Research Square

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Prevalence and Clinical Impact of Smoking and Obesity Among Thalassemia Patients in Egypt: A Single-Center Study

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Abstract

Background

Thalassemia is a chronic inherited hemoglobinopathy associated with significant multisystem complications. While transfusion dependency and iron overload are well-recognized determinants of morbidity, the contribution of modifiable lifestyle factors such as obesity and smoking remains incompletely defined.

Methods

We conducted a cross-sectional study of 108 adults with thalassemia (≥ 18 years) followed at the Oncology Center of Mansoura University. Patients were classified as transfusion-dependent (TDT) or non–transfusion-dependent (NTDT). Clinical, laboratory, and radiologic data were extracted from electronic records. Overweight/obesity was defined as body mass index (BMI) ≥ 25 kg/m², and smoking status was categorized as active, passive, or non-smoker. Statistical analyses were performed using R (v4.4.3) and SPSS (v27).

Results

The median age was 32 years, with a slight female predominance (52.8%); 81.5% had TDT. Overall, 22.6% were overweight/obese, and 12% were active smokers, while 79.6% had at least one complication. TDT patients exhibited significantly higher rates of cardiac and hepatic complications, splenomegaly, splenectomy, lower hemoglobin levels, and higher red cell distribution width (RDW) than NTDT patients. BMI was modestly higher in NTDT ($p = 0.043$). In TDT, smoking was associated with hypertension, chronic liver disease, and splenomegaly, with a borderline association with renal insufficiency. Obesity correlated with female sex, valvular heart disease, chronic liver disease, and inflammatory hematologic indices.

Conclusion

Beyond transfusion-related factors, obesity and smoking appear to contribute to hepatic, cardiovascular, renal, and inflammatory complications in thalassemia. Incorporating lifestyle risk assessment and targeted preventive strategies may improve long-term patient outcomes.

Introduction

Thalassemia is a group of inherited autosomal recessive anemias caused by globin gene mutations, leading to ineffective erythropoiesis, chronic hemolysis, and red blood cell damage [1]. Globally, an estimated 119,679 new cases occur annually, with ~ 5% of the population carrying pathogenic variants, and the highest prevalence in the Mediterranean, Middle East, and South Asia [2, 3]. In Egypt, carrier rates range from 5–10%, with roughly 1,000 affected children born each year, highlighting the persistent public health burden [4, 5].

Thalassemia spans a broad clinical spectrum, from asymptomatic carriers to severe disease with major complications. Patients are classified as transfusion-dependent thalassemia (TDT), requiring regular transfusions due to severe anemia, or non-transfusion-dependent thalassemia (NTDT) with milder disease [6]. Severe forms, particularly homozygous β-thalassemia, lead to ineffective erythropoiesis, iron overload, and progressive multisystem complications, while α-thalassemia ranges from silent carrier states to hemoglobin H disease and the usually fatal hemoglobin Bart's hydrops fetalis [7, 8]. Management depends on disease severity and includes transfusion therapy, iron chelation, supportive care, stem cell transplantation, and emerging gene-based therapies [9].

Obesity is a chronic multisystemic disease associated with systemic inflammation and multiple comorbidities. In patients with thalassemia, the prevalence and impact of obesity are not well studied. Emerging evidence indicates that adult patients with thalassemia major often exhibit altered body composition, including increased adiposity, reduced lean mass, and decreased

bone mineral density, influenced by factors such as iron chelation therapy (ICT), endocrine complications, and nutritional status [10]. These abnormalities, together with obesity, have been linked to metabolic complications, including insulin resistance, glucose dysregulation, and features of metabolic syndrome, which may further exacerbate cardiovascular and endocrine risks, highlighting the need for systematic evaluation of obesity and its clinical consequences in this population [11, 12].

Smoking is a well-established risk factor for multiple systemic diseases, contributing to chronic inflammation, oxidative stress, endothelial dysfunction, and adverse effects on hematological and non-hematological parameters. In the general population, smoking is linked to increased morbidity and mortality from cardiovascular, respiratory, and metabolic complications [13]. However, the prevalence and impact of smoking in patients with thalassemia have not been adequately characterized. Given the underlying pathophysiology of thalassemia, including chronic hemolysis, iron overload, and endothelial injury, smoking may potentiate oxidative damage, exacerbate anemia, and increase the risk of vascular and organ complications, underscoring the need for focused investigation in this vulnerable population.

This study aims to determine the prevalence of obesity and smoking among patients with thalassemia. Additionally, it seeks to evaluate their impact on clinical and hematological outcomes in this population.

Methodology

1. Study design and study approval

We conducted a cross-sectional study of 108 adult patients diagnosed with thalassemia from 2006 to 2025 who were followed up in the Hematology unit at Oncology Center of Mansoura University (OCMU). Inclusion criteria were patients diagnosed with thalassemia aged ≥ 18 years, excluding those with other types of anemia or malignant conditions.

This study was approved by the Mansoura University Institutional Review Board (IRB) and conducted in accordance with the standards established by the Declaration of Helsinki of 1975, revised in 2008, and was given the code number: **R.25.03.3119**.

2. Data collection

Clinical, laboratory, and radiological data were collected from the electronic health records (Ibn Sina Hospital management system).

Baseline laboratory investigations included a complete blood count (CBC), which was performed using automated hematology analyzers (Cell-Dyn 1700 and Cell-Dyn Emerald). Hemoglobin (Hb) was reported in g/dL, red blood cell (RBC) count in $\times 10^6/\mu L$, total leukocyte count (TLC) in $\times 10^3/\mu L$, and platelet count in $\times 10^3/\mu L$. Red cell distribution width (RDW) was expressed as a percentage, while platelet distribution width (PDW) and mean platelet volume (MPV) were measured in femtoliters (fL). Peripheral blood smears with differential leukocyte counts were examined, and liver and kidney function tests, and serum ferritin were assessed using the Roche Cobas Integra 800 auto-analyzer.

Radiological investigation, including abdominal ultrasound (US), Echocardiogram (ECHO), and Magnetic Resonance Imaging (MRI) on the liver and heart to evaluate hemochromatosis, were done.

Iron chelation therapy was administered according to institutional protocols and individualized based on treatment response, tolerability, and drug availability. Patients received deferoxamine, deferiprone, or deferasirox, either as monotherapy or in combination.

Body mass index (BMI) was calculated using the standard formula: weight (kg) divided by height squared (m^2). Patients with a BMI ≥ 25 kg/m^2 were classified as overweight/obese, while those with a BMI < 25 kg/m^2 were considered non-obese. To minimize measurement bias, weight and height were obtained using standardized, calibrated scales and stadiometers, and measurements were performed by trained healthcare personnel. Self-reported data by the patients were not used.

Smoking status was categorized into three groups: smokers, passive smokers, and non-smokers. Smokers were defined as individuals who had smoked cigarettes for at least six months, either currently or in the past. Passive smokers were individuals regularly exposed to secondhand smoke, while non-smokers did not meet the criteria for either category.

3. Statistical analysis:

The statistical analysis and the visualization of the data were done using the R/R-Studio (version 4.4.3) program and SPSS (version 27). The data were read from Excel (Office program 2010). For the statistical analysis, different packages were used, including *"survival," "condsurv," "ggsigniff," "ggfortify," "Survminer," "rstatix," and "corrplot."* For the visualization of the data, mainly the "tidyverse" package was used for the manipulation of the plots. The Shapiro–Wilk test was used to test the normality of the data. The qualitative and descriptive data were illustrated as numbers and percentages using the chi-square test. Quantitative data were analyzed as means, medians, and standard deviations. The Wilcoxon test was used for the non-parametric data for the comparison between the two paired groups, and the Mann-Whitney test for unpaired groups. The Spearman test was used to measure the association between variables. The Kaplan–Meier test was used for the survival analysis. COX regression was used for univariate and multivariate analysis of the survival predictors. The significant *p-value* was considered when less than 0.05.

Results

1. Clinical and laboratory characteristics of the entire cohort

The study included 108 patients with thalassemia, with a slight female predominance (n = 57, 52.8%). The median age was 32 years (range: 25.25–38.75), and the majority were transfusion-dependent (TDT) (n = 88, 81.5%). Based on BMI classification, most patients were non-obese (n = 82, 77.4%), while 22.6% (n = 24) were overweight/obese; the median BMI was 22.2 kg/m² (range: 19.9–24.4). Regarding smoking status, 56.5% (n = 61) were non-smokers, 31.5% (n = 34) were passive smokers, and 12% (n = 13) were active smokers. Overall, 79.6% (n = 86) of patients experienced at least one complication. The most frequent complications were splenomegaly (88.9%), hepatic complications (55.6%), cardiac complications (48.1%), and gall bladder (GB) stones (37%). Other complications are detailed in Table 1.

Table 1
The descriptive clinical and laboratory data of the whole cohort

Data description				
Clinical Data				
Values	**Mean**	**SD**	**Median**	**Range**
Age (years)	32.52	9.431	32	25.25–38.75
BMI (Kg/m^2)	23.11	5.32	22.196	19.9–24.4
Gender				
Male			51 (47.2%)	
Female			57 (52.8%)	
Disease subtype				
NTDT			20 (18.5%)	
TDT			88 (81.5%)	
Comorbidities				
Hypertension			3 (2.8%)	
DM			5 (4.6%)	
Obesity				
Non-obese			82 (77.4%)	
Overweight/Obese			24 (22.6%)	
Smoking				
Smokers			13 (12%)	
Passive smokers			34 (31.5%)	
Non-smokers			61 (56.5%)	
Virology				
HCV			62 (57.4%)	
HBV			1 (0.9%)	
HIV			0 (0%)	
Complications				
Presence of complications			**86 (79.6%)**	
Cardiac complications			**52 (48.1%)**	
Cardiomyopathy			26 (24.1%)	
Valvular diseases			50 (46.3%)	
Pulmonary hypertension			4 (3.7%)	
Hemochromatosis heart			4 (3.7%)	
Skin ulcers			**6 (5.6%)**	
Endocrinopathy			**6 (5.6%)**	

Data description				
Thrombosis		**5 (4.6%)**		
Osteoporosis		**9 (8.3%)**		
Liver complications		**60 (55.6%)**		
Hepatomegaly		61 (56.5%)		
Hemochromatosis liver		32 (29.6%)		
Renal insufficiency		**6 (5.6%)**		
Splenomegaly		**96 (88.9%)**		
Splenectomy		77 (71.3%)		
Gallstones		**40 (37%)**		
Number of ICTs				
0		9 (8.3%)		
1		56 (51.9%)		
2		28 (25.9%)		
3		15 (13.9%)		
Laboratory Data				
Values	**Mean**	**SD**	**Median**	**Range**
TLC (×10⁶/μL)	23.54	25.71	14.115	7.48–26.975
HB (g/dl)	7.62	1.57	7.6	6.81–8.38
MCV (fL)	69.16	10.66	69.55	62.3–76.555
MCH (pg)	21.68	3.91	21.61	19.03–24.5
MCHC (g/dL)	31.43	2.86	31.5	29.8–33.10
RDW (%)	26.27	7.77	24.8	19.99–32.6
MPV (fl)	8.82	3.52	9.634	7.46–10.7
ANC (k/uL)	6.33	3.78	5.48	3.583–8.19
ALC (k/uL)	15.07	25.45	6.2575	2.68–15.78
AMC (k/uL)	1.04	1.08	0.6759	0.341–1.355
PLT (k/uL)	546.99	311.92	526	297.75–769.5
Indirect bilirubin (mg/dl)	1.83	0.92	1.8	1.285–2.1
Direct bilirubin (mg/dl)	0.53	0.27	0.5	0.34–0.64
Total bilirubin (mg/dl)	2.54	1.42	2.25	1.6–3.02
ALT (U/L)	50.92	65.99	34	17.71–66
AST (U/L)	57.92	38.87	47.5	32–72
Ferritin level before ICT (ng/ml)	2617.88	1793.47	2000	1238–4000
Ferritin level 3–6 months after ICT (ng/ml)	2077.38	1437.92	1690	957–4000
Ferritin level 1 year after ICT (ng/ml)	2315.33	1439.55	1887	1128–4000

Baseline laboratory data at the first visit obtained from the OCMU registry included complete blood count (CBC) parameters, liver function tests, and serum ferritin levels, which are summarized in Table 1.

2. Clinical and laboratory characteristics according to transfusion dependency status

Among 88 patients with TDT and 20 with NTDT, sex distribution did not differ significantly, despite a slight male predominance in TDT (51.1%) and female predominance in NTDT (70%). Obesity prevalence and smoking status were comparable; however, BMI was modestly but significantly higher in NTDT (23.83, range: 17.67–30.47 vs. 21.97, range: 15.94–55.09).

Diabetes mellitus and hypertension were observed exclusively in TDT. TDT patients exhibited a significantly higher burden of cardiac complications (90.38% vs. 9.61%, **p = 0.04**), primarily driven by valvular disease (92% vs. 8%, **p = 0.02**). Although cardiomyopathy showed a trend toward increased occurrence in the TDT group, the difference did not reach statistical significance. Pulmonary hypertension was observed exclusively among TDT patients; however, this finding was not statistically significant, likely due to the small number of affected cases. Liver-related morbidity was also significantly more frequent in TDT, including HCV infection (91.94% vs. 8.06%, **p < 0.001**) and chronic liver disease (91.67% vs. 8.33%, **p = 0.005**). Splenomegaly and splenectomy were markedly more prevalent in TDT (**p < 0.001** for both). No significant intergroup differences were observed for gallstones, endocrinopathies, osteoporosis, or renal impairment (**Supplementary Table 1**).

Hematologic parameters reflected more pronounced disease severity in TDT, with significantly lower hemoglobin and higher RDW (median 7.49 g/dL and 26.8%, respectively; **p = 0.0012** for both), accompanied by elevated bilirubin levels (median 2.4 mg/dL, **p = 0.019**). In contrast, NTDT patients demonstrated a higher neutrophil-to-lymphocyte ratio (NLR) (median 1.28 vs. 0.86, **p = 0.047**), reflecting a relatively greater inflammatory burden in this subgroup. Other hematologic and hepatic indices were comparable (**Supplementary Table 2**).

Baseline ferritin levels before iron chelation therapy were higher in TDT, approaching statistical significance (2000 vs. 1453 ng/mL, p = 0.059), and ICT utilization was significantly more frequent in this group (**p = 0.001**) (**Supplementary Table 1**). While most patients received monotherapy, a subset required sequential or combination regimens due to intolerance or inadequate response. Although NTDT patients exhibited a greater short-term reduction in ferritin at three months (**p = 0.048**), the one-year decline was modest in both subtypes, likely reflecting cumulative therapeutic and adherence-related constraints (**Supplementary Table 2**).

3. Impact of smoking on the clinical and laboratory characteristics of Thalassemia patients

Stratification by smoking status revealed a significant difference in gender distribution across NTDT and TDT subgroups. Males constituted 100% of active smokers in both NTDT and TDT, compared with 33.3% and 38.5% among non-smokers, respectively (**p = 0.001**) **(**Table 2**).**

Table 2
Clinical correlations of smoking in TDT versus NTDT

Variables		NTDT			TDT			X^2	P
		Non smokers (n = 9) (n, %)	Smokers (n = 1) (n, %)	Passive smokers (n = 10) (n, %)	Non smokers (n = 52) (n, %)	Smokers (n = 12) (n, %)	Passive smokers (n = 24) (n, %)		
Gender	Male	3 (33.3%)	1 (100%)	2 (20%)	20 (38.5%)	12(100%)	13 (54.2%)	20.265	**0.001**
	Female	6 (66.7%)	0	8 (80%)	32 (61.5%)	0	11 (45.8%)		
Obesity	Non obese	5 (62.5%)	1 (100%)	6 (60%)	42 (82.4%)	11(91.7)	17 (70.8%)	5.734	0.333
	Obese	3 (37.5%)	0	4 (40%)	9 (17.6%)	1 (8.3%)	7(29.2%)		
Liver hemochromatosis	No	7 (77.8%)	1 (100%)	7 (70%)	37 (71.2%)	7(58.3%)	17(70.8%)	1.51	0.912
	Yes	2 (22.2%)	0	3 (30%)	15 (28.8%)	5(41.7%)	7 (29.2%)		
Cardiac hemochromatosis	No	9 (100%)	1 (100%)	10(100%)	51 (98.1%)	10(83.3%)	23 (95.8%)	6.9	0.228
	Yes	0	0	0	1 (1.9%)	2(16.7%)	1 (4.2%)		
Complications	No	3 (33.3%)	1 (100%)	3 (30%)	10 (19.2%)	1 (8.3%)	4 (16.7%)	6.73	0.242
	Yes	6 (66.7%)	0	7 (70%)	42 (80.8%)	11(91.7%)	20 (83.3%)		
Cardiac complications	No	7 (77.8%)	1 (100%)	7 (70%)	24 (46.2%)	7 (58.3%)	10 (41.7%)	6.546	0.257
	Yes	2 (22.2%)	0	3 (30%)	28 (53.8%)	5 (41.7%)	14 (58.3%)		
Cardiomyopathy	No	9 (100%)	1 (100%)	8 (80%)	38 (73.1%)	9 (75%)	17 (70.8%)	3.839	0.573
	Yes	0	0	2 (20%)	14 (26.9%)	3 (25%)	7 (29.2%)		
Valvular affection	No	7 (77.8%)	1 (100%)	8 (80%)	24 (46.2%)	7 (58.3%)	11 (45.8%)	7.635	0.178
	Yes	2 (22.2%)	0	2 (20%)	28 (53.8%)	5 (41.7%)	13 (54.2%)		
Hypertension	No	9 (100%)	1 (100%)	10 (100%)	52 (100%)	9 (75%)	24 (100%)	24.686	**< 0.001**
	Yes	0	0	0	0	3 (25%)	0		
DM	No	9 (100%)	1 (100%)	10 (100%)	51 (98.1%)	11 (91.7%)	21 (87.5%)	5.573	0.35
	Yes	0	0	0	1 (1.9%)	1 (8.3%)	3 (12.5%)		

*TDT: Transfusion dependent Thalassemia, NTDT: Non-Transfusion dependent Thalassemia, DM: Diabetes Miletus, HTN: Hypertension, GB: Gall Bladder, n: number, p: P-value, X^2 : Value of Pearson Chi-Square test, bold value indicates significant p-value

Hepatomegaly	No	7 (77.8%)	0	4 (40%)	26 (50%)	2 (16.7%)	8 (33.3%)	10.54	0.061
	Yes	2 (22.2%)	1 (100%)	6 (60%)	26 (50%)	10 (83.3%)	16 (66.7%)		
Chronic liver disease	No	7 (77.8%)	1 (100%)	7 (70%)	23 (44.2%)	3 (25%)	7 (29.2%)	12.052	**0.034**
	Yes	2 (22.2%)	0	3 (30%)	29 (55.8%)	9 (75%)	17 (70.8%)		
Splenomegaly	No	4 (44.4%)	0	5 (50%)	2 (3.8%)	0	1(4.2%)	31.013	**< 0.001**
	Yes	5 (55.6%)	1 (100%)	5 (50.0%)	50 (96.2%)	12 (100%)	23 (95.8%)		
Splenectomy	No	4 (44.4%)	1 (100%)	6 (60%)	11 (21.2%)	3 (25%)	6 (25%)	10.049	0.074
	Yes	5 (55.6%)	0	4 (40%)	41 (78.8%)	9 (75%)	18 (75%)		
GB stones	No	5 (55.6%)	1 (100%)	8 (80%)	31 (59.6%)	7 (58.3%)	16 (66.7%)	2.546	0.77
	Yes	4 (44.4%)	0	2(20%)	21 (40.4%)	5 (41.7%)	8 (33.3%)		
Skin ulcers	No	9 (100%)	1 (100%)	10(100%)	50 (96.2%)	10 (83.3%)	22 (91.7%)	4.643	0.461
	Yes	0	0	0	2 (3.8%)	2 (16.7%)	2 (8.3%)		
Pulmonary HTN	No	9 (100%)	1 (100%)	10(100%)	50 (96.2%)	11(91.7%)	23 (95.8%)	1.508	0.912
	Yes	0	0	0	2 (3.8%)	1 (8.3%)	1 (4.2%)		
Endocrinopathy	No	9 (100%)	1 (100%)	10(100%)	47 (90.4%)	11 (91.7%)	24(100%)	4.398	0.494
	Yes	0	0	0	5 (9.6%)	1 (8.3%)	0		
Osteoporosis	No	8 (88.9%)	1 (100%)	10(100%)	48 (92.3%)	12(100%)	20 (83.3%)	4.392	0.495
	Yes	1 (11.1%)	0	0	4 (7.7%)	0	4 (16.7%)		
Renal insufficiency	No	9 (100%)	1 (100%)	10(100%)	50 (96.2%)	9 (75%)	23 (95.8%)	10.201	0.07
	Yes	0	0	0	2 (3.8%)	3 (25%)	1 (4.2%)		

*TDT: Transfusion dependent Thalassemia, NTDT: Non-Transfusion dependent Thalassemia, DM: Diabetes Miletus, HTN: Hypertension, GB: Gall Bladder, n: number, p: P-value, X^2 : Value of Pearson Chi-Square test, bold value indicates significant p-value

Hypertension demonstrated a strong association, occurring exclusively in TDT patients and confined to active smokers, while absent in all NTDT categories and other TDT smoking groups (**p < 0.001**) **(**Table 2**).**

Chronic liver disease was also significantly associated with smoking status and subtype (**p = 0.034**). The highest frequencies were observed among TDT smokers (75.0%) and passive smokers (70.8%), compared with 55.8% in TDT non-smokers and 22.2–30.0% in NTDT subgroups. Splenomegaly showed the strongest association (**p < 0.001**), being highly prevalent in TDT across all smoking categories (96.2% of non-smokers, 100% of smokers, and 95.8% of passive smokers) compared with 50.0–55.6% among NTDT patients **(**Table 2**).**

Borderline associations were observed for hepatomegaly (p = 0.061) and renal insufficiency (p = 0.07). Hepatomegaly was more frequent in TDT smokers (83.3%) and passive smokers (66.7%) compared with NTDT non-smokers (22.2%). Renal insufficiency was predominantly observed among TDT smokers (25.0%), with lower proportions in TDT non-smokers (3.8%) and passive smokers (4.2%), and absent in NTDT **(**Table 2**)**.

No statistically significant associations were identified between smoking status and obesity, hepatic or cardiac hemochromatosis, cardiomyopathy, valvular affection, diabetes mellitus, splenectomy, gallstones, pulmonary hypertension, endocrinopathy, osteoporosis, or skin ulcers **(**Table 2**)**.

No statistically significant differences were observed between smokers and non-smokers regarding CBC indices, liver function parameters, or serum ferritin levels (**Supplementary Table 3**).

4. Impact of Obesity on the clinical and laboratory characteristics of Thalassemia patients

In this cohort, obesity was significantly associated with several clinical parameters. A significant association was observed with gender (**p = 0.004**), with obesity being more prevalent among females, particularly in the TDT group (82.4% of obese TDT patients were female) **(**Table 3**).**

Table 3
Clinical correlations of obesity in TDT versus NTDT

Variables		NTDT		TDT		X^2	P
		Non obese (n = 9) (n, %)	Obese (n = 10) (n, %)	Non obese (n = 73) (n, %)	Obese (n = 14) (n, %)		
Gender	Male	3 (33.3%)	2 (20%)	41 (58.6%)	3 (17.6%)	13.246	**0.004**
	Female	6 (66.7%)	8 (80%)	29 (41.4%)	14 (82.4%)		
Liver hemochromatosis	No	8 (88.9%)	6 (60%)	47 (67.1%)	13 (76.5%)	2.605	0.457
	Yes	1 (11.1%)	4 (40%)	23 (32.9%)	4 (23.5%)		
Cardiac hemochromatosis	No	9 (100%)	10(100%)	67(95.7%)	16 (94.1%)	1.004	0.8
	Yes	0	0	3 (4.3%)	1(5.9%)		
Complications	No	3 (33.3%)	3 (30%)	11 (15.7%)	3 (17.6%)	2.511	0.473
	Yes	6 (66.7%)	7 (70%)	59 (84.3%)	14 (82.4%)		
Cardiac complications	No	6 (66.7%)	8 (80%)	34 (48.6%)	6 (35.3%)	6.092	0.107
	Yes	3 (5.8%)	2 (20%)	36 (51.4%)	11 (64.7%)		
Cardiomyopathy	No	9 (100%)	8 (80%)	52 (74.3%)	11 (64.7%)	4.153	0.245
	Yes	0	2 (20%)	18 (25.7%)	6 (35.3%)		
Valvular affection	No	6 (66.7%)	9 (90%)	35 (50%)	6 (35.3%)	8.558	**0.036**
	Yes	3 (33.3%)	1 (10%)	35 (50%)	11 (64.7%)		
Hypertension	No	9 (100%)	10 (100%)	68 (97.1%)	16 (94.1%)	1.129	0.77
	Yes	0	0	2 (2.9%)	1 (5.9%)		
DM	No	9 (100%)	10 (100%)	68 (97.1%)	14 (82.4%)	7.803	0.05
	Yes	0	0	2 (2.9%)	3 (17.6%)		
Hepatomegaly	No	5 (55.6%)	5 (50%)	32 (45.7%)	4 (23.5%)	3.604	0.308
	Yes	4 (44.4%)	5 (50%)	38 (54.3%)	13 (76.5%)		
Chronic liver disease	No	7 (77.8%)	7 (70%)	26 (37.1%)	6 (35.3%)	8.781	**0.032**
	Yes	2 (22.2%)	3 (30%)	44 (62.9%)	11 (64.7%)		
Splenomegaly	No	4 (44.4%)	4 (40%)	2 (2.9%)	1 (5.9%)	25.292	**< 0.001**
	Yes	5 (55.6%)	6 (60%)	68 (97.1%)	16 (94.1%)		
Splenectomy	No	6 (66.7%)	4 (40%)	12 (17.1%)	8 (47.1%)	14.446	**0.002**
	Yes	3 (33.3%)	6 (60%)	58 (82.9%)	9 (52.9%)		
GB stones	No	7 (77.8%)	6 (60%)	43 (61.4%)	11 (64.7%)	0.977	0.807
	Yes	2 (22.2%)	4 (40%)	27 (38.6%)	6 (35.3%)		
Skin ulcers	No	9 (100%)	10 (100%)	64 (91.4%)	17 (100%)	3.271	0.352

*TDT: Transfusion dependent Thalassemia, NTDT: Non-Transfusion dependent Thalassemia, DM: Diabetes Miletus, HTN: Hypertension, GB: Gall Bladder, n: number, p: P-value, X^2: Value of Pearson Chi-Square test, bold value indicates significant p-value

	Yes	0	0	6 (8.6%)	0		
Pulmonary HTN	No	9 (100%)	10 (100%)	66 (94.3%)	17 (100%)	2.138	0.544
	Yes	0	0	4 (5.7%)	0		
Endocrinopathy	No	9 (100%)	10 (100%)	67 (95.7%)	14 (82.4%)	5.962	0.113
	Yes	0	0	3 (4.3%)	3 (17.6%)		
Osteoporosis	No	8 (88.9%)	10 (100%)	63 (90%)	16 (94.1%)	1.361	0.715
	Yes	1 (11.1%)	0	7 (10%)	1 (5.9%)		
Renal insufficiency	No	9 (100%)	10 (100%)	66 (94.3%)	15 (88.2%)	2.327	0.507
Gender	Yes	0	0	4 (5.7%)	2 (11.8%)		

*TDT: Transfusion dependent Thalassemia, NTDT: Non-Transfusion dependent Thalassemia, DM: Diabetes Miletus, HTN: Hypertension, GB: Gall Bladder, n: number, p: P-value, X^2: Value of Pearson Chi-Square test, bold value indicates significant p-value

Among cardiac complications, valvular affection was significantly associated with obesity (**p = 0.036**), with a higher proportion of valvular involvement among obese TDT patients (64.7% vs. 50% in non-obese TDT) **(**Table 3**).**

Chronic liver disease demonstrated a significant association (**p = 0.032**). In TDT, chronic liver disease was present in 64.7% of obese and 62.9% of non-obese patients, while in NTDT it was observed in 30% of obese and 22.2% of non-obese patients **(**Table 3**)**.

The significant associations observed for splenomegaly (**p < 0.001**) and splenectomy (**p = 0.002**) are likely driven by disease phenotype rather than obesity. Splenomegaly was nearly universal in TDT, irrespective of BMI (97.1% non-obese vs. 94.1% obese) compared with lower rates in NTDT (55.6% vs. 60%), reflecting the higher disease burden in TDT. Splenectomy was more frequent in non-obese TDT patients (82.9% vs. 52.9%), while in NTDT it was higher among obese patients (60% vs. 33.3%), possibly identifying a more severe NTDT subset. Overall, these findings appear related to disease severity and management history rather than a direct impact of obesity **(**Table 3**)**.

A borderline association was observed for DM (p = 0.05). DM was more frequent in obese TDT patients (17.6%) compared with non-obese TDT (2.9%), while no cases were reported among NTDT patients **(**Table 3**)**.

All other variables, including liver and cardiac hemochromatosis, hypertension, hepatomegaly, gallbladder stones, pulmonary hypertension, endocrinopathy, osteoporosis, renal insufficiency, overall complications, cardiomyopathy, and skin ulcers, were not significantly associated with obesity **(**Table 3**)**.

Comparison of laboratory parameters according to BMI demonstrated significant differences in several hematologic indices. Overweight/obese patients exhibited significantly higher total leucocytic count (TLC) counts (median 16.99 vs. 8.02 ×10⁹/L, **p = 0.0035**), absolute lymphocytic count (ALC) (8.7 vs. 2.98 ×10⁹/L, **p = 0.0018**), absolute monocytic count (AMC) (0.86 vs. 0.36 ×10⁹/L, **p = 0.024**), and NLR (1.25 vs. 0.70, **p = 0.0038**) compared with non-obese patients. Hemoglobin levels were modestly but significantly higher in the overweight/obese group (median 7.86 vs. 7.50 g/dL, **p = 0.043**) **(**Table 4**)**.

Table 4
Impact of Obesity on laboratory parameters of thalassemia patients

Values		Mean	SD	Median	Range	P-value*
TLC (×10⁶/μL)	Overweight/obese	28.83	27.90	16.99	3.08–157.80	**0.0035**
	Non-obese	13.37	13.10	8.02	4.48–65.50	
ANC (k/uL)	Overweight/obese	5.20	2.27	4.08	2.21–9.80	0.15
	Non-obese	6.67	4.09	5.58	0.005-21	
ALC (k/uL)	Overweight/obese	18.26	28.37	8.7	1.25–169.30	**0.0018**
	Non-obese	5.11	5.15	2.98	0.37–16.90	
AMC (k/uL)	Overweight/obese	1.18	1.17	0.86	0.05–6.87	**0.024**
	Non-obese	0.54	0.34	0.36	0.22–1.14	
HB (g/dl)	Overweight/obese	8.10	1.81	7.86	3.53–12.70	**0.043**
	Non-obese	7.46	1.49	7.50	3.71–11.40	
MCV (fL)	Overweight/obese	62.80	10.10	64.05	48-80.1	**0.0018**
	Non-obese	70.80	10.07	71.30	45.70-100.3	
MCH (pg)	Overweight/obese	19.51	3.29	20.05	11.78–25.30	**0.0021**
	Non-obese	22.23	3.83	22.4	13.3–32.6	
MCHC (g/dL)	Overweight/obese	31.16	3.08	31.35	22.75–37.20	0.87
	Non-obese	31.48	2.83	31.50	24.6–39.7	
RDW (%)	Overweight/obese	28.02	7.98	26.9	14.4–40.5	0.27
	Non-obese	25.83	7.64	24.2	12.55–46.10	
PLT (k/uL)	Overweight/obese	578.10	303.94	570	146.9–1071	0.44
	Non-obese	538.69	315.13	511	53.73–2126	
MPV (fl)	Overweight/obese	7.74	4.26	9.44	0.54–12.30	0.74
	Non-obese	9.03	3.32	9.58	0.93–20.26	
LMR	Overweight/obese	7.80	5.10	6.29	0.86–18.60	0.16
	Non-obese	21.21	42.04	8.11	1.26-236.68	
NLR	Overweight/obese	2.29	3.65	1.25	0.41–18.06	**0.0038**
	Non-obese	0.96	0.84	0.70	0.001–3.76	
AST (U/L)	Overweight/obese	67.69	57.57	48	22.9–249	0.72
	Non-obese	55.72	31.36	49	14–154	
ALT (U/L)	Overweight/obese	67.89	58.79	50.5	13.4–250	**0.018**
	Non-obese	46.56	68.23	30	5.87–582	

***** TLC: Total leucocytic count, ANC: Absolute neutrophilic count, ALC: Absolute lymphocytic count, AMC: Absolute monocytic count, HB: Hemoglobin, MCV; Mean corpuscular volume, MCH; Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, PLT: platelets, MPV; Mean platelet volume, LMR: lymphocyte-to-monocyte ratio, NLR: neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine Aminotransferase, ICT: Iron chelator, SD: Standard deviation, bold value indicates significant p-value

Values		Mean	SD	Median	Range	P-value*
Bilirubin (mg/dl)	Overweight/obese	2.20	0.95	2.08	0.68–4.80	0.23
	Non-obese	2.67	1.52	2.3	0.6–8.4	
Ferritin before ICT (ng/ml)	Overweight/obese	2149.78	1636.31	1574.5	334–5699	0.12
	Non-obese	2753.90	1834.89	2000	10.85–8108	
Ferritin 3-6m after ICT (ng/ml)	Overweight/obese	1699.46	1014.86	1538	395–4000	0.34
	Non-obese	2197.25	1523.23	1838	116.65–6811	
Ferritin after 1 year of ICT (ng/ml)	Overweight/obese	2197.92	1355.23	1853	516.4–4000	0.62
	Non-obese	2348.21	1469.36	1890	132–5667	

***** TLC: Total leucocytic count, ANC: Absolute neutrophilic count, ALC: Absolute lymphocytic count, AMC: Absolute monocytic count, HB: Hemoglobin, MCV; Mean corpuscular volume, MCH; Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, PLT: platelets, MPV; Mean platelet volume, LMR: lymphocyte-to-monocyte ratio, NLR: neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine Aminotransferase, ICT: Iron chelator, SD: Standard deviation, bold value indicates significant p-value

Red cell indices were significantly lower among overweight/obese patients, including mean corpuscular volume (MCV) (64.05 vs. 71.30 fL, **p = 0.0018**) and mean corpuscular hemoglobin (MCH) (20.05 vs. 22.4 pg, **p = 0.0021**), while mean corpuscular hemoglobin concentration (MCHC) and RDW did not differ significantly. Platelet count, MPV, lymphocyte-to-monocyte ratio (LMR), and Absolute neutrophilic count (ANC) were also comparable between groups **(**Table 4**)**.

Regarding liver function, alanine Aminotransferase (ALT) levels were significantly higher in overweight/obese patients (median 50.5 vs. 30 U/L, **p = 0.018**), whereas aspartate aminotransferase (AST) and total bilirubin showed no significant differences. Markers of iron overload, including baseline ferritin, ferritin at 3–6 months, and ferritin after one year of ICT, did not significantly differ between BMI categories. Overall, obesity was associated with a more pronounced inflammatory hematologic profile and higher ALT levels, without a measurable impact on iron burden **(**Table 4**)**.

Discussion

Thalassemia substantially impairs quality of life and imposes significant health and economic burdens. Multiple factors, including treatment requirements, disease-related complications, and social support, contribute to reduced health-related quality of life compared with the general population [14]. In this study, we evaluated the impact of modifiable risk factors, particularly smoking and obesity, on disease-related complications in patients with thalassemia.

Our cohort demonstrated a slight female predominance (52.8%), consistent with some reports [15], although the overall literature supports an approximately equal sex distribution without a clear gender predisposition [16]. TDT accounted for the majority of cases (81.5%), comparable to rates approaching 90% reported in tertiary care cohorts, reflecting the predominance of more severe disease phenotypes in tertiary care settings [17]. Despite the high regional disease burden, comprehensive epidemiological data on clinically significant β-thalassemia in the Middle East remain limited, underscoring the need for further large-scale population-based studies [18].

The overall complication rate was high, with 79.6% of patients experiencing at least one complication, comparable to previously reported rates ranging from approximately 80% to 86%, underscoring the multisystem burden of the disease, particularly with increasing age and transfusion exposure factors [19, 20].

Our findings demonstrate clear clinical and laboratory distinctions between TDT and NTDT, consistent with the established natural history of these disease subtypes. TDT patients demonstrated a markedly higher prevalence of systemic complications, particularly cardiac and hepatic morbidity, reflecting the cumulative effects of transfusion-related complications, including iron overload and infections such as HCV, in addition to prolonged disease duration. These findings align with prior reports indicating

that TDT patients are at significantly increased risk of cardiac and hepatic complications, forming the major contributors to morbidity and mortality in these patients [15, 21–23].

Although obesity prevalence was similar, the slightly higher BMI in NTDT may reflect lower transfusion burden and fewer iron overload–related endocrine complications compared with TDT, alongside emerging evidence of metabolic and inflammatory alterations in adult NTDT [21–24]. Even modest BMI differences may therefore carry clinical relevance in this subgroup.

Furthermore, the hematological indices differ between both subtypes. TDT patients exhibited more severe anemia and elevated bilirubin levels, reflecting increased hemolysis and ineffective erythropoiesis. Although RDW was elevated in both groups, it was significantly higher in TDT, consistent with prior reports[25, 26] suggesting that RDW mirrors the degree of hemolysis, inflammatory activity, and oxidative stress [27, 28], thereby serving as an indirect marker of disease severity. Whereas the higher NLR observed in NTDT patients may indicate persistent low-grade inflammation related to chronic hypoxia and ineffective erythropoiesis, which aligns with findings reported by some studies [29]. Nevertheless, the clinical and prognostic implications of these inflammatory and hematologic disparities remain insufficiently defined and warrant further prospective investigation on larger cohorts.

Although the impact of smoking in thalassemia has not been extensively investigated, available evidence suggests a plausible biological interaction that may exacerbate disease-related morbidity. Smoking is a well-established inducer of oxidative stress, endothelial dysfunction, and chronic inflammation, mechanisms that overlap with the pathophysiology of iron overload and hemolysis in thalassemia. Emerging studies have demonstrated that smokers with β-thalassemia exhibit altered hematologic indices and higher carboxyhemoglobin levels compared with non-smokers, reflecting amplified hypoxic and oxidative stress. Additional reports indicate that smoking can influence red cell parameters and inflammatory markers, potentially compounding ineffective erythropoiesis and vascular injury, which aligns with our findings [30–32].

The significantly higher prevalence of chronic liver disease among TDT smokers and passive smokers may reflect the combined hepatotoxic effects of iron overload, prior transfusion-related viral exposure, and tobacco-associated oxidative stress, which has been shown to accelerate hepatic fibrosis progression in chronic liver disorders, as reported by some studies [33, 34].

The borderline association observed with renal insufficiency in TDT smokers may indicate additive microvascular injury, given that both iron toxicity and smoking are recognized contributors to renal endothelial dysfunction, as reported by some studies [35, 36]. Notably, the absence of significant associations between smoking and several other complications suggests that disease-related mechanisms remain the dominant drivers of organ morbidity in thalassemia. Nevertheless, these findings highlight the suggested synergistic effect between transfusion-related iron toxicity, the inflammatory nature of thalassemia, and tobacco-induced vascular damage and the potential role of smoking as a modifiable risk factor that may exacerbate vascular and hepatic complications in TDT, warranting further prospective studies to clarify its independent prognostic impact.

Obesity may modulate the pathophysiology of thalassemia and other chronic anemias through complex inflammatory and metabolic mechanisms. Malnutrition has long been recognized as a common complication in thalassemia; historically, this has predominantly manifested as undernutrition. However, emerging evidence indicates a shifting nutritional profile, with a growing prevalence of overweight and obesity, particularly among adult transfusion-dependent patients. Contemporary studies highlight increased adiposity, reduced lean body mass, and a high burden of sarcopenic and truncal obesity in this population [10, 37]. Moreover, obesity in thalassemia has been linked to elevated inflammatory markers and a higher incidence of metabolic complications, including insulin resistance and diabetes mellitus, likely driven by chronic low-grade inflammation and adipokine imbalance [11, 12].

Emerging evidence indicates that obesity may potentiate hepatic injury in thalassemia through the development of metabolic dysfunction–associated steatotic liver disease (MASLD), thereby amplifying iron-mediated hepatotoxicity. In transfusion-dependent patients, the coexistence of excess adiposity and chronic iron overload creates a synergistic pathogenic milieu characterized by enhanced oxidative stress, insulin resistance, and pro-inflammatory signaling. This interaction has been associated with accelerated progression to hepatic fibrosis and cirrhosis, as well as heightened cardiometabolic risk [38–40]. Additionally, studies reported that obesity is associated with an increased risk of valvular heart disease, likely mediated through hemodynamic overload, metabolic dysregulation, and systemic inflammation, which affect cardiac structure and function and

consequently impair quality of life. This observation is consistent with our findings, where valvular involvement was more frequent among obese patients [41]. This pathophysiological interaction may, therefore, provide a biologically plausible explanation for the increased burden of chronic liver disease and cardiac complications identified among obese TDT patients in our cohort.

Furthermore, obesity has been shown in broader hematologic research to influence red cell indices and inflammatory parameters; chronic low-grade inflammation in obesity can alter iron metabolism via hepcidin upregulation, contributing to functional iron dysregulation and modified erythropoiesis, and this is reflected by the significant difference in MCV and MCH noticed in our cohort [42, 43]. In other anemia subtypes, including iron deficiency anemia and anemia of chronic inflammation, and in some malignancies, obesity has been linked to higher leukocyte counts, elevated neutrophil-to-lymphocyte ratio, and altered red cell indices, supporting the inflammatory hematologic profile observed in our overweight/obese patients, and these markers were associated with adverse outcomes in cardiovascular diseases, chronic kidney disease, and poorer prognosis in cancers and this is in concordant to the findings of our study [44–46]. However, direct large-scale mechanistic studies specifically examining obesity as an independent modifier of organ complications and iron overload in thalassemia remain limited. Collectively, available literature supports a biologically plausible association between obesity, inflammation, and altered hematologic parameters in chronic anemias, while underscoring the need for further targeted research in thalassemia populations.

Conclusion

In conclusion, thalassemia imposes a substantial multisystem burden, particularly among TDT patients. While transfusion dependency and iron overload remain major drivers of morbidity, modifiable factors such as smoking and obesity may contribute additional risk through inflammatory, metabolic, and vascular mechanisms. These findings highlight the importance of incorporating lifestyle risk assessment and preventive strategies into comprehensive thalassemia care, while larger prospective studies are needed to clarify their independent impact on long-term outcomes and quality of life.

Declarations

Ethics approval and consent to participate:

The study was approved by the Institutional Review Board (IRB) of Mansoura University (approval code: R.25.03.3119) and conducted in accordance with the Declaration of Helsinki (2008 revision). Written or verbal informed consent was obtained from all participants or their legal representatives prior to inclusion in the study.

Competing interests:

The authors have no financial or non-financial interests in the materials or subjects included in this study.

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Author Contribution

Author Contribution: L.J., K.A., H.H., J.A.L. , and E.J . contributed to the study design. L.J., K.A., H.H., and J.A.L . collected demographic, clinical, treatment, weight, and smoking data under supervision of E.J . E.J. reviewed and verified all clinical data. E.J . developed the statistical plan with input from L.J., K.A., H.H., and J.A.L ., performed the statistical analysis, and interpreted the results. E.J . drafted the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Data Availability

Clinical, laboratory, and radiological data were collected from the electronic health records of Mansoura University Hospitals (Ibn Sina Hospital management system), but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are, however, available upon request and with the permission from Mansoura University Faculty of Medicine.

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