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The Impact of Chelation Compliance in Health Outcome and Health-Related Quality of Life in Thalassaemia Patients: A Systematic Review

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Abstract

Understanding the consequences of poor chelation compliance is crucial given the enormous burden of post-transfusional iron overload complications. We systematically reviewed iron-chelation therapy (ICT) compliance, and the relationship between compliance with health outcome and health-related quality of life (HRQoL) in thalassaemia patients. Several reviewers performed systematic search strategy of literature through PubMed, Scopus, and EBSCOhost. The preferred reporting items of systematic reviews and meta-analyses (PRISMA) guidelines were followed. Of 4917 studies, 20 publications were included. The ICT compliance rate ranges from 20.93% to 75.3%. It also varied per agent, ranging from 48.84-85.1% for desferioxamine, 87.2-92.2% for deferiprone and 90-100% for deferasirox. Majority of studies (N=10/11, 90.91%) demonstrated significantly negative correlation between compliance and serum ferritin, while numerous studies revealed poor ICT compliance linked with increased risk of liver disease (N=4/7, 57.14%) and cardiac disease (N=6/8, 75%), endocrinologic morbidity (N=4/5, 90%), and lower HRQoL (N=4/6, 66.67%). Inadequate compliance with ICT therapy is common. Higher compliance is correlated with the lower serum ferritin, lower risk of complications, and higher HRQoL. These findings should be interpreted with caution given the few numbers of evidence.

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demonstrated significantly negative correlation between compliance and serum ferritin, while numerous studies revealed poor ICT compliance linked with increased risk of liver disease (N=4/7, 57.14%) and cardiac disease (N=6/8, 75%), endocrinologic morbidity (N=4/5, 90%), and lower HRQoL (N=4/6, 66.67%). Inadequate compliance to ICT therapy is common. Higher compliance is correlated with lower serum ferritin, lower risk of complications, and higher HRQoL. These findings should be interpreted with caution given the few numbers of evidence.

Keywords: compliance, iron chelation therapies, thalassaemia, HRQoL, iron overload

Introduction

Thalassaemia is a hereditary disorder, characterised by abnormal globin chain synthesis in the haemoglobin molecules, affecting millions of people around the world and resulting in thousands of deaths annually [1]. Around 1.5% of the world's population was found to be carriers of beta-thalassaemia [2]; with the prevalence estimated to range between 0.16 and 25 per 100,000 population in Europe, 4 per 100,000 population in North Africa, and 11-36 per 100,000 population in the Middle East [3].

Thalassaemia poses a high financial burden and a huge psychological burden on families, societies, and healthcare systems. Clinically, chronic blood transfusion is required for thalassaemia patients to attenuate anaemia and maintain a normal haemoglobin level. However, multiple episodes of blood transfusion to achieve these goals will have an effect on serum ferritin levels. Systemic iron overload can lead to iron accumulation in the heart, liver, spleen, and other organs, which can cause a variety of complications. The risk of serious iron overload complications is an alarming clinical concern, and properly utilized iron chelation therapy (ICT) is crucial to manage post-transfusional iron overload.

However, non-compliance with iron chelators persists as a major and enduring issue in transfusion-dependent thalassaemia patients. The most common obstacle in enhancing chelation compliance is patient-related, such as a lack of psychological willingness and belief in their ability in administering ICT, which is often due to failure in regulating their negative emotions. [4] The estimated mean rate of patients' compliance of desferrioxamine (DFO) is often dissatisfactory, ranging from 59 to 78% [5]. Low compliance to iron chelation therapy jeopardises treatment effectiveness, resulting in significant morbidity and mortality, reducing patients' health-related quality of life, as well as higher expenses to manage iron overload complications.

Many studies on thalassaemia and compliance to iron chelation have been conducted in a limited context around the world. Reddy et al. (2022) [6] systematically reviewed chelation adherence in the population of children and adolescents with thalassaemia, but not adults, while another study by Arian et al. (2019) [7] reviewed the health-related quality of life associated with thalassaemia patients but did not measure the ICT compliance among them. A review by Delea et al. (2007) [5] investigated the rate of compliance of desferrioxamine (DFO) and deferiprone (DFP) only without deferasirox (DFX) and the association between compliance and iron overload complications, focusing on health outcomes such as cardiac diseases, and diabetes using a small number of articles (as limited relevant studies were conducted at that time) [5]. Hence, there still exists some deficit in our knowledge on the impact of ICT therapy compliance on various clinical and patient-relevant outcomes in patients with thalassaemia. The objective of our current study was to further fill the gaps in measuring compliance rate in all ICT (DFO, DFP & DFX and the combination therapy), understanding the impact of chelation compliance on clinical outcomes and health-related quality of life in all populations of thalassaemia patients.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) to achieve high-quality and transparent research reporting. [8]

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Search terms

Relevant articles were searched through PubMed, Scopus, and EBSCOhost from the inception of these databases until 1stFebruary 2022. The medical subject headings (MeSH) terms and keywords used were "medication adherence" OR "medication compliance" OR "treatment adherence" OR "treatment compliance" OR "Treatment Adherence and Compliance"[Mesh] AND "quality of life" OR "SF36" OR "EQ-5D" or "health-related quality of life" OR "survival rate" OR "quality adjusted life years" or "Quality of Life"[Mesh] AND "health outcome*" OR "health result*" OR "medical outcome*" OR "medical result*" OR "MRI" OR "Serum ferritin" OR "Iron overload complication*" OR "iron related complication*" OR "survival rate" OR "Quality adjusted life years" OR "Outcome Assessment, Health Care"[Mesh] OR "clinical outcome*" OR "clinical result*" OR "healthcare outcome*" OR "healthcare result*" OR "medical care outcome*" OR "medical care result" OR "health related outcome*" OR "health related result*" OR "medical related outcome*" OR "medical related result*" AND "Thalassemia" OR "thalassaemia" OR "beta thalassemia" OR "beta thalassaemia" OR "beta thalassemia" [Mesh].

Inclusion and exclusion criteria

The selection of publications was based on the population, intervention, comparison, outcome, and study (PICOS) approach.

- Population: Thalassaemia patients were prescribed iron chelation therapy (ICT). ICT utilisation in patients with comorbidities of sickle cell disease (SCD), myelodysplastic syndrome (MDS) and other diseases was excluded.
- Types of interventions: Monotherapy or combination of iron chelation therapy such as desferrioxamine (DFO), deferiprone (DFP), deferasirox (DFX), DFO& DFP, DFO & DFX and DFX & DFP
- Types of outcome measures: The compliance outcomes in terms of the rates or percentage. Health outcomes include serum ferritin levels, MRI T2*, iron overload complications and health-related quality of life (HRQoL). The outcomes must be reported as comparisons between the compliant and non-compliant groups. Articles focusing on determinants of chelation compliance were not included.
- Study design: Study designs included in this review were original clinical studies, i.e., cross-sectional studies, cohort studies and randomised controlled trials were included. Only full-text original articles in English were included. Editorials, expert opinions, conference abstracts, case studies or series, study protocols or reviews were excluded.

Study selection

The title and abstract of the articles were independently evaluated based on the inclusion and exclusion criteria by two investigators (WJ and GY). Subsequently, the full text targeted articles were retrieved and accessed for eligibility to be included. The reason for the articles' exclusion was documented. The process of study selection, data extraction and quality appraisal were conducted independently by two investigators (WJ and GY). Any disagreements or differences in opinion between the two researchers (WJ and GY) were handled through discussions and consensus, followed by a third researcher's independent opinion (NAMT). The three researchers (WJ, GY and NAMT) would need to reach an agreement before making a final decision.

Data extraction

Variables assessed included the study's characteristics, such as the year of publication, the country where the study was conducted, sample size, study design, and study duration through a standardized data collection form. The compliance outcomes in terms of rates and/or percentages were extracted from the included

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articles. Health outcome measures such as serum ferritin levels, cardiac and iron loading, endocrine related complications, and health-related quality of life were collected and tabulated accordingly.

Quality appraisal

The risk of bias and the methodology quality of the identified publications were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and a NOS adapted version for cross-sectional studies [9]. NOS is a star-rating based system, with a maximum of 9 scores for cohort studies, randomized controlled trials and a maximum of 10 scores for cross-sectional studies. Each study's quality is assessed using the following grading algorithms: with a NOS score of 7 and above, it is considered a high-quality study, studies with 4 to 6 points are considered medium-quality, while those with 0 to 3 scores are considered low-quality [10].

Results

Literature selection

A total of 4917 studies was identified from the selected databases of PubMed, Scopus and EBSCOHost and 696 studies were eliminated due to duplication of titles. The remaining 4221 articles were screened, and 3980 articles were excluded because of irrelevant titles. Meanwhile, 44 articles involving other haemoglobin disorders such as sickle cell disease (SCD) and myelodysplastic syndrome (MDS), 6 non-English articles, 13 abstract-only articles, and 18 review articles were removed after assessing the abstracts. The eligibility of the remaining 160 full-text articles was evaluated. In this process, 82 publications without adherence/compliance measures, 5 studies focused on intervention or healthcare providers' services, and 53 articles that only evaluated the determinants of chelation measure without comparing the outcomes among the compliant and non-compliant population were removed. Finally, only 20 articles were eligible for synthesis after the culling process. The summary of the literature selection process in this review is shown in Figure 1.

Study characteristics

The characteristics of the studies included in the research are tabulated in Table 1. The published articles were of worldwide origins and were conducted in countries including the United Kingdom, Italy, the United States, Canada, Australia, Singapore, Malaysia, Thailand, Iran, Egypt, Syria, and India. Most of the studies were cross-sectional studies (N=16, 80%) [11-26], followed by cohort studies (N=3, 15%) [27-29], and only one randomised controlled trial [30]. The majority of the studies were single-centred (N=13, 65%) and about 30% of the studies were conducted in multiple settings [12, 17, 24, 25, 27, 30], while the remaining study did not mention the setting [11]

A variety of medication measures was used across the studies. Most of the studies (N= 7, 35%) examined the rate of compliance using the frequency of ICT's administration [11, 12, 14, 16, 18, 19, 23], followed by studies that evaluated patients' compliance status using vial or pill count (N=5, 25%) [13, 27-30]. Several studies (N = 3, 15%) used the Likert Scale [17, 21, 26], while some studies (N = 3, 15%) measured compliance using self-reported questionnaires such as Morisky Medication Adherence Scale (MMAS-8) [22], the Medication Compliance Questionnaire (MCQ) [24], and standardised questionnaire (not mentioned in the study) [25]. Meanwhile, a study [20] reported the compliance with medication possession ratio (MPR), and another study [15] did not mention the method of compliance measurement.

Quality assessment

The details of the methodological quality assessment of the studies are tabulated and summarised in Table 2 and Table 3. To sum up, more than half of the studies (N=12, 60%) were considered high-quality studies,

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while the remaining studies (N=8, 40%) were considered medium-quality studies.

Newcastle-Ottawa Scale for cross-sectional study (N=16)

Overall, most of the cross-sectional studies (N=11) clearly defined the representative sample of the thalassaemia population, but there were no descriptions of the population in 5 of the studies [11, 12, 20, 23, 26]. Only 5 studies reported having a sufficient sample size following an appropriate formula of sample size estimation [12-14, 19, 24].

One study had an unsatisfactory response rate (less than 80%) [25] while there were no descriptions of the response rate nor the characteristics of the respondents and the non-respondents in 4 studies [14, 16, 22, 26].

All of the studies measured compliance rates using validated measurement tools or were able to describe the measurement tool except in the study by Haghpanah et al. (2013) [15].

Aside from that, 6 studies were not adequately designed or analysed to control confounders with regard to demographic factors such as education level, age, income, and treatment type[11, 13, 19-22]. For the remaining 10 studies, the comparability among the different outcome groups was shown and the confounding factors were controlled. In these studies, recruited samples were matched in age, gender or other significant factors [12, 16, 17, 19]; data analysed in multiple logistic regression while controlling multiple factors such as income levels, and family history that would affect compliance [14, 15, 23, 24]; or the outcome stratified based on gender [26], sociodemographic and clinical factors [25]. The data in all the 16 cross-sectional studies were assessed from reliable resources such as medical records, laboratory investigation, and validated questionnaires. They also used appropriate statistical tests and described the measurement of the relationship among outcomes of interest.

Newcastle-Ottawa Scale for cohort study (N=3)

All the cohort studies [27-29] had representative samples of the thalassaemia population and their non-exposed cohort were drawn from the same population as the exposed cohort. During the selection of the cohort study, only Wolfe et al. (1985) [27] reported that all the patients did not have a cardiac disease (outcome of interest). The comparability of cohorts on the basis of the design or analysis was appropriate and justifiable. Two studies recruited both arms from a similar sociodemographic background, while the other study [28] used logistic regression to explain the relationship between multiple variables and the outcome of interest. All the studies assessed the outcome through independent blind assessment. All studies had an adequate period for assessing the outcome ranging between 6 years to 12 years and complete follow-up of the subjects. Wolfe et al. (1985) [27] prospectively followed up the patients for 6 years without any dropouts, while the other studies retrospectively review patients attended the clinic for 12 years [28] and 10 years [29].

Newcastle-Ottawa Scale for randomized controlled trial (N=1)

The sole randomized controlled trial in this study is considered to have high quality. [30] The participants of the study were regular thalassaemia attendees of the Thalassaemia Centers, Ain Shams University, Egypt and Sultan Qaboos University Hospital Oman who had severe iron overload defined as serum ferritin >2500ng/mL, liver iron concentration >7mg/g and cardiac T2* <20 and >6 ms without heart dysfunction. The case and control groups were adequately defined and appropriately represented the targeted population.. The cases and controls were age and gender matched. The data were then assessed through laboratory test and SF-36 health survey for both groups without dropouts.

Compliance towards ICT

The included studies that reported the rate of ICT compliance are summarised in Table 3. Among these studies, 8 evaluated the compliance rate toward DFO monotherapy [11-15, 20, 27, 28], one compared DFO,

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DFP and DFX [29], and another compared DFO and DFX [16]. The compliance rates were compared between the groups of DFO & DFP and DFO & DFX in one study [30], while a different study compared DFO, DFP and DFX, and measured overall compliance [21]. Two studies [17, 23] measured but did not report the compliance rate while the remaining studies examined compliance toward ICT as a whole.

Generally, the rate of ICT compliance ranged from 20.93% to 75.3%. Specifically, the ICT compliance rate of the different agents ranged from 48.84 - 85.1% for DFO, 87.2- 92.2% for DFP, and 90 -100% for DFX. Based on the frequency of ICT administration, the rates of compliance ranged from 27.5% to 85.1%. There were a variety of ways to define compliance in the included studies with compliance defined as at least 4-7 days per week on DFO [11, 16], the number of DFO infusions >50% of the calculated doses per month [23] or >80% of the prescribed doses per year [12], percentage of the day in a month administering DFO >90% [14], using the drugs at least 27 out of 36 months [18], and >50mg/kg/day of DFO or >30mg/kg/day of DFX [19]. The average compliance rates based on the vial or pill count were reported to range from 20.93% to 100% [13, 27-30]. In comparison, the average compliance rate was reported to be 54.9% in the study using MPR [20].

Meanwhile, six articles evaluated compliance using self-reported measurements. Among these studies, four reported a range between 75.3% to 91.4% of patients being compliant to ICT [21, 24-26] with the study by Theppornpitak et al. (2021) [22] reporting 22.9% of patients had high compliance levels. Haghpanah et al. (2013) [15] also reported that 85.1% of patients had good compliance levels although the authors did not mention how they defined compliance in the study.

Studies' findings based on outcomes

Overall, our review revealed a trend toward the advantages of ICT compliance in reducing serum ferritin, risk of cardiac and liver complications, and increasing patients' HRQoL. For studies that reported these outcomes, the majority of the studies (N=10/11, 90.9%) found a significant association between patients' compliance and serum ferritin levels while most of the studies revealed that ICT compliance was linked to a lower risk of liver disease (N=4/7, 57.14%) and cardiac disease (N=6/8, 75%), endocrinologic morbidity (N=4/5, 90%), and lower HRQoL (N=4/6, 66.67%).

In total, 11 studies [11, 13, 14, 16, 20-22, 24, 27, 28, 30] examined the relationship between compliance rate and serum ferritin levels. Nine studies found a significant negative correlation between patients' compliance, the average serum ferritin [11, 13, 16, 20, 21, 24, 28], and the mean decrease in serum ferritin prior enrolment to end of study [22, 27]. Concurrently, a study [30] showed better result (trend) in mean reduction in serum ferritin from baseline to the end of therapy in compliant group although there is no significance difference among the groups while the remaining one study [14] showed no significant relationship between compliance and serum ferritin levels despite most of the non-compliant patients having high serum ferritin levels (>6000µg/L). Furthermore, serum ferritin is proven as an important predictor of liver and cardiac iron load [19, 25], and endocrine complications [23, 25].

Seven studies in the review evaluated the relationship between the degree of ICT compliance and liver iron overload or complications. Compliance was shown to have a significant inverse association with liver iron overload or complication in 3 of the studies [21, 24, 28] Meanwhile, it showed the trend of higher compliance with higher mean decrease in mean liver iron concentration (LIC) level from baseline to end of treatment [30] while the remaining 3 studies revealed opposite results in liver iron load in MRI finding [19, 25] and prevalence of liver morbidities [29]

In addition, six studies revealed that compliance significantly reduces cardiac iron overload [19, 21], cardiac complications [13, 29], and the risk of developing the cardiac disease [27, 28] and a study revealed the better effectiveness in increasing the mean cardiac T2* value from the baseline.[30] In contrast, two articles reported no significant relationship between cardiac iron overload and compliance status [24, 25]. Mokhtar et al. (2013) [29] reported a significantly higher incidence rate of impaired left ventricular contractility in the non-compliant group ($p<0.001$). The MRI finding reported in the study by Sukhmani et al. (2020)

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[21] revealed that non-compliant patients tend to have cardiac and severe hepatic overload, but there were no significant differences in the incidence of complications due to these findings between compliant and non-compliant groups.

Furthermore, endocrinologic complications or morbidities were shown to be significantly associated with poor ICT compliance (N=4/5, 90%) [20, 21, 23, 25, 29] except in the study of Sukhmani et al. (2021) [21]. The endocrinologic morbidities in the studies including hypothyroidism, subclinical hypothyroidism, impaired glucose tolerance, impaired fasting glucose, diabetes mellitus, osteoporosis, and others. The number of non-compliant patients with hypothyroidism, overt and subclinical hypothyroidism were found significant higher [20] while the remaining studies examined the relationship using the number of patients with endocrinopathy (without specify) among the groups. The thyroid function tests such as thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4) and parathyroid hormone test (PHT) were used as parameter for the diagnosis of endocrine disorders in the studies [20, 21, 23], however, only the study by Yassouf et al. (2019) [20] evaluated the readings of TSH and FT4 among the groups and concluded non-compliance with DFO therapy raised the risk of thyroid dysfunction by 6.38 times. Meanwhile, the studies by Mokthar et al. (2013) [29] and Lam et al. (2021) [25] did not mention or evaluate the thyroid function.

In this review, only six studies evaluated the association between compliance and quality of life. The tools to measure HRQoL were Quality of Care (QoC) and Quality of Life (QoL) questionnaires [12]; Pediatric Quality of Life Inventory (PedsQL) [18]; Short Form-36 (SF-36) [15, 17, 30] and Transfusion-dependent QoL (TranQoL) [25] Four of the studies concluded the positive relationship between HRQoL and compliance, i.e., patients with higher compliance had better HRQoL [12, 15, 18, 30]. However, the remaining two studies demonstrated no association between compliance and HRQOL for patients [17, 25]

Discussion

Clinically, good compliance to chelation therapy has a great impact on disease control and the quality of life in thalassaemia patients. A high level of compliance is associated with significantly lower serum ferritin levels which tend to produce lower risk of iron overload complications, as well as a better quality of life. However, inadequate compliance to ICT therapy is common and patients are generally considered to have the lowest level of compliance to DFO and the highest level of compliance to DFX. Indeed, many studies measured the patients' compliance or the clinical burden of thalassaemia itself, but not many studies measured the association among them. This systematic review identified and evaluated 20 medium to high quality articles that measured and compared the impact of chelation compliance on health outcomes or health-related quality of life. This would provide a clearer and a more comprehensive picture of the importance of compliance on various clinical outcomes for optimal management of thalassemia patients.

Almost all of the included studies (10 out of 11) that evaluated the association between compliance and serum ferritin levels reported significant negative correlations or trend among them, except the study by Lee et al. (2011) conducted in paediatric patients in Malaysia. This might be due to the markedly high average serum ferritin levels (6156 ± 4296 mg/L) of the patients in the study. Generally, iron chelator correlates better with a lower level of total body iron and leads to better therapy results [31]. However, it should be noted that the patients in the study by Lee et al. (2011) had only received DFO therapy for 2 years even though they had an average of 9 years of regular blood transfusions. A longer period of iron-chelation therapy will be needed to observe a significant decline in serum ferritin. This is further supported by the findings of Richardson and his colleagues which showed a prolonged administration of ICTs (early commencement) was associated with a greater reduction of serum ferritin [28].

Besides, the relationship between compliance levels and the risk of complications associated with ICT is still inconclusive. Several studies in our current review measured the risk of liver or cardiac iron overload complications through MRI [16, 19, 24] or cardiac evaluation such as clinical examination, echocardiography and, electrocardiography [27-29]. MRI T2* is an accurate and reliable tool to assess iron status in patients but it is sometimes not feasible due to high cost, and patients' uncooperativeness to hold their breath throughout

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the process. Furthermore, MRI T2* is only applicable for patients aged 10 and above [32]. As a result, only a few articles reported the findings of MRIs involving a small sample size of patients explaining the unequivocal findings. Furthermore, previous literature showed that cardiac iron overload was discovered in cases of severe iron accumulation in the myocardium only [17]. Moreover, the age of the participants of these studies was relatively young. A large clinical study revealed that thalassaemia patients over 40 years old tend to develop and have a higher incidence of cardiac complications such as atrial fibrillation as well as a higher risk of stroke even without any evidence of iron overload [33]. This would suggest that further studies requiring a longer follow-up of participants are important to identify patients with iron overload complications.

Another interesting point to discuss regarding the association between medication compliance and HRQoL is that thalassaemia is a progressive disease. Symptoms of hyperferritinemia are often ambiguous and non-specific, and commonly present without causing any early real clinical manifestations. Hence, a high level of serum ferritin may not affect thalassaemia patients in their daily life, but the accumulation of excess iron may result in the occurrence of life-threatening complications in later life. Some thalassaemia patients receiving DFO therapy have lower chelation compliance due to the inconvenient administration procedure and pain at the injection site. Avoiding such an inconvenient procedure may temporarily improve their current quality of life, however, the long-term consequences of increased iron loading will be more likely to result in reduced quality of life in the future [34]. Additionally, generalising and comparing patients' health-related quality among these studies is challenging due to thevariations in the tools used for measuring HRQoL.

Anyway, the objective of our systematic review is very similar to the review by Delea et al in 2007 [5]. In terms of compliance rate, Delea et al. found a slightly lower range of mean scores towards DFO (59%-78%) and DFP (79%-98%) in comparison to our study. However, they were unable to include any studies that looked into DFX (not available during the conduct of the review by Delea et al. 2007). Although Delea et al. systematically reviewed 18 studies on compliance rates with ICT, they only managed to include 5 articles to discuss the association between compliance and the incidence of iron overload complications. The review demonstrated a higher incidence of cardiac and endocrinopathies complications in poor compliant patients. The five articles included in the previous review represented studies conducted in Western and developed countries only (the United States, Australia, and Italy) and all were performed before 2000, making it difficult to generalise the findings for developing countries such as Malaysia. Moreover, after two decades, the clinical management of thalassaemia population has improved due to more options of ICT and improved healthcare technologies in recent years. Our review also included two articles from the previous review since they fulfilled our inclusion criteria. As a result, our review provided updated information on the impact of compliance on thalassaemia patients.

Based on the findings from our study, several recommendations for future studies could be suggested in regard to the impact of chelation compliance on iron overload complications. In the included studies in our current review, the sample sizes used to assess the relationship between compliance and iron overload complications were relatively small, ranging from 36 to 90, except for the study by Mokhtar et al. (2013) which had a sufficient sample size (n=447). For any study, an adequate sample size always allows statistically more reliable conclusion to be derived from the results. Secondly, researchers should consider and recruit patients of older age in the study as higher risk and incidence of iron overload complications were found in older thalassaemia patients (>40 years old) [33]. In the studies included in our review, the median age of the samples ranged from 11.34 to 22.7 years old. Researchers may also design studies with different age groups and compare the impact of poor compliance. Besides, to appropriately identify patients with incidence of iron overload complications, a longer period of study is needed.

Lastly, our review does contain some limitations. We did not include non-English language studies in this review. In addition, grey literature was also not included due to its diversity and challenges to assess the quality of the literature. The exclusion of these articles may cause the exclusion of potentially valuable data. However, the available evidence in our review is considerably more appropriate and robust to fill the gaps in the topic.

To our best knowledge, this is the first review with worldwide data from developed and developing countries

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that demonstrated the positive impact of compliance in improving health outcomes (especially serum ferritin, cardiac, liver, and endocrinologic complications), and patients' HRQoL. The conclusion of the current review was drawn and supported by more than 50% of the studies reviewed. Nevertheless, we were unable to perform a meta-analysis to provide a more precise estimate of the association between compliance and the various outcomes due to the limited number and heterogeneity of studies reporting the different outcomes of interest.

Conclusion

Congruent with expectation, our review demonstrated that compliance to iron chelators maximises the benefits of the therapy in reducing serum ferritin, iron overload complications and HRQoL. The serum ferritin levels appear to be the most affected outcome by compliance, while the relationship between ICT compliance, iron overload complications, and HRQoL was shown but further investigation is needed. To fully understand the impact of compliance on the most vulnerable patient groups, more comprehensive research with larger sample size and comparing the impact of ICT to the outcomes of interest among different age groups is needed.

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Statement of Ethics

An ethics statement is not required since this review is based solely on published studies and not an original clinical research.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

The authors confirm the following contribution to the review: conception or design of the review: Wan Jin Lee, Geok Ying Chun, Nurul Ain Mohd Tahir; data collection, analysis and interpretation: Wan Jin Lee, Geok Ying Chun; drafting the review: Wan Jin Lee; critical revision of the paper: Nurul Ain Mohd Tahir, Shu Chuen Li, Wan Jin Lee. All authors gave final consent to the published version.

Data Availability Statement

Not applicable

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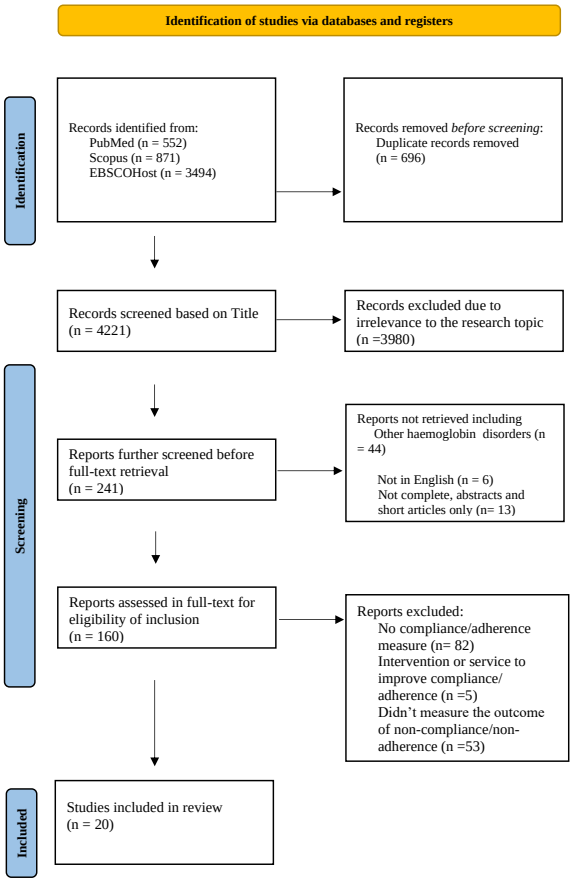

Figure 1: PRISMA 2020 Flow Diagram on the literature selection process for a systematic review of the impact of chelation compliance on health outcomes and health-related quality of life on thalassaemia patients

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20221122 Table 1. Study characteristics of published literature.docx available at https://authorea.com/users/544205/articles/601599-the-impact-of-chelation-compliance-in-health-outcome-and-health-related-quality-of-life-in-thalassaemia-patients-a-systematic-review

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20221122 Table 2. Methodological assessment of the studies through Newcastle Ottawa Scale.docx available at https://authorea.com/users/544205/articles/601599-the-impact-of-chelation-

compliance-in-health-outcome-and-health-related-quality-of-life-in-thalassaemia-patients-a-systematic-review

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20221122 Table 3. Chelation compliance measure and outcomes of published studies.docx available at https://authorea.com/users/544205/articles/601599-the-impact-of-chelation-compliance-in-health-outcome-and-health-related-quality-of-life-in-thalassaemia-patients-a-systematic-review

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