OBJECTIVE
To evaluate the association between iron overload and serious morbidities through longitudinal follow-up of patients with 

β-thalassemia intermedia.

METHODS
• Retrospective cohort study of β-thalassemia intermedia patients attending five comprehensive care centers in Lebanon, Oman, Iran and Egypt.
• All patients attending the centers on 1 January 2000 were followed until 31 December 2009, death, or loss to follow-up.
• Data were retrieved for the occurrence of nine pre-defined serious morbidities, both as part of the patients’ history prior to inclusion as well as during the 10-year follow-up period.
• As part of standard management in participating centers, some of the morbidities are often assessed on an annual basis except for certain complications for which assessment is only indicated if patients present with relevant symptoms.
• Patient’s records were also reviewed for detailed data on spleenectomy, use of hydroxyurea, blood transfusions, and iron chelation therapy, both as part of the patients’ history prior to inclusion as well as during the 10-year follow-up period.

RESULTS
• All 52 patients were followed-up for 10 years or until death, and on the average, the follow-up was 9.0 ± 1.1 years (range: 6.6-11.4 years).
• The mean age of patients at study entry was 24.2 ± 11.3 years (median: 24.7, interquartile range [IQR]: 10.4-38.4 years, min: 0.6, max: 53.6 years). Of 52 patients, 31 (60.4%) patients were females and 21 (40.4%) patients were males. Thirty (57.7%) patients were splenectomized prior to study entry (i.e., throughout the follow-up period) and all patients had never received blood transfusion or iron chelation therapy until their last follow-up.
• Thirty-six patients (69.2%) experienced at least one serious morbid ty during the follow-up period. Of the total, 19 (36.5%) had a single morbid ty while 17 (32.7%) had multiple morbidities.
• The most common morbidity was osteoporosis (46.2%) followed by extramedullary hematopoeis (19.2%), liver disease (biopsy-confirmed fibrosis, cirrhosis, or cancer; 17.3%), hypothyroidism (9.6%), diabetes mellitus (7.7%), hypoparathyroidism (7.7%), bronchitis (6.9%), pulmonary hypertension (3.9%), and hyperprolactinemia (1.9%).

CONCLUSIONS
• On bivariate logistic regression analysis, older age at study entry was significantly associated with a higher probability of developing a morbidity (p<0.001) as well as multiple morbidities (p<0.03) over the 10-year follow-up period (Figure 1).
• On multivariate logistic regression analysis, the association between SF-Index and the development of morbidity remained significant after adjustment for potential confounders: age at study entry, sex, splectomy status and Hb-Index (p<0.01).
• There was a statistically significant correlation between age at study entry and SF-Index (Spearman’s correlation coefficient: 0.405, p<0.001).
• Both the mean and median SF-index values were significantly higher in patients who developed a morbidity compared with those who did not (p<0.001). Figure 2.
• On bivariate logistic regression analysis, higher SF-index values were significantly associated with a higher probability of developing a morbidity (p<0.001) or multiple morbidities (p<0.001) over the 10-year follow-up period (Figure 3).
• On receiver operating characteristic curve analysis (Figure 4), the SF-Index value of 266.8 ng/mL was the lowest threshold after which all patients had at least one morbidity (i.e., 100% specificity).
• On multivariate logistic regression model, other factors significantly associated with morbidity in β-thalassemia intermedia patients were sex (p<0.001), duration of morbidty (p<0.001), liver disease (p<0.001), and hypothyroidism (p<0.001).
• Moreover, in a separate multivariate logistic regression model the association between advanced age at study entry and higher probability of developing morbidity was no longer observed after adjustment for SF-Index (p=0.243) indicating that the observed effect of advanced age on morbidity development is mediated by increased iron levels.

REFERENCES

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This study was funded by Novartis Pharma AG.