Introduction
Beta-thalassemia is an inherited disorder caused by genetic mutations in genes encoding the β-globulin subunit of hemoglobin A (Hb A), which reduces or stops the expression of the β subunit. The impaired synthesis of the β chain causes the upregulation and accumulation of the α chain, leading to the destruction of erythroid precursors and ineffective erythropoiesis and hemolysis. The individuals with β-globulin gene mutations are categorized into minor thalassemia, thalassemia intermedia (TI), and thalassemia major (TM). TI and TM are homozygotes with two mutated beta-globin genes, but patients with TM reveal a more severe form of anemia compared to patients with TI (1). Currently, TM patients are successfully treated using frequent blood transfusion in conjunction with iron chelating drugs, hydroxyurea, and splenectomy. Therefore, the survival of TM patients has significantly improved, and most survive into adulthood (2). Consequently, chronic complications such as cardiovascular diseases (3) and metabolic disorders (4) are current challenges in the management of TM patients. Pulmonary hypertension (PH) is among the most prevalent cardiovascular disease complications in patients with TM and TI (5). PH is defined as mean pulmonary arterial pressure higher than 25 mmHg (through catheterization), along with several...
symptoms such as chest pain, weakness, dyspnea, and syncope. These symptoms can worsen over time and threaten the life of TM patients (6, 7).

Right heart catheterization (RHC) is the gold standard method for the diagnosis of PH (8). However, echocardiography (Echo) is usually applied for detecting PH because it is more available, cheaper, and non-invasive (9). PH is screened by tricuspid regurgitation jet velocity (TRV), and TRV ≥ 2.5 m/sec represents PH in thalassemia (10). Based on RHC findings, the prevalence of PH in TM patients ranges from 1.1% to 4.5%; however, Echo data have estimated the prevalence of 4.8-59% and 10-75% for TI and TM, which are higher than those estimated by RHC. The risk of PH is increased with several risk factors, including smoking, advanced age, the severity of hemolysis, splenectomy, iron overload, and thromboembolism.

The prevalence of beta-thalassemia carriers in Iran is significantly greater than the world average TM prevalence (11). Furthermore, the prevalence of beta-thalassemia carriers varies across Iran’s provinces double the country’s average rate in Hormozgan province (12). Concerning the high prevalence of TM, the present study sought to determine the frequency of PH among TM and TI patients in Hormozgan province. Further, the association of risk factors such as splenectomy, anemia, and advanced age with the presence of PH was evaluated as well.

Materials and Methods

Study Design and Participants

Eighty-nine patients, including 65 patients with TM and 24 patients with TI, were enrolled in this cross-sectional study. The patients were admitted to Shahid Mohammadi Hospital, Hormozgan Province, Iran during 2019-2020. The patients received blood transfusions every 3-4 weeks, and iron chelation therapy was performed with deferriprone and deferoxamine. Patients with any infection, congenital heart disease, renal failure, and arrhythmia and those receiving any therapy due to cardiac disease were excluded from the study.

Outcome Measurement

The demographic data were obtained, and mean serum ferritin levels during one year and the last Hb, and hematocrit before transfusion were measured using appropriate methods.

In all patients, the echocardiographic assessment was performed on the parasternal and apical 2 and 4-chamber views using a Vivid 3 machine (General Electric, USA). Left ventricular ejection fraction (LVEF) was estimated using the visual assessment and through the LV volume study. In addition, the tricuspid regurgitant jet velocity (TRV) was evaluated through a continuous Doppler study, and the patients were categorized into TRV ≥ 2.5 m/s and TRV < 2.5 m/s groups.

Statistical Analysis

All statistical analyses were performed using SPSS, version 16. Student t test or Mann-Whitney U test was employed to compare parametric and non-parametric variables between groups. Further, the χ² test was utilized to compare nominal data between groups. The data are shown as means ± standard deviations (SDs) and percentages for continuous and categorical variables, respectively, and a P value<0.05 was considered statistically significant.

Results

Eighty-nine beta-thalassemia patients were enrolled in this cross-sectional study. Their mean age was 27.54 ± 8.56 years (13-66 years), of which 30 patients were males (33.7%) and 59 (66.3%) were females. Sixty-five patients (73.0%) had TM and 24 (27.0%) had TI. The biochemical and echocardiographic parameters of the TM and TI patients are summarized in Table 1. The mean of HCT was significantly lower in TI patients compared to TM patients. No significant difference was observed in other parameters between the patients with TI and TM.

Comparison of the Patients According to Tricuspid Regurgitation Jet Velocity Values

Based on TRV values, the patients were categorized into two groups, including those with TRV < 2.5 m/s (n = 70) and TRV ≥ 2.5 m/s (n = 19) (Table 2). The frequency of TRV ≥ 2.5 in all patients was estimated at 21.3%, and only three (3.3%) of them had TRVs greater than 3.0 m/s. In the TM and TI groups, the frequencies of individuals with TRV ≥ 2.5 m/s were 21.5% and 20.8%, which was not significantly different. The biochemical characteristics and cardiac indices of patients with TRV < 2.5 m/s and TRV ≥ 2.5 m/s are presented in Table 2. No significant difference was detected in other parameters between the patients with TRV < 2.5 m/s and TRV ≥ 2.5 m/s.

Association of Tricuspid Regurgitation Jet Velocity ≥ 2.5 m/s With PH Risk Factors

Previous studies have suggested the role of several factors that predispose beta-thalassemia patients to PH. Therefore, the current study evaluated the association of TRV ≥ 2.5 m/s with possible risk factors, including age, gender, splenectomy, iron overload, and anemia. Out of 59 women patients, TRV ≥ 2.5 m/s was observed in nine patients (15.2%), and from 30 men, 10 patients (33.3%) had TRV ≥ 2.5 m/s, which was significantly higher compared to that of women (P = 0.047). When using logistical regression modeling, the male gender was significantly associated with TRV ≥ 2.5 m/s (Odds ratio: 3.07; 95% confidence interval: 1.03-9.14). Similarly, the frequency of TRV ≥ 2.5 m/s in men patients with
Table 1. Demographic, Laboratory, and Echocardiographic Parameters of the Patients With Beta-Thalassemia Major and Intermedia

<table>
<thead>
<tr>
<th>Variable</th>
<th>TI Patients (n = 24)</th>
<th>TM Patients (n = 65)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>Mean ± SD</td>
<td>Min.</td>
<td>Max.</td>
</tr>
<tr>
<td>30.6 ± 10.8</td>
<td>18</td>
<td>66</td>
<td>26.9 ± 7.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 ± 2.2</td>
<td>17.3</td>
<td>27.3</td>
</tr>
<tr>
<td>Ferritin (mg/mL)</td>
<td>5648 ± 5475</td>
<td>335</td>
<td>20288</td>
</tr>
<tr>
<td>SPAP (mm Hg)</td>
<td>24.7 ± 6.8</td>
<td>15.0</td>
<td>43.0</td>
</tr>
<tr>
<td>TRV (m/s)</td>
<td>2.25 ± 0.36</td>
<td>1.60</td>
<td>3.20</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.0 ± 5.5</td>
<td>55.0</td>
<td>71.0</td>
</tr>
<tr>
<td>E/e´ ratio</td>
<td>9.2 ± 1.5</td>
<td>5.8</td>
<td>12.4</td>
</tr>
<tr>
<td>EDV (mg/mL)</td>
<td>46.5 ± 7.3</td>
<td>35.0</td>
<td>65.8</td>
</tr>
<tr>
<td>Hb (mg/mL)</td>
<td>8.5 ± 0.9</td>
<td>6.3</td>
<td>10.0</td>
</tr>
<tr>
<td>HCT</td>
<td>26.4 ± 2.6</td>
<td>19.5</td>
<td>30.2</td>
</tr>
</tbody>
</table>

Note: SD: Standard deviation; Min.: Minimum; Max.: Maximum; BMI: Body mass index; SPAP: Systolic pulmonary artery pressure; TRV: Tricuspid regurgitation jet velocity; LVEF: Left ventricular ejection fraction; E: Early diastolic mitral inflow velocity; e´: Early diastolic mitral annulus velocity; EDV: End diastolic volume; Hb: Hemoglobin; HCT: Hematocrit.

Table 2. The Characteristics of Patients With TRV < 2.5 m/s and TRV ≥ 2.5 m/s

<table>
<thead>
<tr>
<th>Variable</th>
<th>TRV &lt; 2.5 m/s (n = 70)</th>
<th>TRV ≥ 2.5 m/s (n = 19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>26.4 ± 11.8</td>
<td>27.9 ± 7.5</td>
<td>0.505</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.9 ± 1.8</td>
<td>21.5 ± 2.1</td>
<td>0.210</td>
</tr>
<tr>
<td>Ferritin (mg/mL)</td>
<td>5636 ± 3709</td>
<td>6997 ± 4679</td>
<td>0.268</td>
</tr>
<tr>
<td>SPAP (mm Hg)</td>
<td>22.0 ± 3.8</td>
<td>30.6 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TRV (m/s)</td>
<td>2.0 ± 0.23</td>
<td>2.7 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.4 ± 6.3</td>
<td>60.8 ± 6.2</td>
<td>0.135</td>
</tr>
<tr>
<td>E/e´ ratio</td>
<td>9.0 ± 2.0</td>
<td>9.9 ± 2.7</td>
<td>0.112</td>
</tr>
<tr>
<td>EDV (mg/mL)</td>
<td>46.7 ± 8.1</td>
<td>45.5 ± 9.9</td>
<td>0.582</td>
</tr>
<tr>
<td>Hb (mg/mL)</td>
<td>8.8 ± 1.1</td>
<td>8.6 ± 0.9</td>
<td>0.366</td>
</tr>
<tr>
<td>HCT</td>
<td>27.5 ± 3.1</td>
<td>26.6 ± 2.9</td>
<td>0.269</td>
</tr>
<tr>
<td>Have performed</td>
<td>21 (30%)</td>
<td>5 (26.3%)</td>
<td>0.565</td>
</tr>
</tbody>
</table>

Note: SD: Standard deviation; BMI: Body mass index; SPAP: Systolic pulmonary artery pressure; TRV: Tricuspid regurgitation jet velocity; LVEF: Left ventricular ejection fraction; E: Early diastolic mitral inflow velocity; e´: Early diastolic mitral annulus velocity; EDV: End diastolic volume; Hb: Hemoglobin; HCT: Hematocrit.

TM (36.3%) was significantly higher (P=0.038) than that of women (13.9%). However, in patients with TI, the frequency of TRV ≥ 2.5 m/s in men (25.0%) was not significantly different compared to that of women (18.7%). Likewise, the mean age in patients with TRV ≥ 2.5 was not significantly different compared to patients with TRV < 2.5 m/s (Table 2). Furthermore, the frequency of TRV ≥ 2.5 m/s did not significantly differ between the adults (age ≥ 18 years) and children (age 13-17) with thalassemia. Finally, the serum ferritin level, Hb, hematocrit, and splenectomy were not significantly associated with TRV ≥ 2.5 m/s.

**Discussion**

A TRV value ≥2.5 m/s, measured by Doppler Echo, is suggested as a predictive marker of PH in transfusion-dependent beta-thalassemia patients (9). In this study, this criterion was used to determine the prevalence of PH and possible associated risk factors in a population of TM and TI patients from Hormozgan province, Iran. Our findings revealed a TRV ≥ 2.5 m/s in 21.3% of beta thalassemic patients enrolled in the present study, which is closely related to those reported by some previous studies (13, 14). A higher prevalence of TRV ≥ 2.5 m/s has been reported in other populations (15, 16). However, some studies reported a lower prevalence of PH in beta thalassemic patients (17-20). PH is a complex disorder that develops as a consequence of multiple pathogenic mechanisms, including iron overload, chronic hemolysis, splenectomy, and hypercoagulability. Thus, differences in the prevalence of PH among different populations may be due to variations in the contribution of these risk factors in various populations (21, 22). Furthermore, this discrepancy may be due to the use of different methods for the diagnosis of PH (i.e., heart catheterization vs, echocardiogram). In addition, the lower prevalence of PH in some studies can be due to better care of thalassemia patients who participated in those studies (23).

Prior studies have documented a higher prevalence of PH among patients with TI compared to TM (17, 24). Regular and more frequent transfusion in patients with TM has been suggested to be the main contributor to this issue (25). Nevertheless, our findings represented an equal prevalence of TRV ≥ 2.5 in TI (20.8%) and TM (21.5%) patients. No significant difference was observed in the various characteristics of TI and TM patients in our study (Table 1). A high prevalence of PH was observed among TM patients with poor control of the disease, while some studies revealed the absence of PH among well-controlled TM patients (26, 27). It appears that timely and adequate transfusion and chelating therapy can delay the development of PH. Based on the level of
Hb and ferritin level, the management of both TI and TM patients in the current study was less than optimal. Therefore, the same prevalence of PH among patients with TI and TM may be described by the same severity of risk factors of PH in both groups. A smaller sample size of TI patients, compared to TM patients, can be another reason for this finding.

It is expected that children with TM exhibit a lower prevalence of TRV due to the shorter duration of the disease and lesser cardiac damage. However, the findings of the present study showed abnormal TRV in both children and adults, and 44.4% of children (age < 18 years) had TRV ≥ 2.5, and children as young as 13 years old were affected, which is consistent with the results of previous research (28,29). Moreover, El-Beshlawy et al demonstrated a high prevalence of PH (37.5%) among children with TM (30). Although the low number of children in our study hinders us to interpret the results, these findings indicate that PH can develop even in young patients with thalassemia.

Some studies indicated that the female gender is a risk factor for the development of PH (31,32). However, other investigations failed to find any association between gender and PH in patients suffering from beta-thalassemia. The results of the current study demonstrated a higher frequency of TRV ≥ 2.5 in men patients (33.33%) compared to women (15.2%), which is in line with the results of previous studies (14, 24). Logistic regression analysis revealed a higher chance of PH development (3.07 times) in men patients with thalassemia compared to women. A higher but not significant value of serum ferritin was observed in male patients compared to women. No significant difference was observed between the frequency and severity of other risk factors, including values of Hb, HCT, age, and frequency of splenectomy among the male and female subjects enrolled in the present study. Thus, a lower control of the disease may underline the higher prevalence of TRV ≥ 2.5 m/s in men compared to women.

Previous studies confirmed the role of splenectomy (33) and higher serum ferritin levels in an increased risk of PH. However, our data showed a higher but not significant frequency of TRV ≥ 2.5 m/s among patients with and without splenectomy. Furthermore, a higher but no statistically significant level of serum ferritin was detected in patients with TRV ≥ 2.5 m/s, which conforms to the results of some other studies (14, 28). Although the reasons for discrepancies between the results of studies are unclear, the difference in the number of patients and methods for the diagnosis of PH may involve in this issue.

The main limitation of the current study was the use of TRV ≥ 2.5 m/s for screening the subjects at higher risk of PH risk without measuring the exact values of SPAP using RHC—the gold standard in the diagnosis of PH.

**Conclusion**

The results of our study revealed that PH is prevalent in both pediatric and adult patients affected by TM and TI within our population. This should be taken into account when deciding how to treat patients with TM and TI.

**Authors’ Contribution**

**Conceptualization:** Marzieh Nikparvar, Sedighe Pirdadi, Atefeh Ghareghani, Shideh Rafati.

**Formal analysis:** Sedighe Pirdadi, Atefeh Ghareghani, Shideh Rafati.

**Investigation:** Sedighe Pirdadi, Atefeh Ghareghani, Shideh Rafati, Mohammad Hamed Ersi, Hanie Bagheri.

**Project administration:** Marzieh Nikparvar.

**Supervision:** Marzieh Nikparvar.

**Writing–original draft:** Sedighe Pirdadi, Atefeh Ghareghani, Shideh Rafati.

**Writing–review & editing:** Mohammad Hamed Ersi, Hanie Bagheri.

**Competing Interests**

The authors declare that they have no conflict of interests.

**Ethical Approval**

This study was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1397.153) and informed consent was obtained from the patients or their legal guardians.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**References**


9. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of
Thalassemia and pulmonary hypertension


