Not Limited At All	13	10	23
Yes, Limited A Little	1	1	2
Bathing or dressing yourself?			
No, Not Limited At All	14	10	24
Yes, Limited A Little		1	1
Cut down on the amount of time you spent on work/school or other activities?			
No	9	7	16
Yes	5	4	9
Accomplished less than you would like?			
No	9	6	15
Yes	5	5	10
Were limited in the kind of work or other activities?			
No	11	9	20
Yes	3	2	5
Had difficulty performing the work, school or other activities (for example it took extra effort)?			
No	9	5	14
Yes	5	6	11
Cut down on the amount of time you spent on work/school or other activities?			
No	9	9	18

Yes	5	2	7
Accomplished less than you would like?			
No	10	8	18
Yes	4	3	7
Didn't do work or other activities as carefully as usual?			
No	9	8	
Yes	5	3	
During **the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?			
Not at all	5	3	8
Slightly	3	1	4
Moderately	6	5	11
Extremely		2	2
How much bodily pain have you had during the past 4 weeks?			
None	6	2	8
Mild	3	6	9
Moderate	1	1	2
Severe	3	2	5
Very severe	1		1
During **the past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?			
Not at all	6	1	7
Slightly	3	3	6
Moderately	3	6	9

Quite a bit	1		1
Extremely	1	1	2
Did you feel full of pep?			
Most of the time		2	2
A good bit of the time	4	3	7
Some of the time	2	1	3
A little of the time	6	3	9
None of the time	2	2	4
Have you been a very nervous person?			
All of the time	1	1	2
Most of the time	6	3	9
A good bit of the time	3	5	8
Some of the time		2	2
A little of the time	3		3
None of the time	1		1
Have you felt so down in the dumps that nothing could cheer you up?			
All of the time	3	4	7
Most of the time	3	4	7
A good bit of the time	4	1	5
A little of the time	3	1	4
None of the time	1	1	2
Have you felt calm and peaceful?			
All of the time		1	1
Most of the time	1		1
A good bit of the time	3	1	4
Some of the time	3	3	6

A little of the time	4	3	7
None of the time	3	3	6
Did you have a lot of energy?			
All of the time	1		1
Most of the time	2	2	4
A good bit of the time	2	5	7
Some of the time		1	1
A little of the time	6	1	7
None of the time	3	2	5
Have you felt downhearted and blue?			
All of the time	4	4	8
Most of the time	7	4	11
A good bit of the time	2	2	4
Some of the time		1	1
None of the time	1		1
Do you feel worn out?			
All of the time	1	3	4
Most of the time	5	4	9
A good bit of the time	4	3	7
Some of the time	1	1	2
A little of the time	1		1
None of the time	2		2
Have you been a happy person			
All of the time	1	1	2
Most of the time	3	1	4
A good bit of the time	1		1

Some of the time	1	1	2
A little of the time	5	4	9
None of the time	3	4	7
Did you feel tired?			
All of the time	4	1	5
Most of the time	3	4	7
A good bit of the time	3	3	6
Some of the time	2	2	4
A little of the time	2	1	3
During **the past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?			
All of the time	4	4	8
Most of the time	6	4	10
Some of the time	3	2	5
A little of the time		1	1
None of the time	1		1
seem to get sick a little easier than other people?			
Definitely true	3	3	6
Mostly true	2	4	6
Don’t know	5		5
Mostly false	4	2	6
Definitely false		2	2
I am as healthy as anybody I know?			
Definitely true	1		1
Don’t know	2		2

Mostly false	8	7	15
Definitely false	3	4	7
I expect my health to get worse?			
Definitely true	1	2	3
Mostly true	1	3	4
Don’t know	7	5	12
Mostly false	3		3
Definitely false	2	1	3
My health is excellent?			
Mostly true		1	1
Don’t know	3	1	4
Mostly false	8	5	13
Definitely false	3	4	7

Appendix 4: Patient and clinical data sheet

Name					
Age					
Educational Level	Not at school	Primary school	Secondary School	More	
Sex			Male	Female	
Age at which Thalassemia was diagnosed	< 1 year	1 -3 years	3-5 years	> 5 years	
Consanguineous marriage of the parents			Yes	No	
Siblings status of thalassemia			Yes	No	
Family history of thalassemia			Yes	No	
Family history of any other blood diseases like (sickle cell anemia , G6PD deficiency anemia, hemophilia)			Yes	No	
Types of Thalassaemia					
Rate of Blood transfusion /year		<12	12 – 24	>24	
Hemoglobin level at the time of transfusion					

Number of times patient should get chelation (desferroxamine)/month	<5	6 – 10	11-15
Splenectomy (removal of the spleen)	Yes		No
Effectiveness of splenectomy in reducing blood transfusion	Yes		No
Laboratory Investigations: **Pre transfusion Hemoglobin level:** **Serum Ferritin:** **MCV** **Hemoglobin Electrophoresis:** **Rate of blood transfusion:**			

Appendix 5: SF-36 questionnaire

In general, would you say your health?

Excellent	Very good	Good	Fair	Poor
1	2	3	4	5

Compared to one year, how would you rate your health in general now? :

Much better now than one year ago	Somewhat better now than one year ago	About the same	Somewhat worse now than one year ago	Much worse now than one year ago.
1	2	3	4	5

3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	1. Yes, Limited A Lot	2. Yes, Limited A Little	3. No, Not Limited At All
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?			
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?			
c) Lifting or carrying groceries?			
d) Climbing **several flights** of stairs?			
e) Climbing **one** flight of stairs?			
f) Bending, kneeing or stooping?			
g) Walking **more than a mile**?			
h) Walking **several** blocks?			
i) Walking **one** block?			
j) Bathing or dressing yourself?			

4-During the **past 4 weeks**, have you had any of the following problems with your work, school, or other regular activities *as a result of your physical health*

	□ 1. yes	□ 2. No

a) Cut down on the **amount of time** you spent on work/school or other activities?		
b) **Accomplished less** than you would like?		
c) Were limited in the **kind** of work or other activities?		
d) Had **difficulty** performing the work, school or other activities (for example it took extra effort)?		

5-During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	□ 1. yes	□ 2. No
a) Cut down on the **amount of time** you spent on work/school or other activities?		
b) **Accomplished less** than you would like?		
d) Didn't do work or other activities as **carefully** as usual?		

6- During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

7.How much **bodily pain** have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very sever
1	2	3	4	5	6

8- During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

9- These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week**.

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?						
b) Have you been a very nervous person?						
c) Have you felt so down in the dumps that nothing could cheer you up?						
d) Have you felt calm and peaceful?						
e) Did you have a lot of energy?						
f) Have you felt downhearted and blue?						
g) Do you feel worn out?						
h) Have you been a happy person?						
i) Did you feel tired?						

10- During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time.	Some of the time	A little of the time.	None of the time.
1	2	3	4	5

11. How TRUE or FALSE is each of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?					
b) I am as healthy as anybody I know?					
c) I expect my health to get worse?					
d) My health is excellent?					

Appendix 6: Arabic version of the questionnaire

Name الاسم					
Age العمر					
Educational Level المستوى التعليمي	Not at school ليس في المدرسة	Primary school المرحلة الابتدائية	Secondary School المرحلة الثانوية	More اكثر	
Sex الجنس			Male ذكر	Female انثى	
Age at which Thalassemia was diagnosed العمر الذي تم فيه تشخيص الثالاسيميا	< 1 year اقل من عام	1 -3 years من سنة- 3 سنوات	3-5 years من ثلاث سنوات- خمس سنوات	> 5 years اكثر من خمسة سنوات	
Consanguineous marriage of the parents هل الوالدين من الاقارب			Yes نعم	No لا	
Siblings status of thalassemia هل هناك اشقاء مصابين بالثالاسيميا			Yes نعم	No لا	
Family history of thalassemia هل هناك تاريخ عائلي للاصابة بالثالاسيميا			Yes نعم	No لا	
Family history of any other blood diseases like (sickle cell anemia , G6PD deficiency anemia, hemophilia) هل هناك تاريخ عائلي للاصابة باحد انواع امراض الدم (مثل فقر الدم المنجلي ، مرض نقص الخميرة جي سكس بي دي (انيميا الفول) ، الهيموفيليا).			Yes نعم	No لا	
Types of Thalassaemia نوع الثالاسيميا					
Rate of Blood transfusion /year كمية نقل الدم في السنة	<12 اقل من 12	12 – 24 24--من 12	>24 اقل من 24		
Hemoglobin level at the time of transfusion نسبة الهيموغلوبين عند التشخيص					
Number of times patient should get chelation (desferroxamine)/month عدد المرات خلال الشهر التي يحتاج فيها المريض الحصول على العلاج الطارد للحديد ديسفيروكسامين) الديسفيرال.	<5	6 – 10	11-15		
Spleenectomy (removal of the spleen) هل تمت ازالة الطحال			Yes نعم	No لا	
Effectiveness of spleenectomy in reducing blood transfusion هل ادت عملية ازلة الطحال الة تقليل عدد مرات نقل الدم ؟			Yes نعم	No لا	
Laboratory Investigations:					

1- In general, would you say your health is : 1- ما هو تقييمك لصحتك بصورة عامة :

Excellent ممتازة	Very good جيدة جدا	Good جيدة	Fair مقبعة	Poor سيئة
1	2	3	4	5

2- Compared to one year, how would you rate your health in general now? :
2-كيف تقيم صحتك الان مقارنة بالعام الفائت

Much better now than one year ago افضل بكثير من العام الفائت	Somewhat better now than one year ago افضل قليلا من العام الفائت	About the same مساوية للعام الفائت	Somewhat worse now than one year ago نوعا ما اسوأ بقليل من العام الفائت	Much worse now than one year ago. اسوأ بكثير من العام الفائت
1	2	3	4	5

3- The following items are about activities you might do during a typical day. **Does your health now limit you in these activities? If so, how much?**
3-الفقرات التالية تتضمن الفعاليات التي من الممكن ان تقوم بها خلال اليوم العادي . هل ان صحتك الان تمنعك من القيام بهذه الفعاليات ؟ اذا كان الجواب نعم فالى اي مدى ؟

Activities	1. Yes, Limited A Lot نعم لها تاثير كبير	2. Yes, Limited A Little نعم ، لها تاثير قليل	3. No, Not Limited At All لا ، ليس لها تاثير
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports? الفعاليات الشاقة مثل الركض ورفع الاجسام الثقيلة والمشاركة بالرياضات العنيفة			
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? الفعاليات المتوسطة مثل تحريك منضدة والالعاب الخفيفة وتحريك بعض الادوات المنزلية			
c) Lifting or carrying groceries? حمل المشتروات من السوق او البقالة			
d) Climbing **several flights** of stairs? صعود عدة درجات من السلم			
e) Climbing **one flight** of stairs? صعود درجة واحدة من السلم			
f) Bending, kneeling or stooping? الانحناء والجلوس على الركبة			
g) Walking **more than a mile**? المشي لاكثر من ميل			
h) Walking **several blocks**? المشي لاكثر من زقاق			
i) Walking **one block**? المشي لزقاق واحد			
j) Bathing or dressing yourself? الاستحمام وتغيير الملابس بدون مساعدة			

4- During the **past 4 weeks**, have you had any of the following problems with your work, school, or other regular activities *as a result of your physical health*?

4- خلال الاسابيع الاربعة الماضية ، هل عانيت من اي من المشاكل التالية خلال العمل او المدرسة او اي من الفعاليات المنتظمة الاخرى نتيجة لحالتك البدنية :

	☐ 1. yes	☐ 2. No
a) Cut down on the **amount of time** you spent on work/school or other activities? قمت بتقليل الوقت الذي تقضيه في العمل او المدرسة او اي من الفعاليات الاخرى		
b) **Accomplished less** than you would like? قمت بانجاز اعمال اقل مما تريد		
c) Were limited in the **kind** of work or other activities? هنالك تقييد بانواع الاعمال او الفعاليات التي تقوم بها		

d) Had **difficulty** performing the work,school or other activities (for example it took extra effort)? هل تواجه صعوبة في القيام بالعمل او في المدرسة او اي من الفعاليات الاخرى (مثلا تحتاج الى جهد اكثر للقيام بالعمل)		

5- During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

5- خلال الاسابيع الاربعة الماضية ، هل عانيت من اي من المشاكل التالية خلال العمل او المدرسة او اي من الفعاليات المنتظمة الاخرى نتيجة لحالتك النفسية (مثل الشعور بالاكتئاب او العصبية) :

	☐ 1. yes	☐ 2. No
a) Cut down on the **amount of time** you spent on work/school or other activities? قمت بتقليل الوقت الذي تقضيه في العمل او المدرسة او اي من الفعاليات الاخرى		
b) **Accomplished less** than you would like? قمت بانجاز اعمال اقل مما تريد		
d) Didn't do work or other activities as **carefully** as usual? لا تستطيع القيام بالعمل والفعاليات الاخرى بالدقة المطلوبة كالمعتاد؟		

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

6- خلال الاسابيع الاربعة الماضية الى اي مدى اثرت حالتك البدنية او النفسية على علاقاتك الاجتماعية مع العائلة او الاصدقاء او الجيران او اي من المجاميع الاخرى ؟

Not at all كلا ابدا	Slightly قليلا	Moderately بصورة متوسطة	Quite a bit بنسبة لا بأس بها(اكثر من المتوسط)	Extremely بصورة كبيرة جدا
1	2	3	4	5

7.How much **bodily pain** have you had during the **past 4 weeks**?

7- هل عانيت من اوجاع جسمانية خلال الاسابيع الاربعة المنصرمة ؟

None ابدا لم اعاني اي الام	Very mild بصورة خفيفة جدا	Mild بصورة خفيفة	Moderate بصورة متوسطة	Severe بصورة حادة	Very sever بصورة حادة جدا
1	2	3	4	5	6

8- During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

8- خلال الاسابيع الاربعة الماضية الى اي مدى ادت الاوجاع الجسمانية الى التأثير على اعمالك الطبيعية (داخل وخارج المنزل)

Not at all كلا ابدا	Slightly قليلا	Moderately بصورة متوسطة	Quite a bit بنسبة لا بأس بها(اكثر من المتوسط)	Extremely بصورة كبيرة جدا
1	2	3	4	5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week**.

9- هذه المجموعة من الاسئلة عن شعورك وكيف جرت الامور معك خلال الاسابيع الاربعة المنصرمة . لكل سؤال الرجاء اعطي اجابة واحدة والتي هي اقرب الى ما كنت تشعر به. كم من الوقت خلال الاسابيع الاربعة الماضية:

	1. All of the time دم طول الوقت	2. Most of the time اغلب الاحيان	3. A good bit of the time بنسبة جيدة من الوقت	4. Some of the time احيانا	5. A little of the time احيانا قليلة	6. None of the time ابدا لم اشعر
a) Did you feel full of pep? هل تشعر انك مفعم بالحيوية						
b) Have you been a very nervous person? هل كنت عصبي جدا						
c) Have you felt so down in the dumps that nothing could cheer you up? هل شعرت انه ليس هناك اي شي يبهجك او يفرحك حتى مع النكات او المقالب المضحكة						
d) Have you felt calm and peaceful? هل شعرت بانك هادئ و مسالم						
e) Did you have a lot of energy? هل شعرت انك مليء بالطاقة						
f) Have you felt downhearted and blue? هل شعرت بانك مكتئب						
g) Do you feel worn out? هل شعرت بانك متعب						
h) Have you been a happy person? هل انت انسان سعيد						
i) Did you feel tired? هل شعرت بالتعب						

10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

10- خلال الاسابيع الاربعة المنصرمة كم من الاوقات اعاقت صحتك الجسمانية(البدنية) او حالتك النفسية القيام بالفعاليات الاجتماعية (مثل زيارة الاصدقاء او الاقارب) ؟

All of the time طوال الوقت	Most of the time. اغلب الاحيان	Some of the time احيانا	A little of the time. احيانا قليلة جدا	None of the time. ولا مرة
1	2	3	4	5

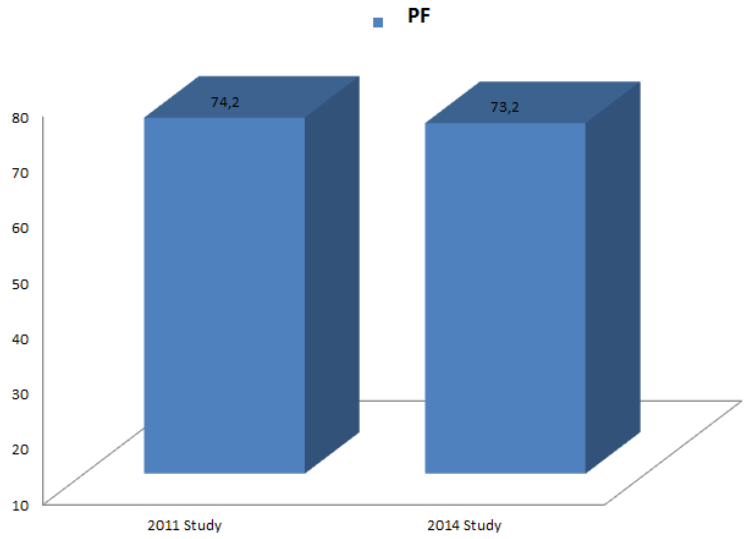
11. How TRUE or FALSE is each of the following statements for you?

11- ما هي درجة الصواب والخطأ في كل من الجمل الاتية بالنسبة اليك:

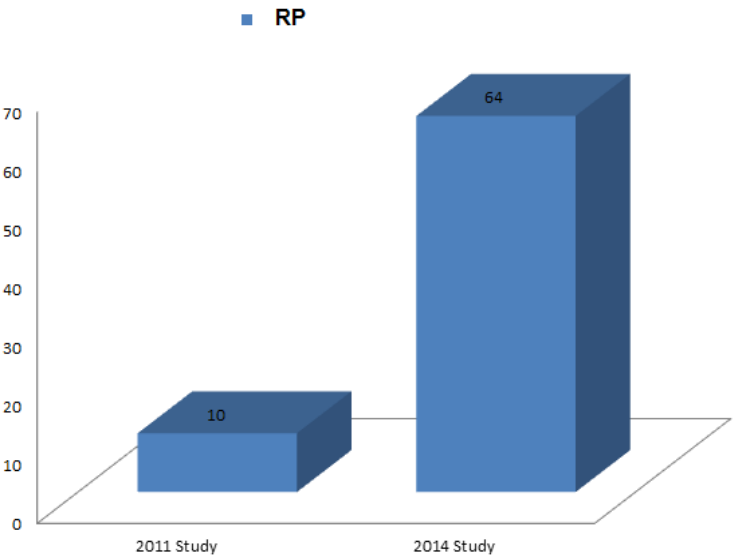
	1. Definitely true صحيحة مئة بالمئة	2. Mostly true صحيحة بنسبة كبيرة	3. Don't know لا اعرف	4. Mostly false خطأ بنسبة كبيرة	5. Definitely false خطأ مئة بالمئة
a) I seem to get sick a little easier than other people? انا اعاني من الامراض بصورة اسهل من الاخرين					
b) I am as healthy as anybody I know? انا سليم صحيا مثل الاشخاص الاخرين الذين اعرفهم					
c) I expect my health to get worse? اتوقع ان تسوء حالتي الصحية					
d) My health is excellent? حالتي الصحية ممتازة					

Appendix 7: Charts showing a comparison of the quality of life domains between patients in the former study of 2011 and the current 2014 study:

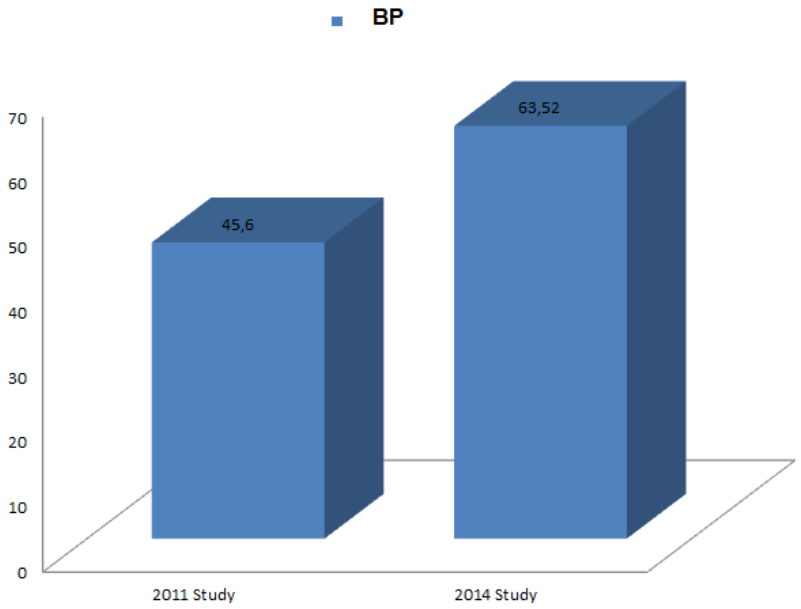
A. PF is nearly the same in the two studies.



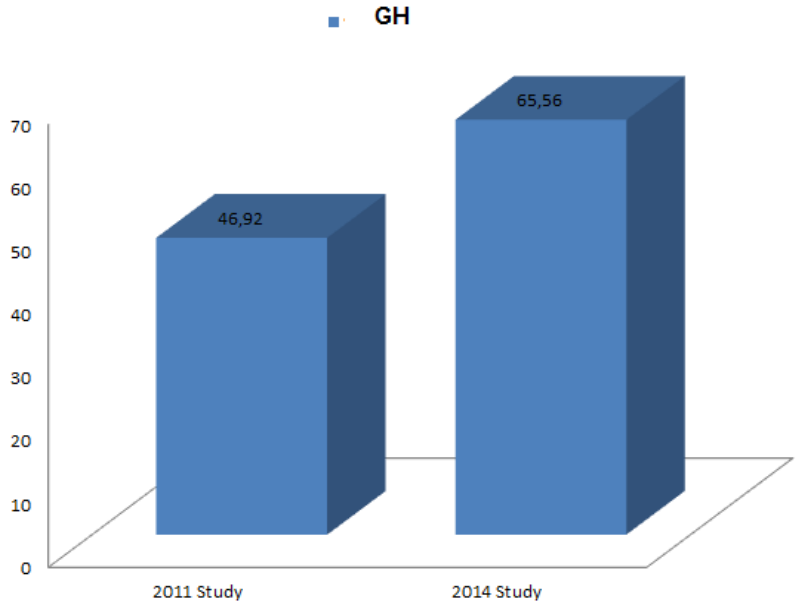
B. RP is higher in the current study than the former study. RP showed the highest difference between the two studies



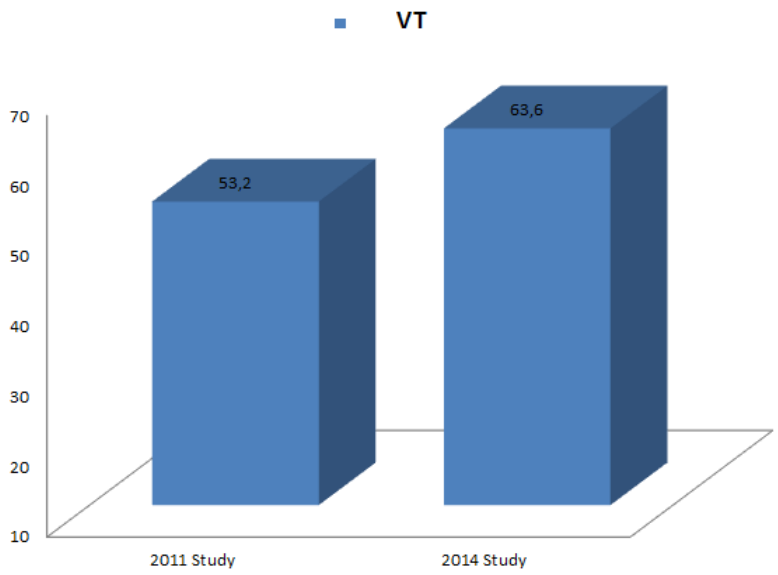
C. BP is higher in the current study than the former study.



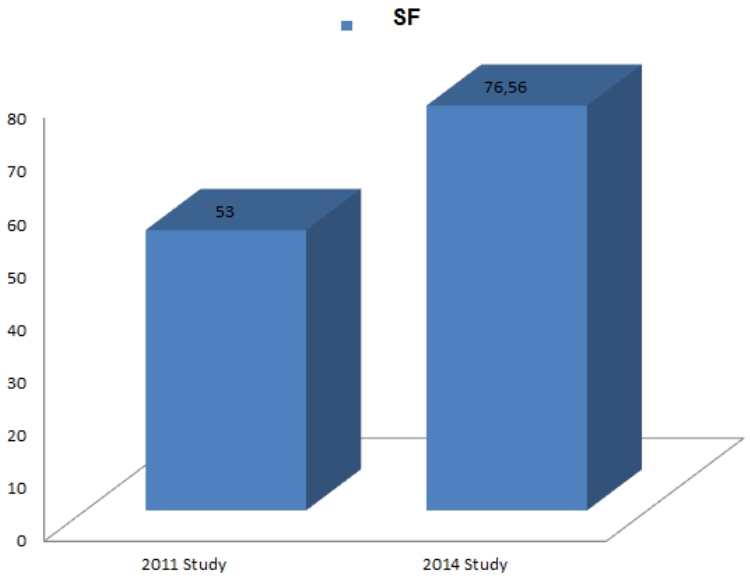
D. GH is higher in the current study than the former study.



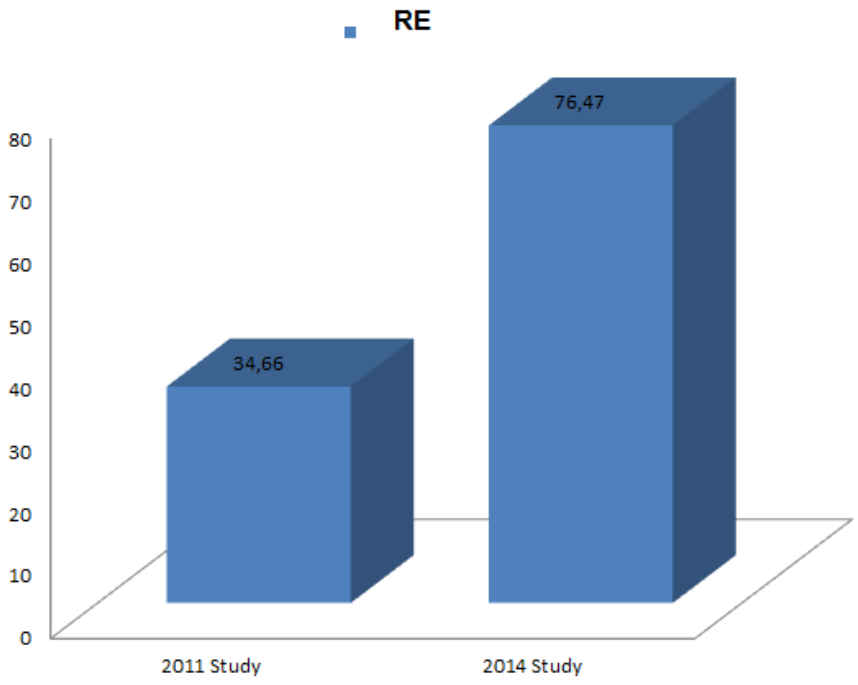
E. VT is higher in the current study than the former study.



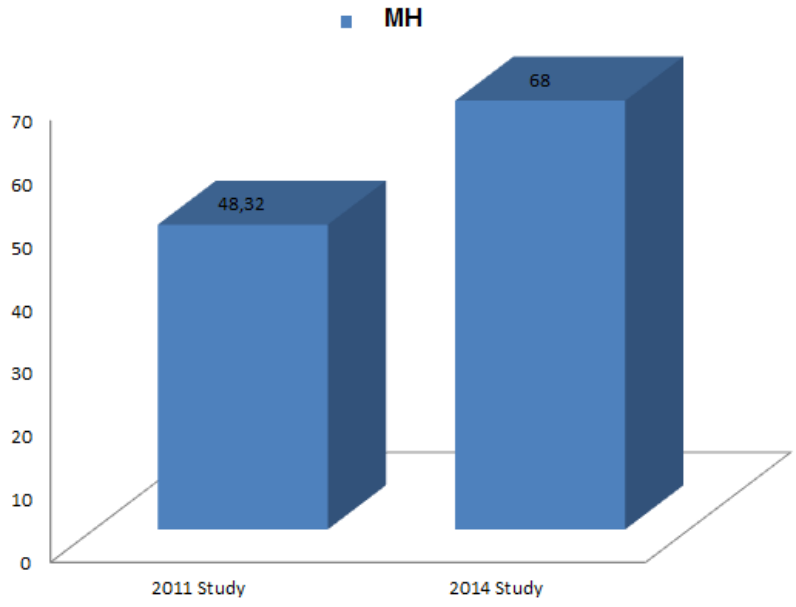
F. SF is higher in the current study than the former study.



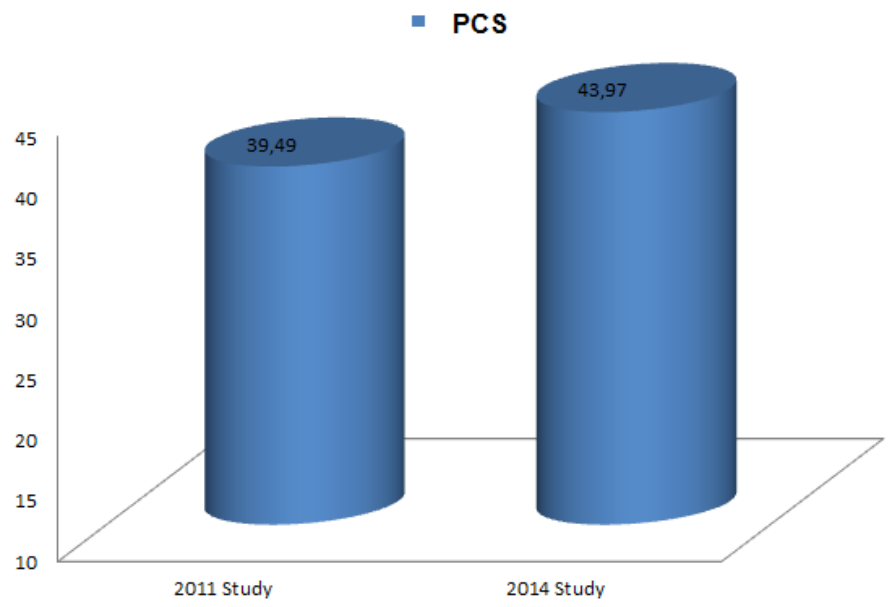
G. RE is higher in the current study than the former study.



H. MH is higher in the current study than the former study.



I. PCS is higher in the current study than the former study.



J. MCS is higher in the current study than the former study.