

Behandlung der Eisenüberladung bei nicht-transfusionsabhängigen Thalassämien und anderen

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Hämatologie Heute 20. April 2013



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Was sind eigentlich „Iron loading anemias“

- Kongenitale dyserythropoetische Anämien (CDA)
- Pyruvatkinasemangel
- Nicht-transfusionsabhängige Thalassämien (NTDT):

β-Thalassämie intermedia (β-TI)

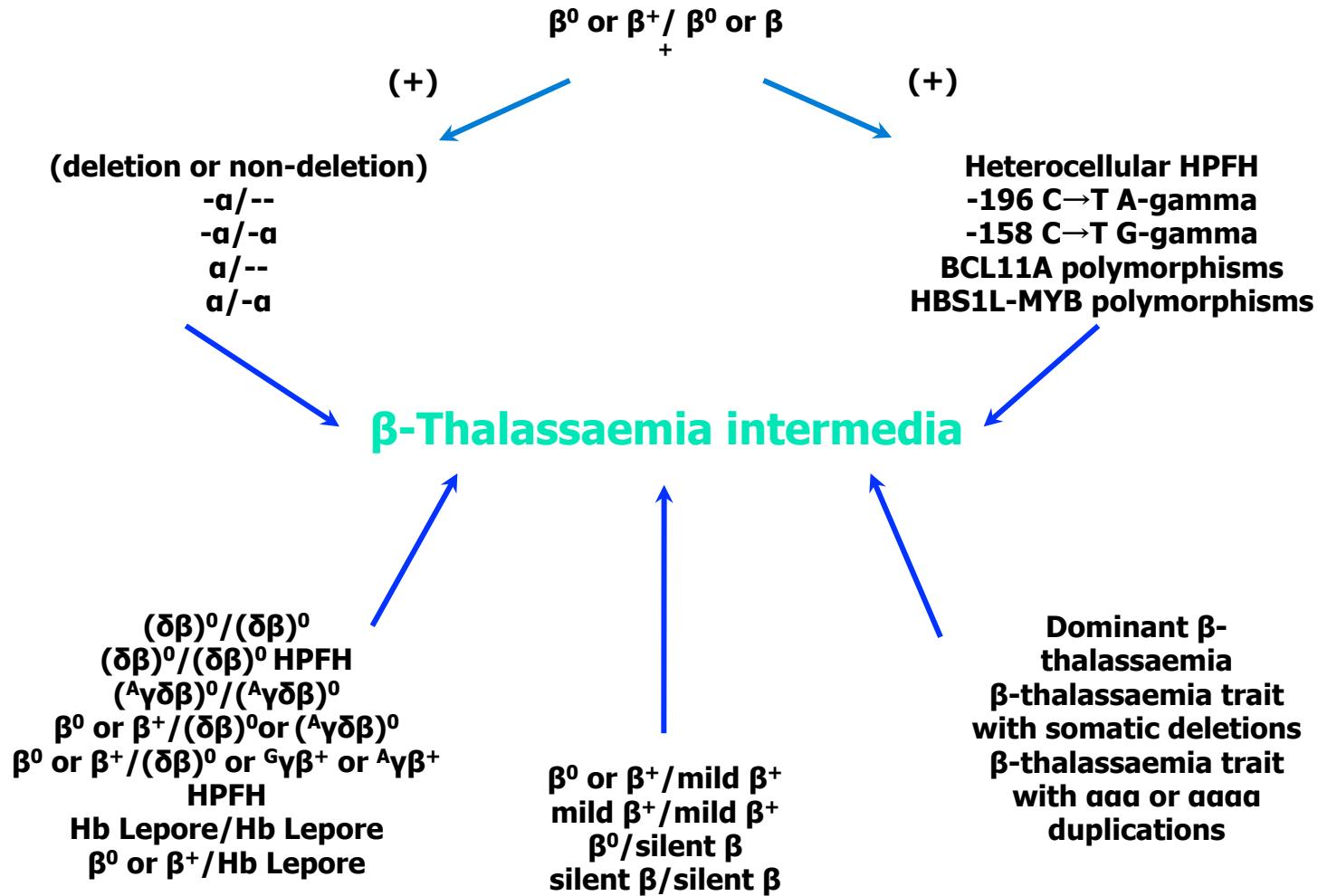
Hämoglobin E (HbE)/β-Thalassämie (β-TM)

Hämoglobin H (HbH) Erkrankung

Hämoglobin S (HbS)/β-Thalassämie

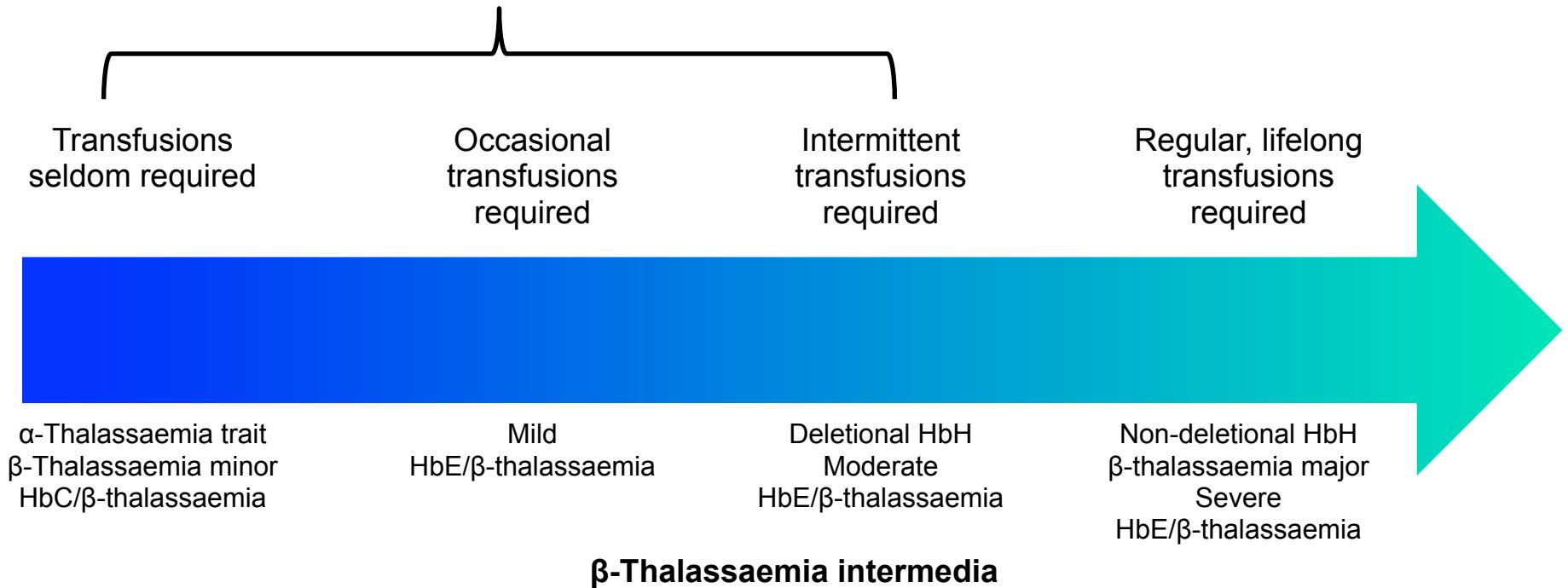
Hämoglobin C (HbC)/Thalassämie

Molekulare Formen einer Hb-Mutation, die zu einer β -TI führen kann



Krankheitsspektrum Thalassämien

Non-transfusion-dependent thalassaemias



Cohen AR, et al. Hematology Am Soc Hematol Educ Program. 2004;14-34. Galanello R, Origa R. Orphanet J Rare Dis. 2010;5:11. Harteveld C, Higgs D. Orphanet J Rare Dis. 2010;5:13. Muncie HL, Campbell JS. Am Fam Physician. 2009;80:339-44.

Nicht-transfusionsabhängige Thalassämien (NTDT)



Thalassämien, die nicht regelmäßig Bluttransfusionen für das Überleben benötigen. Gegebenenfalls Transfusionen bei klinischen Komplikationen oder bei Progress der Erkrankung

Unterschied TI zu TM

| | β-TM more likely | β-TI more likely |
|----------------------------------|--|--|
| Clinical | | |
| Presentation (years) | < 2 | > 2 |
| Haemoglobin (Hb) levels (g/dL) | 6–7 | 8–10 |
| Liver/spleen enlargement | Severe | Moderate to severe |
| Haematological | | |
| HbF (%) | > 50 | 10–50 (may be up to 100%) |
| HbA ₂ (%) | < 4 | > 4 |
| Genetic | | |
| Parents | Both carriers of high HbA ₂ β-thalassaemia | 1 or both atypical carriers <ul style="list-style-type: none"> ● High HbF β-thalassaemia ● Borderline HbA₂ |
| Molecular | | |
| Type of mutation | Severe | Mild/silent |
| Co-inheritance of α-thalassaemia | No | Yes |
| Hereditary persistence of | | |
| HbF | No | Yes |
| δβ-thalassaemia | No | Yes |
| Gy XMN1 polymorphism | No | Yes |

OPTIMAL CARE Study

| Parameter | Frequency n (%) | Treatment | Frequency n (%) |
|-------------------------|-------------------------|----------------------------|--------------------|
| Age (years) | | | |
| < 18 | 172 (29.5) | Hydroxyurea | 202 (34.6) |
| 18–35 | 288 (49.3) | Transfusion | |
| > 35 | 124 (21.2) | Never | 139 (23.8) |
| Male:female | 291 (49.8) : 293 (50.2) | Occasional | 143 (24.5) |
| Splenectomized | 325 (55.7) | Regular | 302 (51.7) |
| Serum ferritin (µg/L) | | Iron chelation | |
| < 1,000 | 376 (64.4) | None | 248 (42.5) |
| 1,000–2,500 | 179 (30.6) | Deferoxamine | 300 (51.4) |
| > 2,500 | 29 (5) | Deferiprone | 12 (2.1) |
| Complications | | Deferiprone + deferoxamine | 3 (0.5) |
| Osteoporosis | 134 (22.9) | Deferasirox | 21 (3.6) |
| EMH | 124 (21.2) | | |
| Hypogonadism | 101 (17.3) | | |
| Cholelithiasis | 100 (17.1) | | |
| Thrombosis | 82 (14) | | |
| Pulmonary hypertension | 64 (11) | | |
| Abnormal liver function | 57 (9.8) | | |
| Leg ulcers | 46 (7.9) | | |
| Hypothyroidism | 33 (5.7) | | |
| Heart failure | 25 (4.3) | | |
| Diabetes mellitus | 10 (1.7) | | |

EMH = extramedullary haemopoiesis.

Taher AT, et al. Blood. 2010;115:1886-92.

OPTIMAL CARE Study

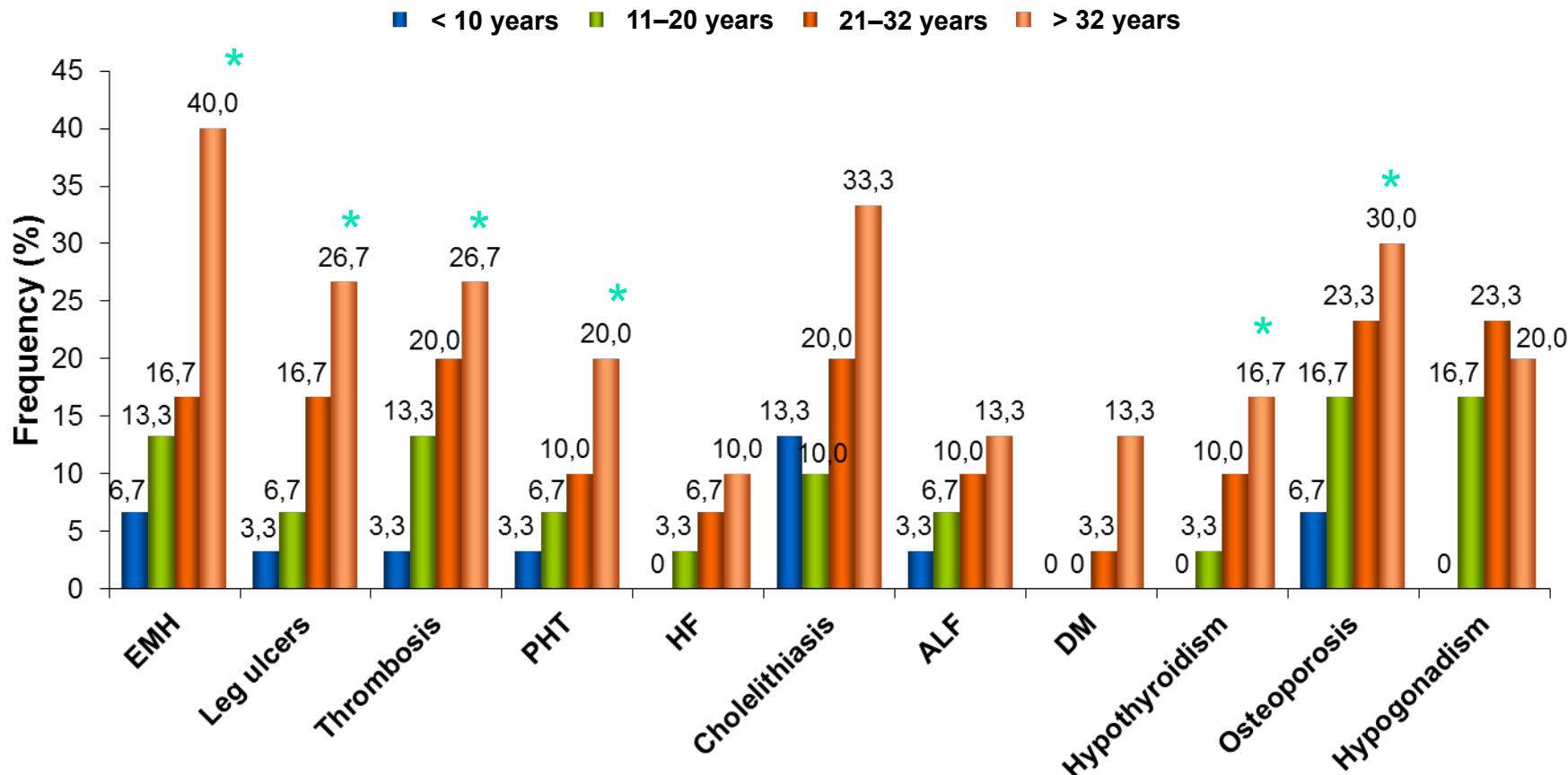
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Komplikationen bei TI-Patienten im Altersverlauf

Complications in 120 treatment-naive patients with TI

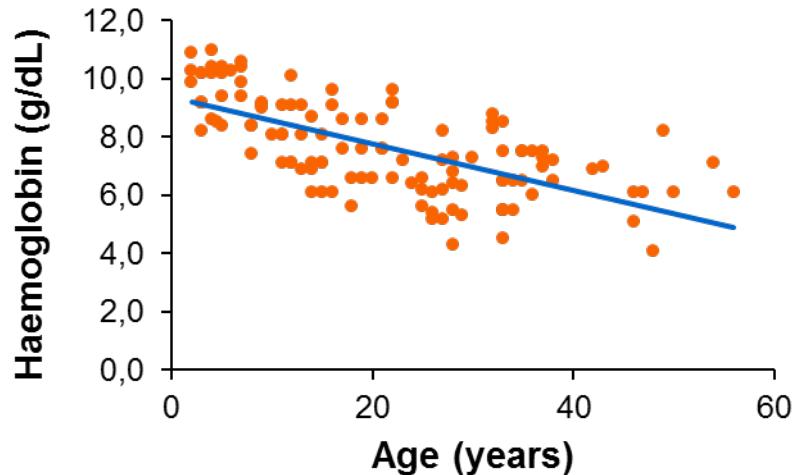


* = statistically significant trend.

ALF = abnormal liver function; DM = diabetes mellitus;
HF = heart failure; PHT = pulmonary hypertension.

Taher A, et al. Br J Haematol. 2010;150:486-9.

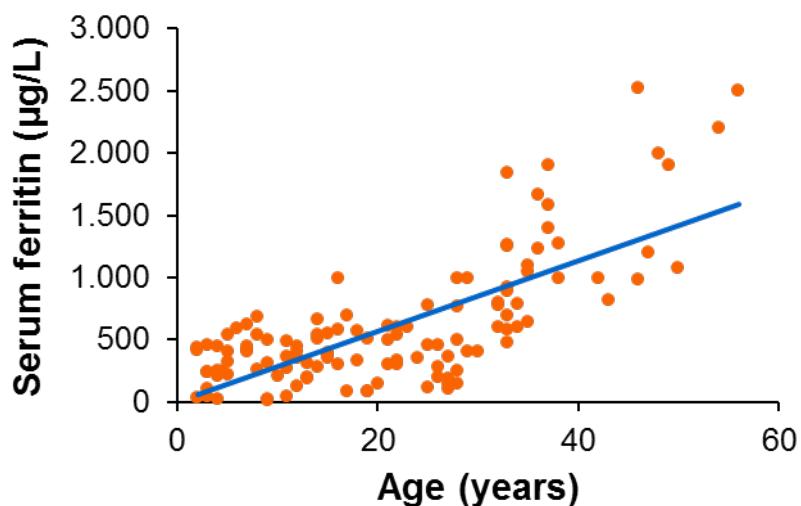
OPTIMAL CARE: sFerritin bei nichtbehandelten TI-Patienten steigt im Alter



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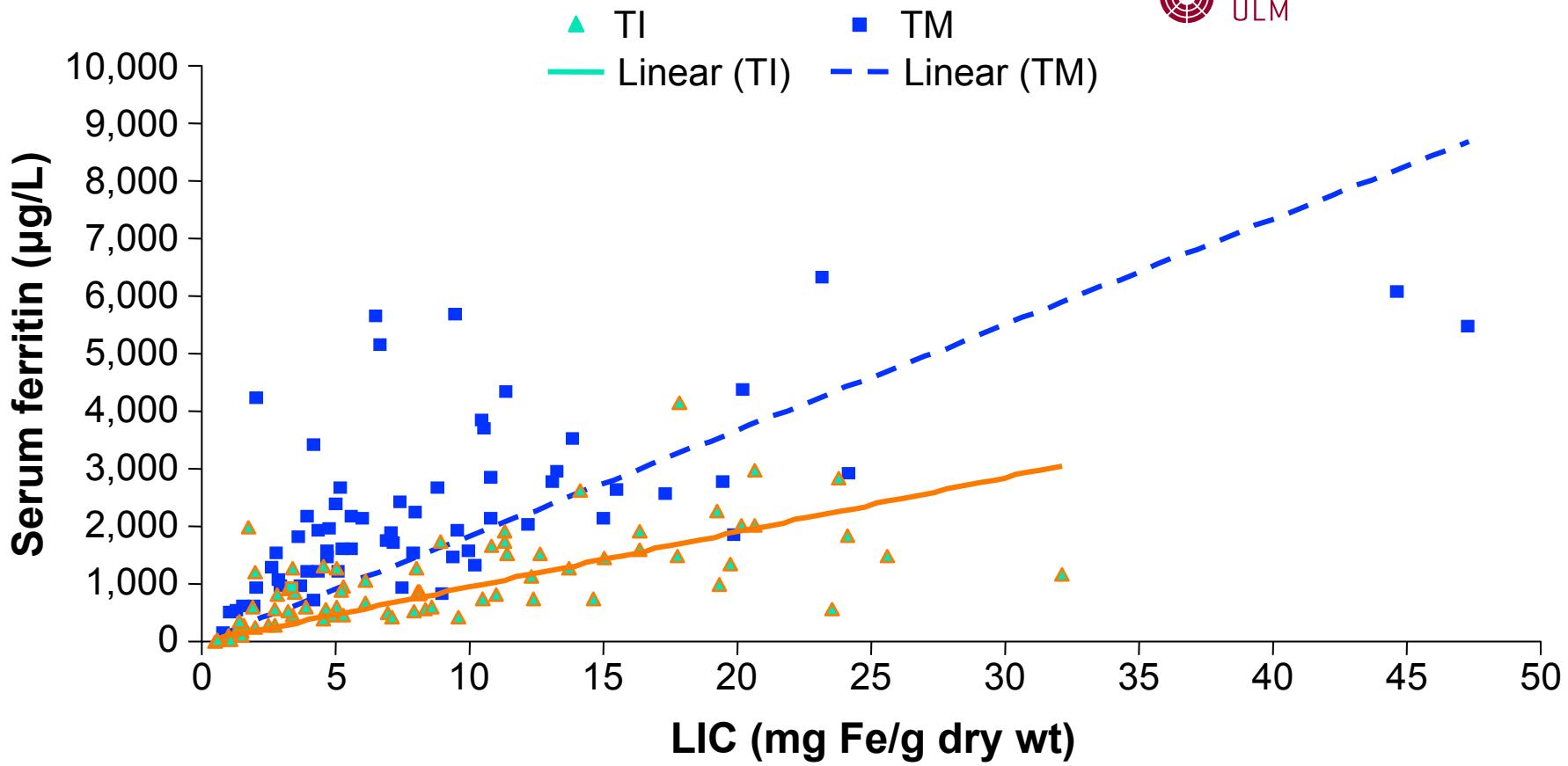
(n = 120)

Age vs haemoglobin level
($r = -0.679$; $p < 0.001$)



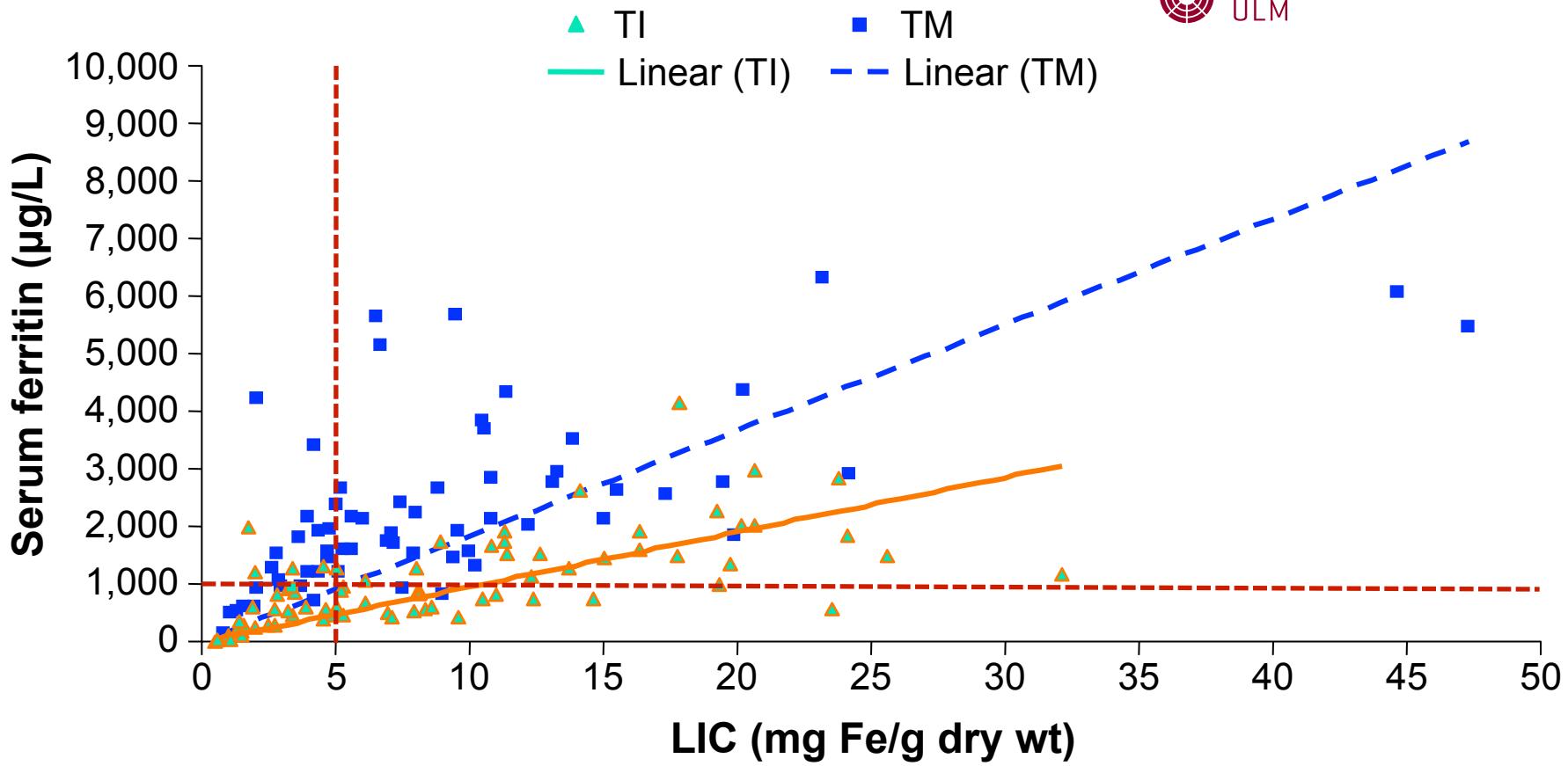
Age vs serum ferritin level
($r = 0.653$; $p < 0.001$)

Eisenüberladung (LIC) bei TI und TM Patienten



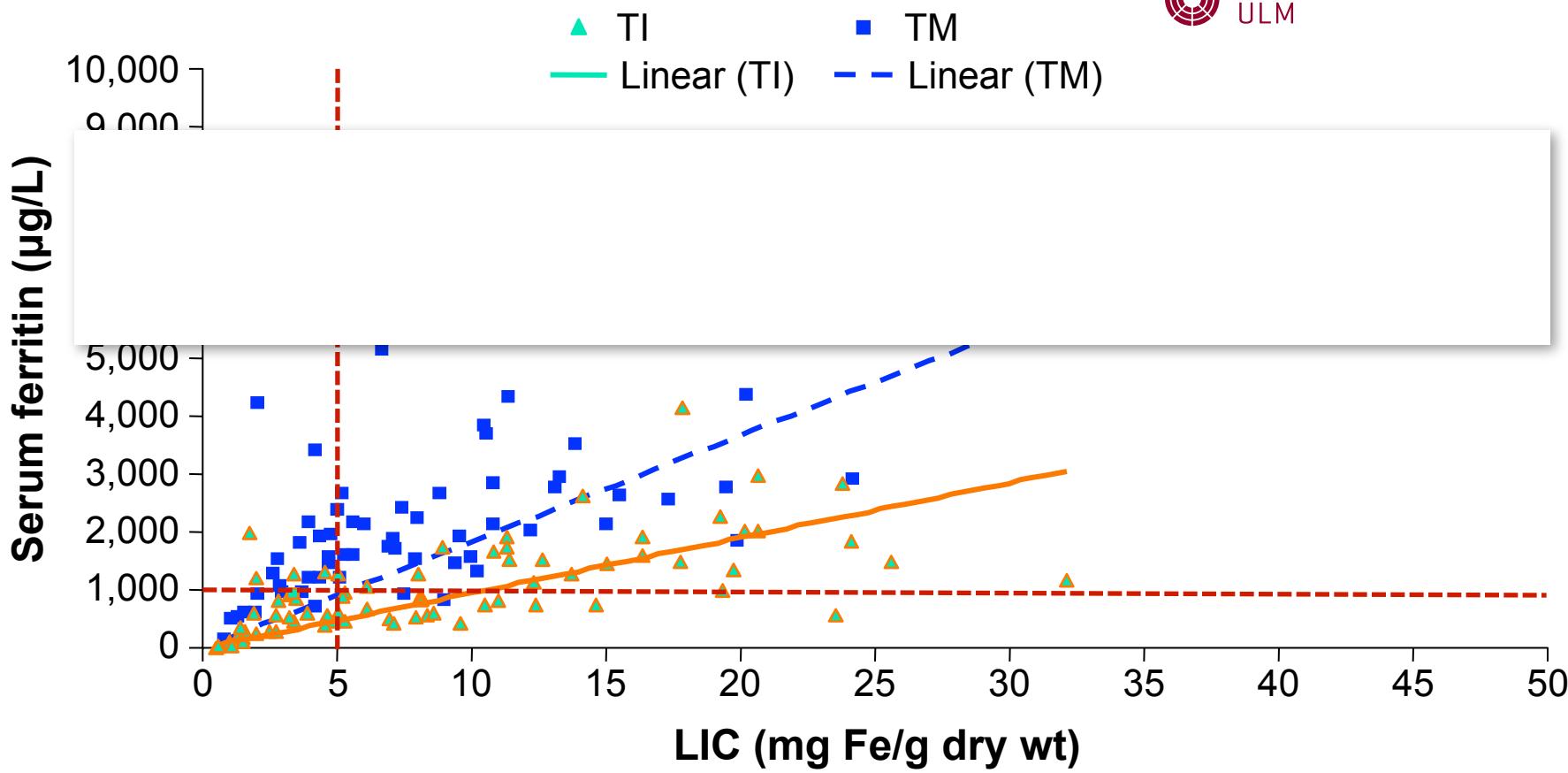
LIC korreliert mit sFerritin in Patienten mit TI ($R = 0.64$; $p < 0.001$)

Eisenüberladung (LIC) bei TI und TM Patienten



LIC korreliert mit sFerritin in Patienten mit TI ($R = 0.64$; $p < 0.001$)

Eisenüberladung (LIC) bei TI und TM Patienten



LIC korreliert mit sFerritin in Patienten mit TI ($R = 0.64$; $p < 0.001$)

Kardiale Eisenüberladung bei TI Patienten

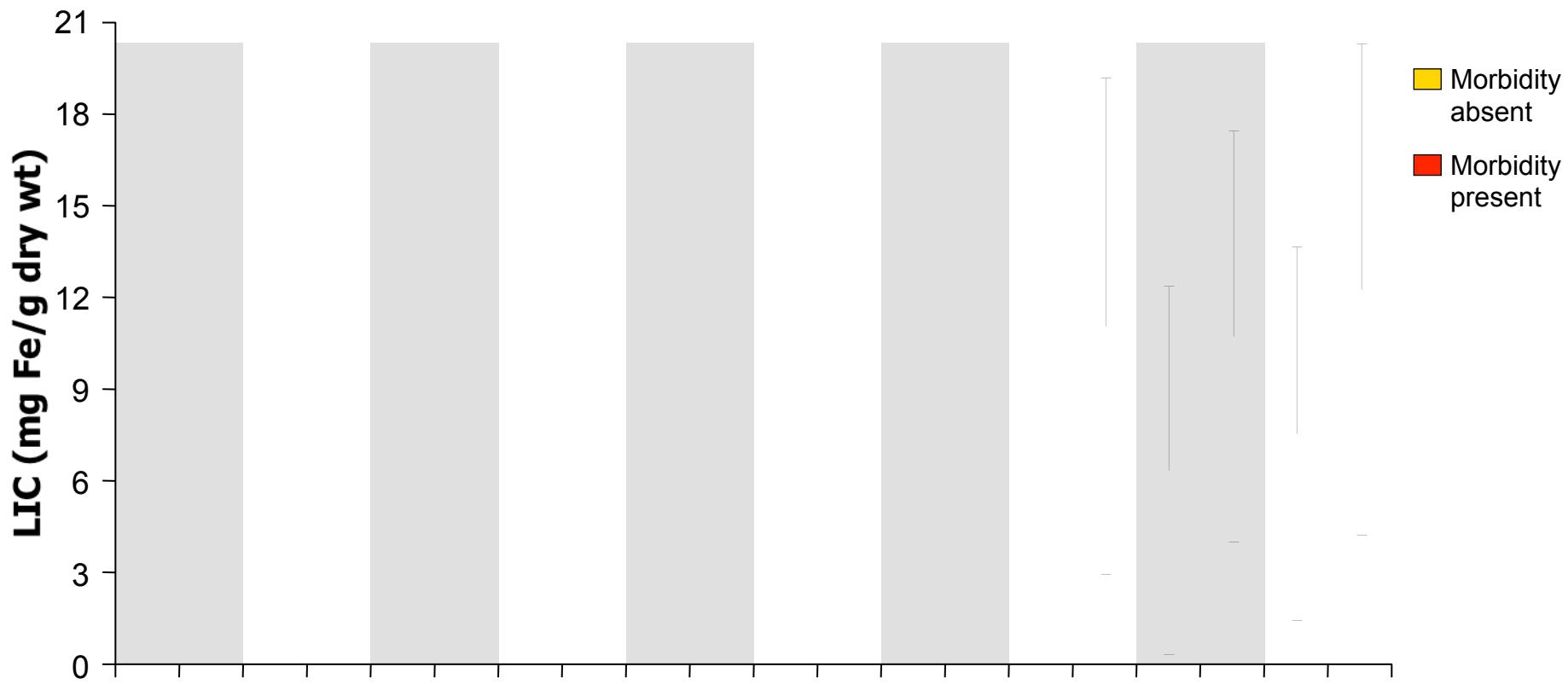
| Parameter | TI (n = 19) | TM (n = 19) | p value |
|--|---------------------------|-------------------------------|---------|
| Mean SF ± SD, µg/L (range) | 1,317 ± 652 (460–3157) | 3,724 ± 2,569 (827–10,214) | 0.001 |
| Mean LIC ± SD, mg Fe/g dry wt (range) | 15.0 ± 7.4 (3.4–32.1) | 15.7 ± 9.9 (1.7–32.6) | 0.095 |
| Mean cardiac T2* ± SD, ms (range) | 47.3 ± 7.1 (35.0–66.9) | 21.5 ± 15.2 (5.1–50.7) | < 0.001 |

Kardiale Eisenüberladung bei TI Patienten

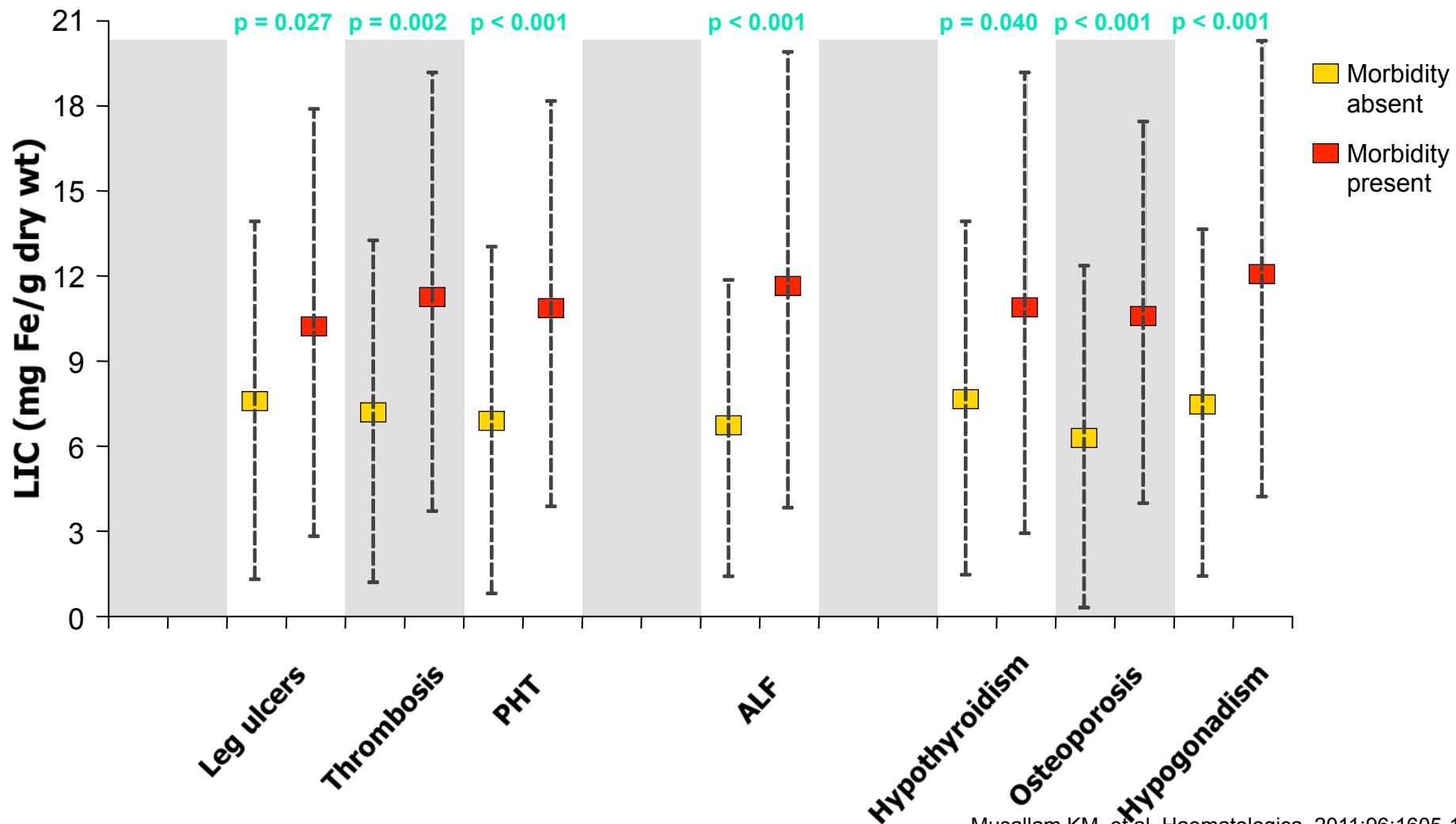
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Auch bei vergleichbarem LIC von TI und TM Patienten scheinen
TI Patienten keine kardiale Siderose zu entwickeln.

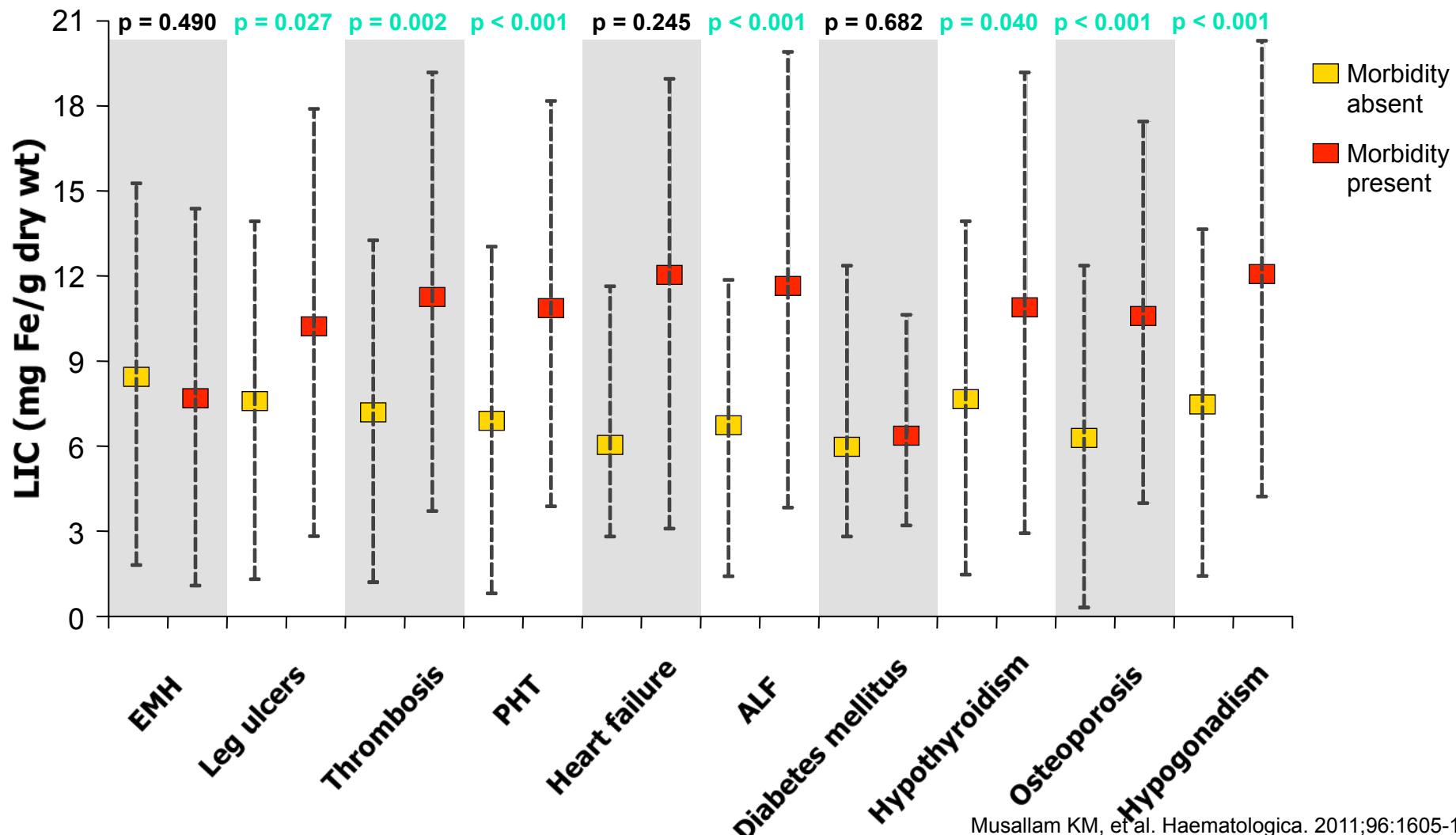
Einfluß von LIC auf die Morbidität von TI-Patienten



Einfluß von LIC auf die Morbidität von TI-Patienten



Einfluß von LIC auf die Morbidität von TI-Patienten



Wie entsteht Eisenüberladung bei TI?

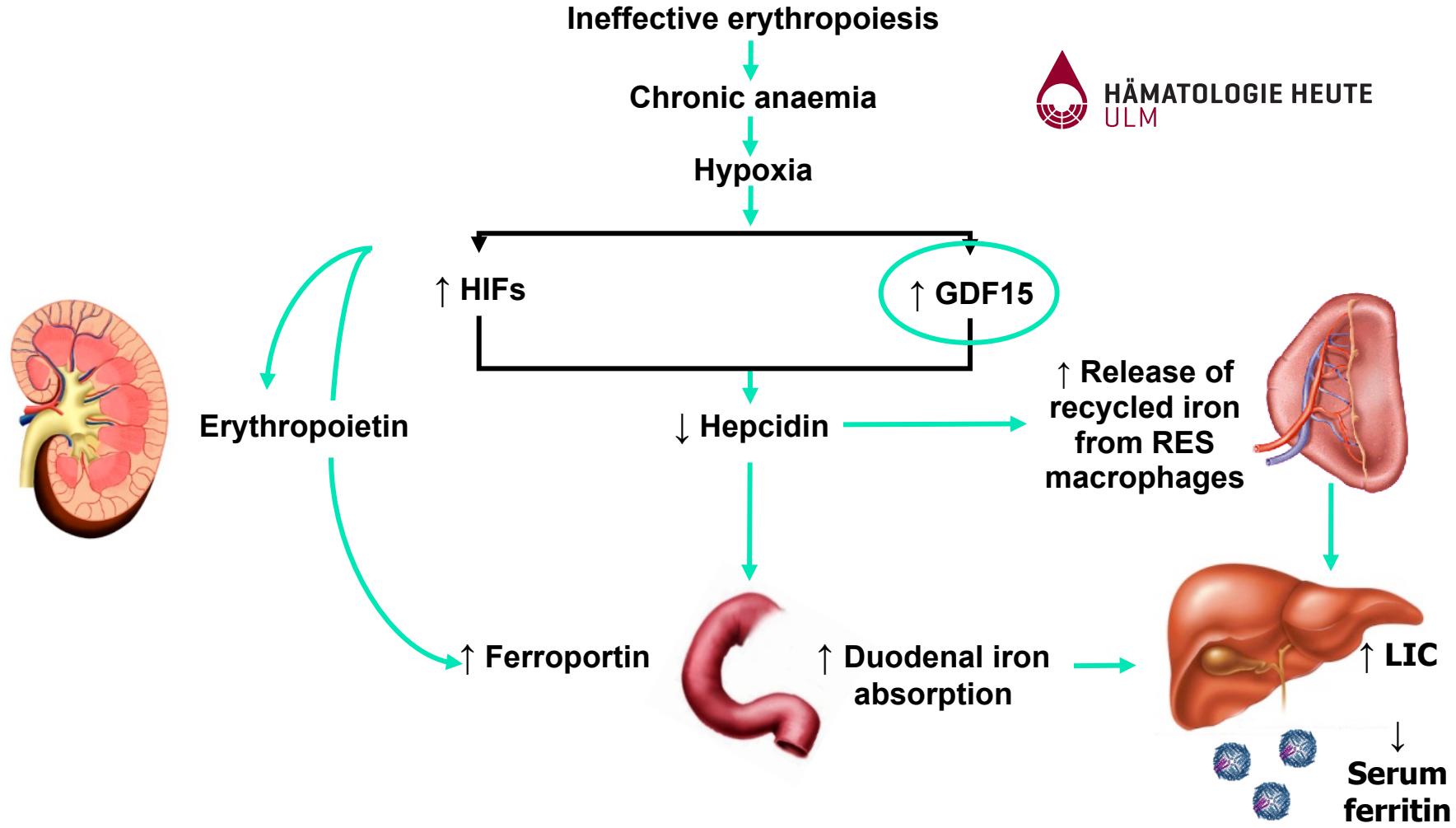


β-TI Patienten haben eine erhöhte gastrointestinale Absorption von Eisen aufgrund der ineffektiven Erythropoese^{1,2}

β-TI Patienten mit Eisenüberladung können aufgrund der Anämie nicht phlebotomiert werden.

1. Pippard M, et al. Lancet. 1979;2:819-21. 2. Pootrakul P, et al. Birth Defects Orig Artic Ser. 1988;23(5B):3-8.

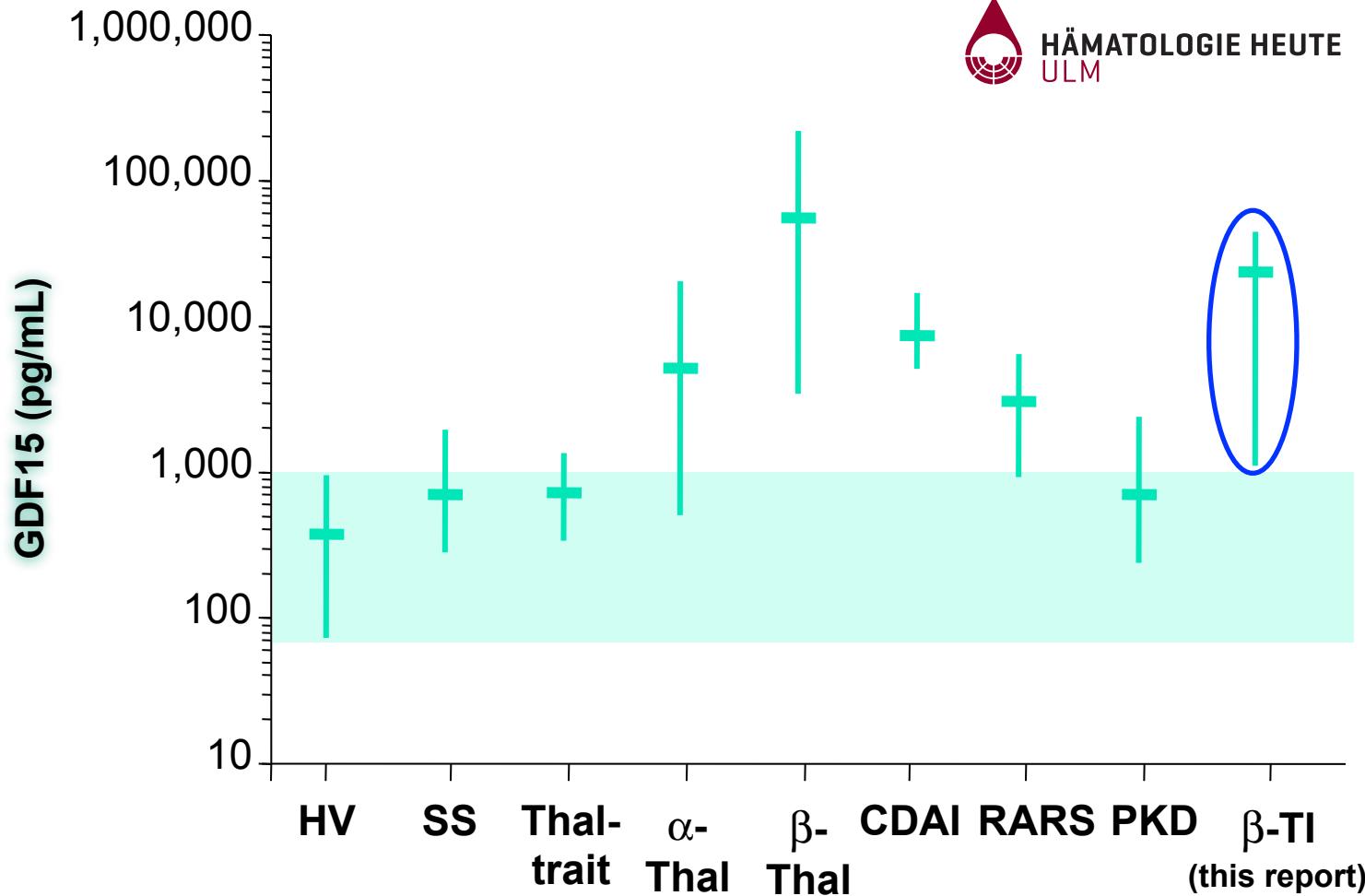
Pathophysiologie der Eisenüberladung bei nicht trasfundierten Patienten mit TI



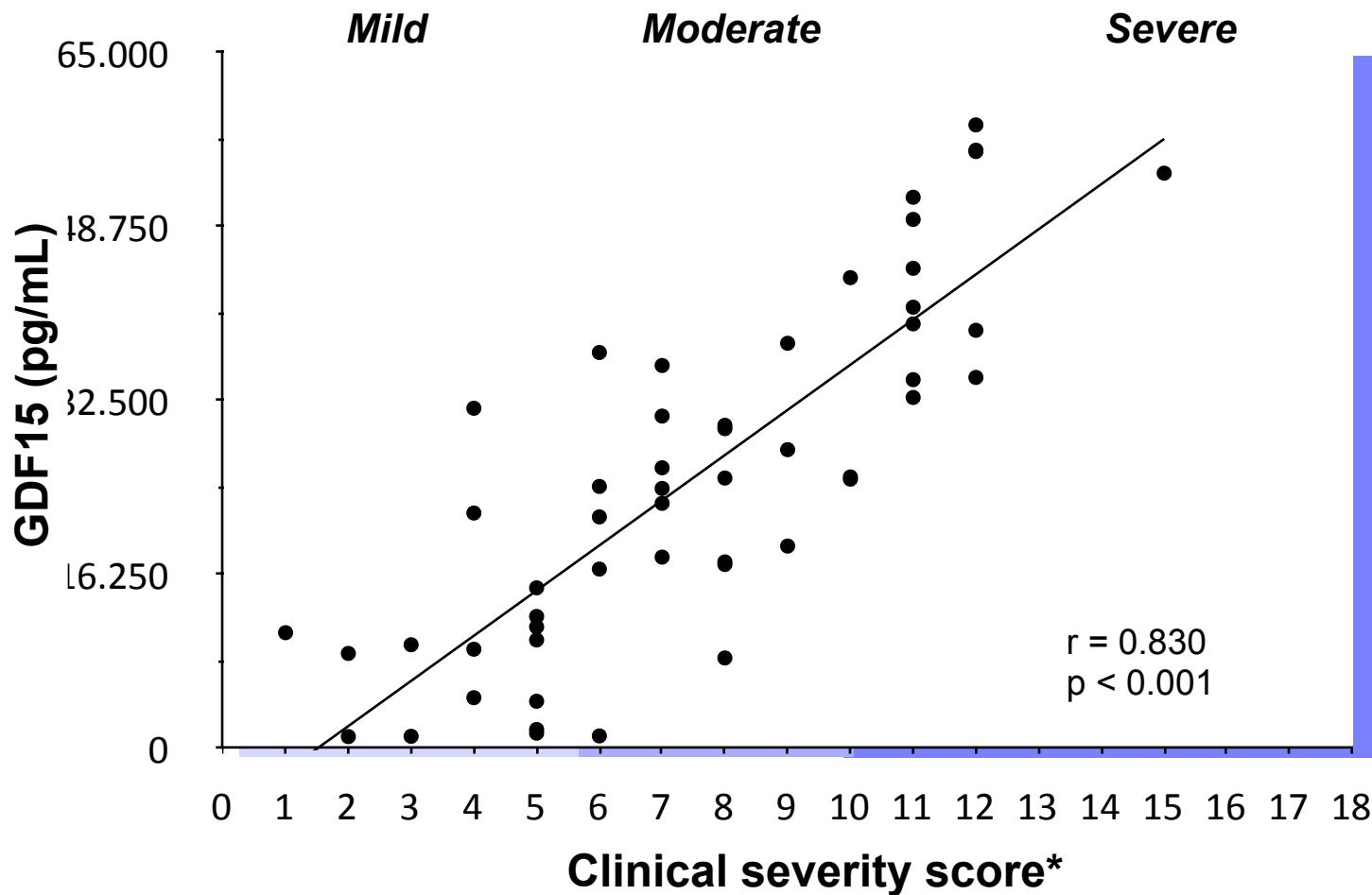
GDF15 = growth differentiation factor 15; HIF = hypoxia-inducible transcription factor;
LIC = liver iron concentration; RES = reticuloendothelial system.

Taher A, et al. Br J Haematol. 2011;152:512-23.

GDF-15 Level in 55 unbehandelten Patienten mit TI



GDF-15 Level korrelieren mit dem klinischen Verlauf

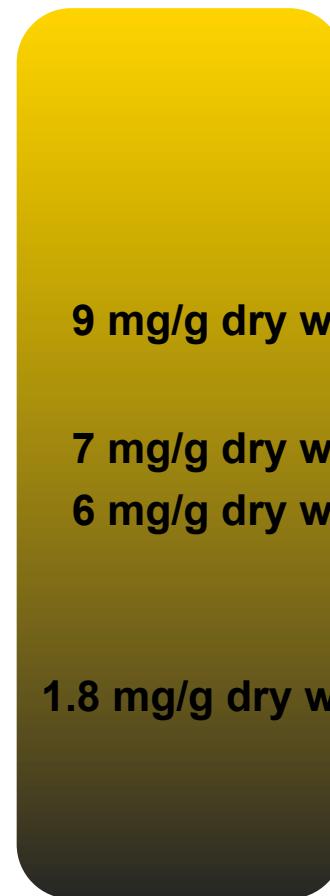


*Severity score is a combination of age, IO status, splenectomy, and number of clinical morbidities.

Musallam KM, et al. Blood Cells Mol Dis. 2011;47:232-4.

β -TI entwickeln z.T. schwere Lebereisen-überladung, wenn sie nicht cheliert werden

| Mean age \pm SD | β -TI | β -TM |
|--------------------------------|----------------------------------|-----------------|
| Taher et al. 2010 ¹ | | |
| n | 19 | 19 |
| Age (years) | 32.8 \pm 7.9 | 33.0 \pm 7.4 |
| LIC (mg Fe/g dry wt) | 15.0 \pm 7.4 | 15.7 \pm 9.9 |
| Origa et al. 2007 ² | | |
| n | 22 | 22 |
| Age (years) | 20.0 \pm 5.0 | 23.0 \pm 10.0 |
| LIC (mg Fe/g dry wt) | 11.3 \pm 6 | 11.8 \pm 7 |



RISK THRESHOLDS³

- Osteoporosis
 - Thrombosis
 - Vascular complications
 - Pulmonary hypertension
 - Hypothyroidism
 - Hypogonadism
 - Endocrine/bone complications
- Normal liver iron level

1. Taher A, et al. Am J Hematol. 2010;85:288-90. 2. Origa R, et al. Haematologica. 2007;92:583-8.
3. Musallam KM, et al. Hematologica. 2011;96:1605-12.

Hepatzelluläre Karzinome bei β-Thalassämie intermedia Patienten

- Thalassämie Patienten und andere transfusionsabhängige Anämien erkranken häufiger an einen HCC aufgrund von Hepatitis-Infektionen und Eisenüberladung
- β-TI Patienten haben eventuell ein höheres Risiko an einem HCC zu erkranken als TM Patienten
 - Von 36 Thalassämie Patienten mit HCC, 22 (71%) hatten eine β-TI, davon 6 Hep-C negativ
- Mögliche Gründe für ein erhöhtes Risiko:
 - Eisenüberladung ist unerkannt und unbehandelt (sFerritin repräsentiert nicht die Eisenüberladung in β-TI Patienten)
 - β-TI Patienten überleben länger



Hepatzellkarzinome in Patienten mit TI

| Sex | Age* | Survival | HCV Ab | HCV RNA | HBV Ab | HBs Ag | AFP (kU/L) | Serum ferritin ($\mu\text{g}/\text{L}$) | Serum ferritin peak ($\mu\text{g}/\text{L}$) | LIC |
|-----|------|---------------|--------|---------|------------|--------|------------|---|--|------|
| M | 48 | Alive at 26 m | - | - | - | - | 2,851 | 1,520 | 5,250 | NA |
| F | 61 | 5 m | + | - | - | - | 132 | 369 | 6,000 | NA |
| F | 59 | 25 m | + | - | NA | NA | NA | 990 | NA | NA |
| M | 73 | 7 m | - | - | NA | NA | NA | 574 | NA | NA |
| M | 54 | 1 m | - | - | - | - | 17.8 | 1,291 | 2,490 | 12.3 |
| M | 51 | 4 y | - | - | Vaccinated | - | 3.8 | 5,602 | 7,138 | 23.9 |

*At diagnosis

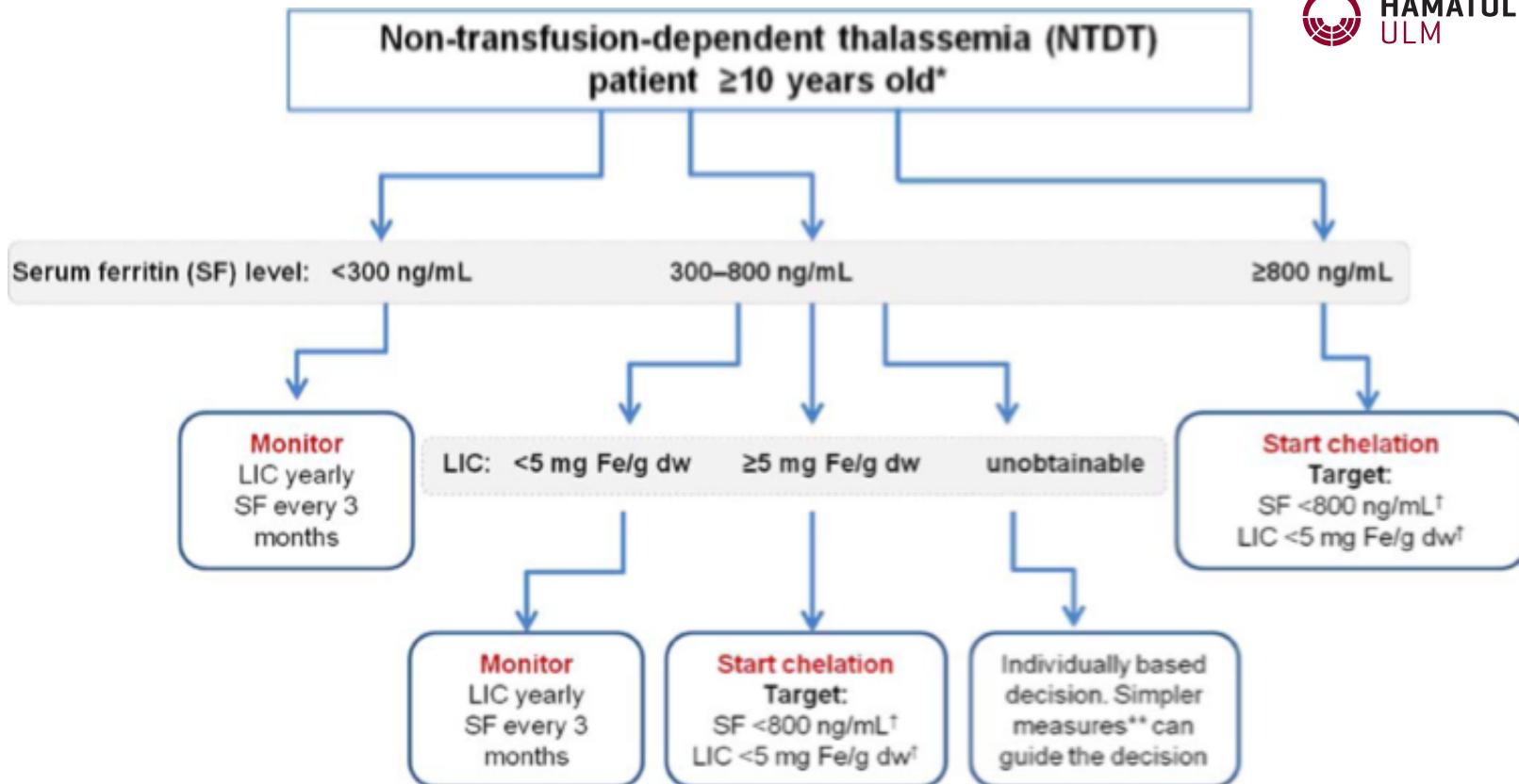
- In 6 β-TI patients with HCC who were HCV- and HBV-negative, no parameter was consistently elevated or depressed
- Suggested screening algorithm for HCC in β-TI
 - measure LIC using non-invasive R2* MRI yearly
 - if LIC $\geq 5 \text{ mg Fe/g dry wt}$, screen for HCC using abdominal ultrasound every 6 months

Indikation für Beginn einer Transfusions-therapie bei Patienten mit β-TI

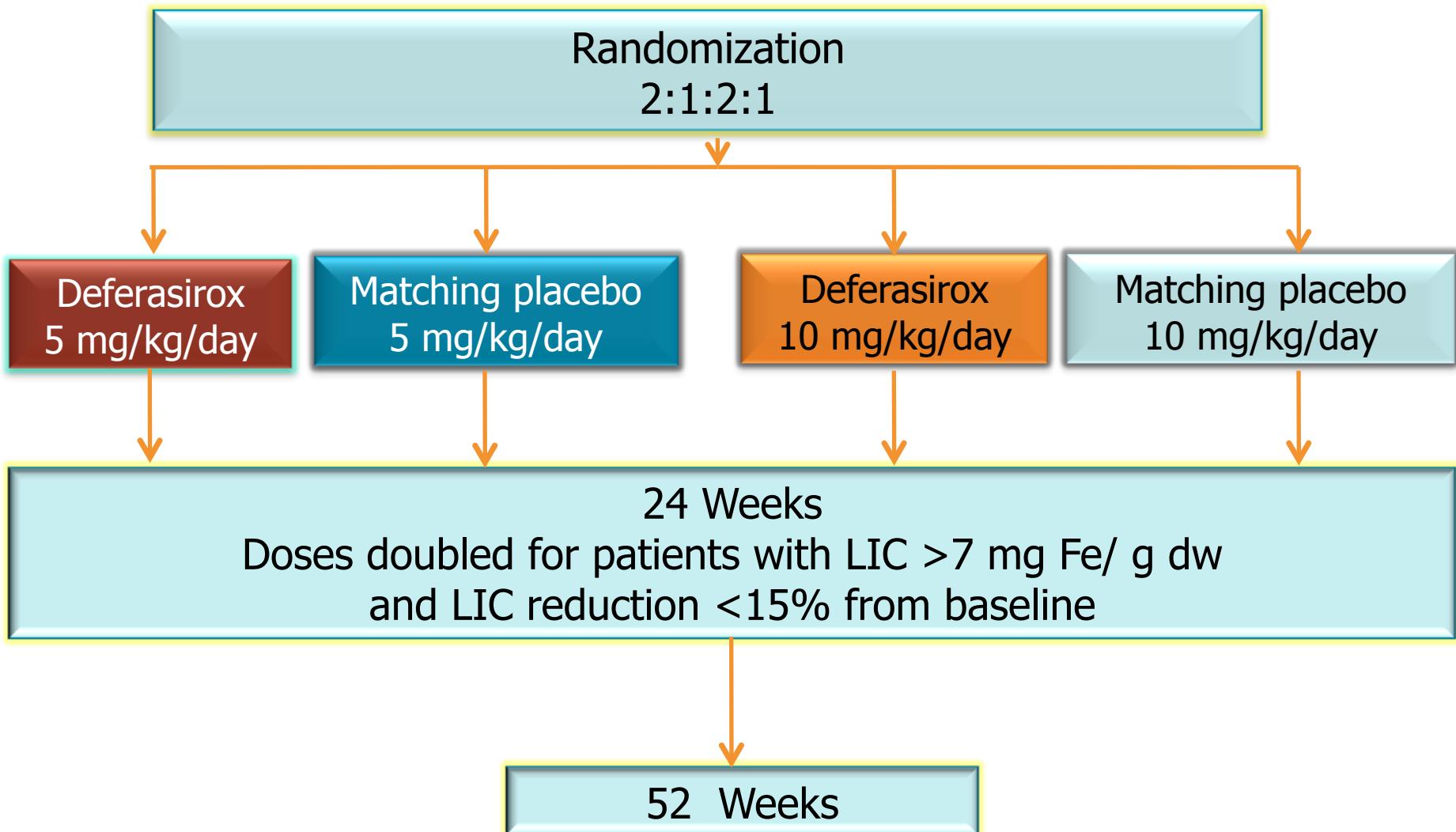


- Wachstumsstörungen in der Kindheit bei signifikanter Anämie
- verspätetes Einsetzen der Pubertät
- zunehmende Anämie
- zunehmende Splenomegalie
- während der Schwangerschaft und Infektionen
- vor operativen Eingriffen
- Thrombosen, silent strokes

Algorithmus zum Management der Eisenüberladung in TI Patienten



THALASSA-Studie, n=166



Effektivität von Deferasirox nach 1 Jahr Therapie bei Patienten mit TI

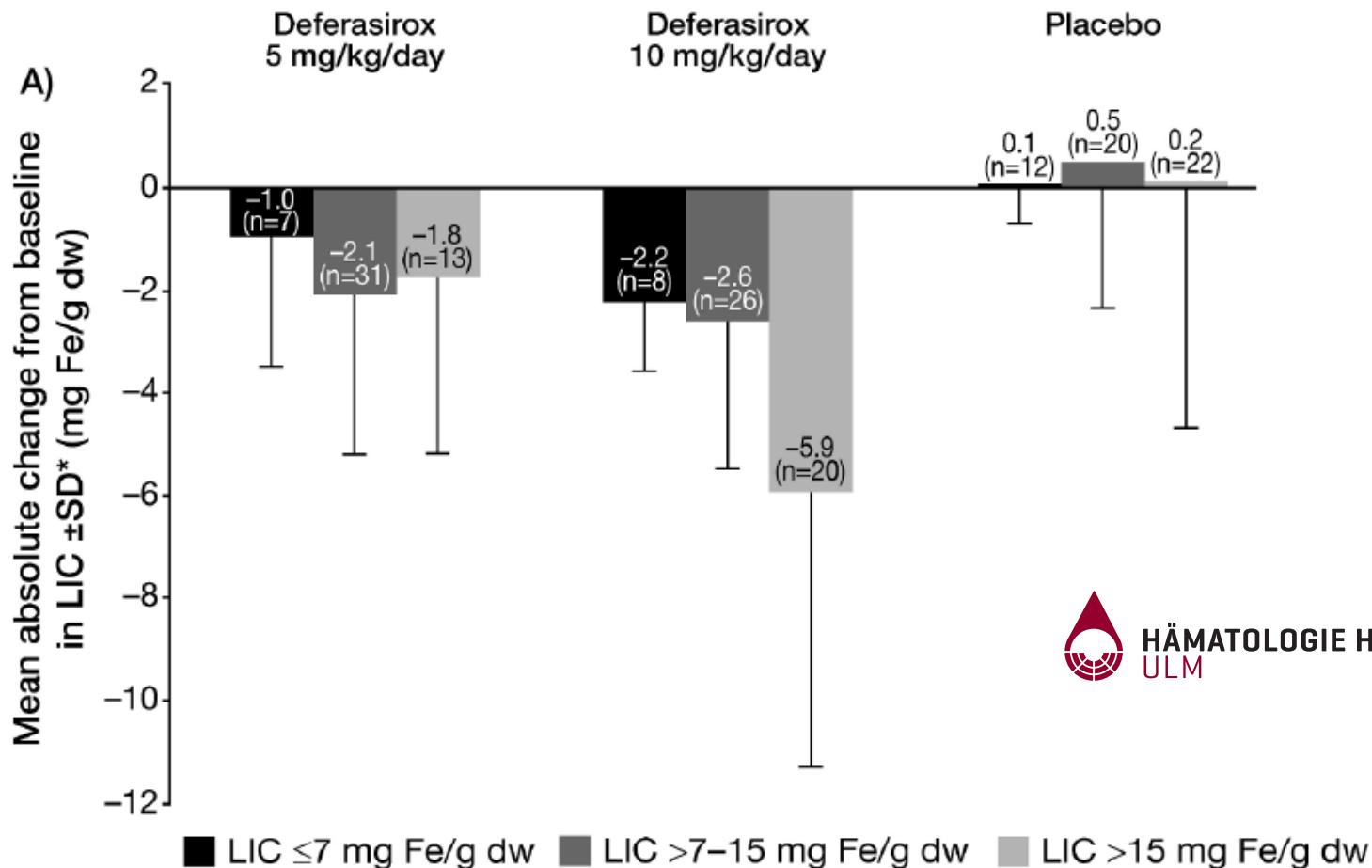
| Mean values | Baseline | 12 months | p value |
|------------------------------------|-------------------|-----------------|---------|
| Serum ferritin ($\mu\text{g/L}$) | $2,030 \pm 1,340$ | $1,165 \pm 684$ | 0.02 |
| LVEF (%) | 66.3 ± 8.1 | 66.9 ± 7.9 | 0.76 |
| AST (U/L) | 64.8 ± 29.6 | 42.5 ± 18.1 | 0.04 |
| ALT (U/L) | 63.5 ± 29.5 | 36.5 ± 17.6 | 0.02 |
| Serum creatinine (mg/dL) | | No change | |
| Cystatin C (mg/L) | | No change | |

- Mean LVEF (both normal at baseline), serum creatinine, and cystatin C did not significantly change after 12 months of treatment with deferasirox

Deferasirox* can effectively reduce iron burden in patients with TI

* Deferasirox dose used in the study was 10–20 mg/kg/day

Effektivität Deferasirox auf LIC nach 1 Jahr Therapie bei 166 Patienten mit TI



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Thalassa Study: Taher et al., Blood 2012

THALASSA: Safety

Most common (≥ 3 patients overall) investigator-assess drug-related AEs

| Adverse event, n (%) | Deferasirox 5 mg/kg/ day n=55 | Placebo 5 mg/kg/ day n=28 | Deferasirox 10 mg/kg/ day n=55 | Placebo 10 mg/kg/ day n=56 | Total |
|----------------------|--|------------------------------------|---|-------------------------------------|----------|
| Nausea | 3 (5.5) | 1 (3.6) | 4 (7.3) | 3 (10.7) | 11 (6.6) |
| Skin rash | 2 (3.6) | 0 | 5 (9.1) | 1 (3.6) | 8 (4.8) |
| Diarrhea | 0 | 0 | 5 (9.1) | 1 (3.6) | 6 (3.6) |
| Headache | 2 (3.6) | 0 | 1 (1.8) | 2 (7.1) | 5 (3.0) |
| Upper abdominal pain | 2 (3.6) | 0 | 1 (1.8) | 0 | 3 (1.8) |
| Abdominal pain | 1 (1.8) | 1 (3.6) | 1 (1.8) | 0 | 3 (1.8) |

- Most investigator-assessed drug-related AEs were mild to moderate and resolved without discontinuing therapy

Zusammenfassung

- NTDT zeigen ein breites Spektrum an verschiedenen Formen von Thalassämien, die durch gelegentlichen oder keinen Transfusionsbedarf charakterisiert sind.
- Regelmäßige Evaluierung der NTDT Patienten (Transfusionsindikation) ist notwendig.
- Zunehmende Evidenz, dass NTDT (speziell β-TI) an einer Vielzahl von Komplikationen im späteren Leben erkranken.
- Eisenüberladung ist ein Risiko für NTDT, auch bei nicht-transfusionbedürftige Patienten aufgrund der erhöhten gastrointestinalen Eisenresorption bei ineffektiver Erythropoese.

Zusammenfassung

- sFerritin Werte in β-TI Patienten spiegeln nicht das Maß an Eisenüberladung, speziell LIC wieder.
Lebereisenmessungen sind daher notwendig.
- Regelmäßiges Monitoring der Eisenüberladung und gegebenenfalls Beginn einer Chelattherapie.
- Chelattherapie mit Deferasirox ist effektiv und sicher bei TI Patienten.

Today's Deal: Non-iron patients



Vielen Dank für Ihre
Aufmerksamkeit



Stammzelltransplantationszentrum Frankfurt a. M.

Pädiatrische Hämatologie und Onkologie

T. Klingebiel, P. Bader,
J. Sörensen, A. Jarisch,
G. Lucchini,



Impact of LIC on morbidity in TI patients: multivariate analysis (cont.)

| Variable | Morbidity | | | | | | | | | |
|--------------------------------|-------------------------|-----------|-------------------|------------|----------------|-----------|--------------|-----------|--------------|-----------|
| | Abnormal liver function | | Diabetes mellitus | | Hypothyroidism | | Osteoporosis | | Hypogonadism | |
| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| LIC, 1 mg Fe/g dry wt increase | 1.05 | 0.97–1.13 | 0.92 | 0.78–1.07 | 1.05 | 1.01–1.11 | 1.10 | 1.04–1.16 | 1.10 | 1.03–1.16 |
| Age, 1 year increase | 1.09 | 1.05–1.14 | – | – | – | – | 1.05 | 1.02–1.08 | – | – |
| Gender | | | | | | | | | | |
| Female | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Male | – | – | – | – | – | – | – | – | – | – |
| Splenectomized | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | – | – | – | – | – | – | 3.67 | 1.57–8.55 | – | – |
| Transfusion | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | – | – | 5.49 | 1.21–24.85 | 2.54 | 1.34–4.84 | – | – | 2.97 | 1.39–6.35 |

Model was built using forward-stepwise selection. $p \leq 0.1$ was used as the criterion for inclusion. The following factors were also evaluated in the multivariate analysis: total and fetal Hb, platelet count, NRBC count, and serum ferritin. Multi-collinearity was absent in the model as evident from a variation inflation factor ≤ 3 (acceptable limit up to 10).

Musallam KM, et al. Haematologica. 2011;96:1605-12.

Impact of LIC on morbidity in TI patients: multivariate analysis (cont.)

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| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| LIC, 1 mg Fe/g dry wt increase | 1.05 | 0.97–1.13 | 0.92 | 0.78–1.07 | 1.05 | 1.01–1.11 | 1.10 | 1.04–1.16 | 1.10 | 1.03–1.16 |
| Age, 1 year increase | 1.09 | 1.05–1.14 | – | – | – | – | 1.05 | 1.02–1.08 | – | – |
| Gender | | | | | | | | | | |
| Female | | | | | | | | | | Referent |
| Male | | | | | | | | | | – |
| Splenectomy | | | | | | | | | | |
| No | | | | | | | | | | Referent |
| Yes | | | | | | | | | | – |
| Transfusion | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | – | – | 5.49 | 1.21–24.85 | 2.54 | 1.34–4.84 | – | – | 2.97 | 1.39–6.35 |

Model was built using forward-stepwise selection. $p \leq 0.1$ was used as the criterion for inclusion. The following factors were also evaluated in the multivariate analysis: total and fetal Hb, platelet count, NRBC count, and serum ferritin. Multi-collinearity was absent in the model as evident from a variation inflation factor ≤ 3 (acceptable limit up to 10).

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Impact of LIC on morbidity in TI patients: multivariate analysis

| Variable | Morbidity | | | | | | | | | |
|--------------------------------|-----------------------------|-----------|------------|-----------|------------|------------|------------------------|-----------|---------------|-----------|
| | Extramedullary haemopoiesis | | Leg ulcers | | Thrombosis | | Pulmonary hypertension | | Heart failure | |
| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| LIC, 1 mg Fe/g dry wt increase | 1.01 | 0.94–1.08 | 1.04 | 0.99–1.10 | 1.12 | 1.05–1.20 | 1.08 | 1.02–1.14 | 1.06 | 0.97–1.16 |
| Age, 1 year increase | – | – | – | – | 1.04 | 1.01–1.07 | 1.05 | 1.02–1.09 | – | – |
| Gender | | | | | | | | | | |
| Female | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Male | – | – | – | – | 0.35 | 0.16–0.81 | – | – | – | – |
| Splenectomized | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | – | – | – | – | 5.82 | 1.77–19.19 | 2.99 | 1.20–7.44 | – | – |
| Transfusion | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | 1.81 | 1.07–3.08 | 2.01 | 1.17–3.47 | – | – | – | – | – | – |

Model was built using forward-stepwise selection. $p \leq 0.1$ was used as the criterion for inclusion. The following factors were also evaluated in the multivariate analysis: total and fetal Hb, platelet count, NRBC count, and serum ferritin. Multi-collinearity was absent in the model as evident from a variation inflation factor ≤ 3 (acceptable limit up to 10).

AOR = adjusted odds ratio; CI = confidence interval.

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| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| LIC, 1 mg Fe/g dry wt increase | 1.01 | 0.94–1.08 | 1.04 | 0.99–1.10 | 1.12 | 1.05–1.20 | 1.08 | 1.02–1.14 | 1.06 | 0.97–1.16 |
| Age, 1 year increase | – | – | – | – | 1.04 | 1.01–1.07 | 1.05 | 1.02–1.09 | – | – |
| Gender | | | | | | | | | | |
| Female | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Male | – | – | – | – | 0.35 | 0.16–0.81 | – | – | – | – |
| Splenectomized | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | – | – | – | – | 5.82 | 1.77–19.19 | 2.99 | 1.20–7.44 | – | – |
| Transfusion | | | | | | | | | | |
| No | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Yes | 1.81 | 1.07–3.08 | 2.01 | 1.17–3.47 | – | – | – | – | – | – |

Model was built using forward-stepwise selection. $p \leq 0.1$ was used as the criterion for inclusion. The following factors were also evaluated in the multivariate analysis: total and fetal Hb, platelet count, NRBC count, and serum ferritin. Multi-collinearity was absent in the model as evident from a variation inflation factor ≤ 3 (acceptable limit up to 10).

AOR = adjusted odds ratio; CI = confidence interval.

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First attempt at understanding complications in β -thalassaemia intermedia vs β -thalassaemia major

| Complication (% of patients affected) | β -TI | | β -TM | |
|--|---------------------|-------------------|---------------------|-------------------|
| | Lebanon (n = 37) | Italy (n = 63) | Lebanon (n = 40) | Italy (n = 60) |
| Splenectomy | 90 | 67 | 95 | 83 |
| Cholecystectomy | 85 | 68 | 15 | 7 |
| Gallstones | 55 | 63 | 10 | 23 |
| Extramedullary haemopoiesis | 20 | 24 | 0 | 0 |
| Leg ulcers | 20 | 33 | 0 | 0 |
| Thrombotic events | 28 | 22 | 0 | 0 |
| Cardiopathy* | 3 | 5 | 10 | 25 |
| Pulmonary hypertension† | 50 | 17 | 10 | 11 |
| Abnormal liver enzymes | 20 | 22 | 55 | 68 |
| HCV infection | 7 | 33 | 7 | 98 |
| Hypogonadism | 5 | 3 | 80 | 93 |
| Diabetes mellitus | 3 | 2 | 12.5 | 10 |
| Hypothyroidism | 3 | 2 | 15 | 11 |

*Fractional shortening < 35%. †Defined as pulmonary artery systolic pressure > 30 mmHg; a well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.