# High transferrin saturation predicts inferior clinical outcomes in patients with myelodysplastic syndromes

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# High transferrin saturation predicts inferior clinical outcomes in patients with MDS

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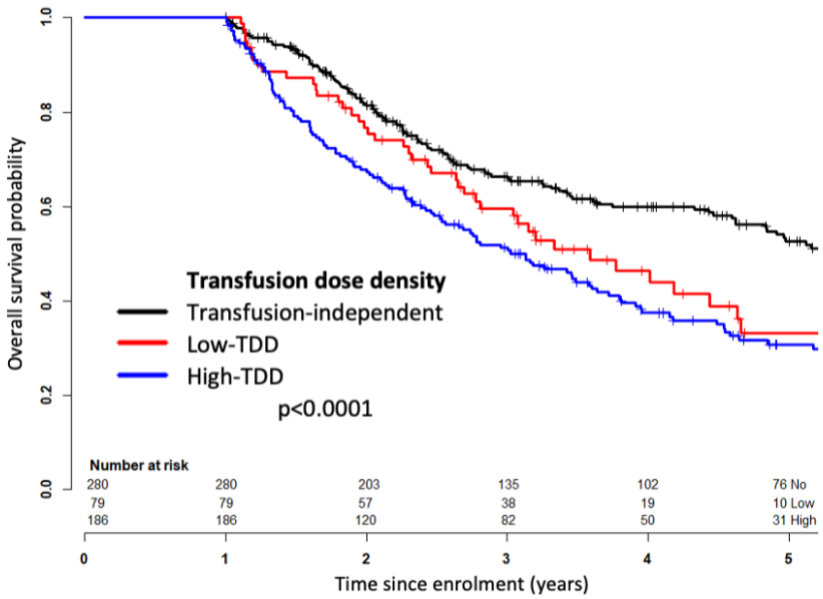
## Supplementary Material

**Table S1.** Demographic and clinical variables stratified by transfusion density (TD), where TD-low and TD-high were defined as below and above the median TD, respectively.

| | *At Landmark Year 1 (calculation from the first transfusion date)* | | | |
|---|---|---|---|---|
| | ***No transfusions (n=259)*** | ***Low transfusion dose (n=138)*** | ***High transfusion dose (n=148)*** | ***p-value*** |
| Age categories | | | | 0.1573 |
| ≤ 60 | 33 (12.74%) | 7 (5.07%) | 16 (10.81%) | |
| 61-70 | 65 (25.10%) | 35 (25.36%) | 40 (27.03%) | |
| > 70 | 161 (62.16%) | 96 (69.57%) | 92 (62.16%) | |
| Sex | | | | 0.1566 |
| M | 170 (65.89%) | 77 (56.20%) | 95 (64.19%) | |
| F | 88 (34.11%) | 60 (43.80%) | 53 (35.81%) | |
| WHO subtype | | | | 0.1736 |
| 5q- | 13 (5.02%) | 9 (6.52%) | 5 (3.38%) | |
| Secondary AML, AML (previously RAEBT) or T-AML | 8 (3.09%) | 4 (2.90%) | 2 (1.35%) | |
| MDS-EB1 | 17 (6.56%) | 16 (11.59%) | 24 (16.22%) | |
| MDS-EB2 | 16 (6.18%) | 11 (7.97%) | 19 (12.84%) | |
| MDS-MLD | 80 (30.89%) | 41 (29.71%) | 44 (29.73%) | |
| MDS-MPN, CMML-0, CMML-1 or CMML2 | 80 (30.89%) | 8 (5.80%) | 13 (8.78%) | |
| MDS-MPN-RS-T | 3 (1.16%) | 3 (2.17%) | 2 (1.35%) | |
| MDS-RS-MLD | 13 (5.02%) | 8 (5.80%) | 8 (5.41%) | |
| MDS-RS-SLD | 23 (8.88%) | 20 (14.49%) | 12 (8.11%) | |
| MDS-SLD | 29 (11.20%) | 8 (5.80%) | 11 (7.43%) | |
| MDS-U | 15 (5.79%) | 10 (7.25%) | 7 (4.73%) | |
| Not available | 2 (0.77%) | 0 (0.00%) | 1 (0.68%) | |
| **IPSS-RR category** | | | | **<.0001** |
| Very Low | 53 (21.81%) | 10 (7.81%) | 11 (7.64%) | |
| Low | 91 (37.45%) | 40 (31.25%) | 46 (31.94%) | |
| INT | 61 (25.10%) | 50 (39.06%) | 49 (34.03%) | |
| High | 25 (10.29%) | 18 (14.06%) | 17 (11.81%) | |
| Very high | 13 (5.35%) | 10 (7.81%) | 21 (14.58%) | |
| Cytogenetics | | | | 0.6413 |
| Very good | 8 (3.25%) | 4 (3.10%) | 3 (2.05%) | |
| Good | 184 (74.80%) | 92 (71.32%) | 102 (69.86%) | |
| Intermediate | 36 (14.63%) | 25 (19.38%) | 25 (17.12%) | |
| Poor | 8 (3.25%) | 2 (1.55%) | 4 (2.74%) | |
| Very poor | 10 (4.07%) | 6 (4.65%) | 12 (8.22%) | |

**Figure S1.** Overall survival of MDS patients based on transfusion dose density, using the revised International Working Group definition of low transfusion density (≥0.75 to <2 units per month) and high transfusion dose density (≥2 units per month).




TDD = transfusion dose density.

**Figure S2:** Higher transfusion density was significantly associated with inferior OS in lower risk MDS patients (A) but not in higher risk MDS patients (B)

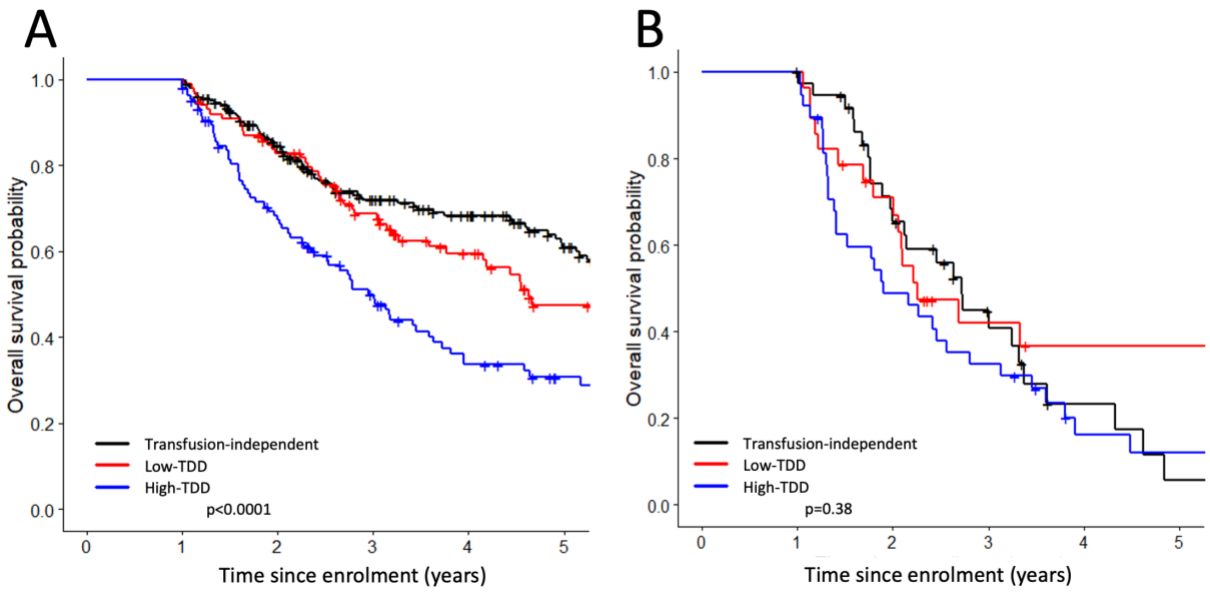


**Figure S3:** Higher TSAT was significantly associated with inferior OS in lower risk MDS patients (A) with a trend toward significance among higher risk MDS patients (B)

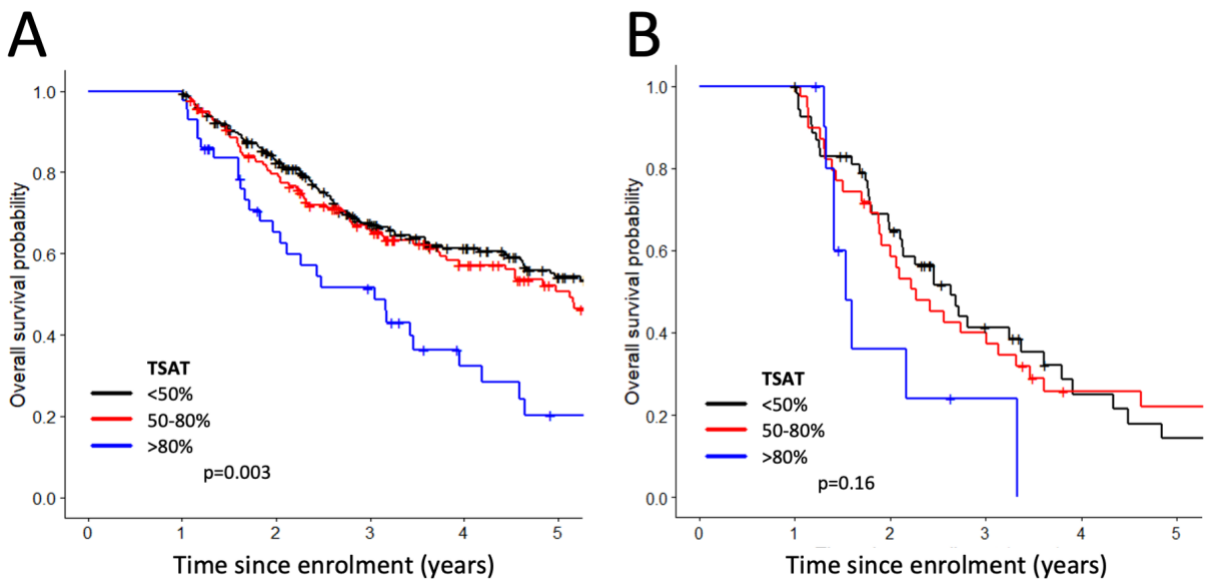


**Figure S4:** Higher TSAT was significantly associated with inferior PFS (B) and LFS (D) in higher risk MDS patients, but not in lower risk MDS (A,C), although a trend toward significance was seen in LFS among lower risk patients (C).

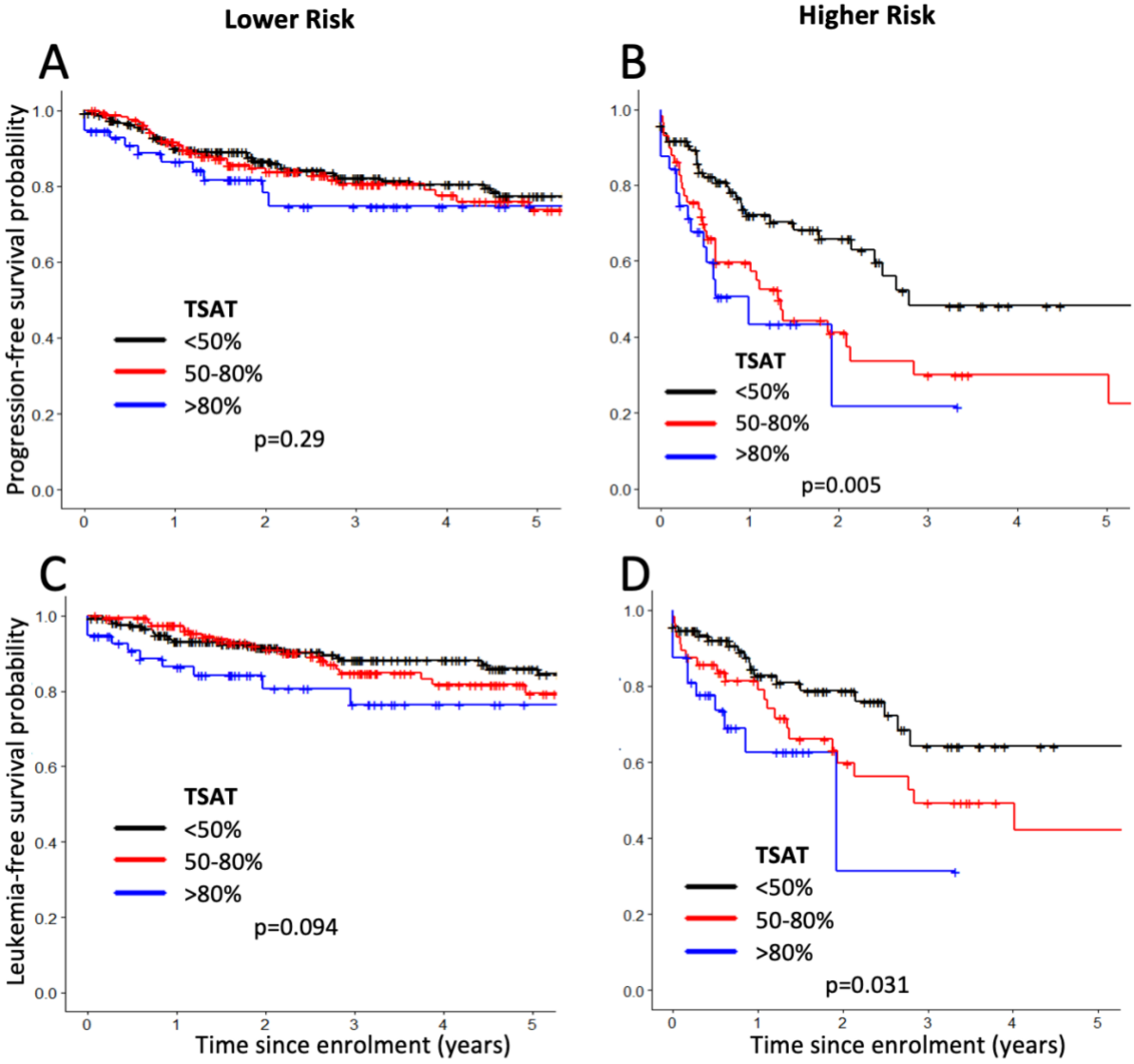


**Figure S5:** Iron chelation therapy had an attenuating effect on the impact of TSAT on progression-free survival and leukemia-free survival, although sample sizes were limited.

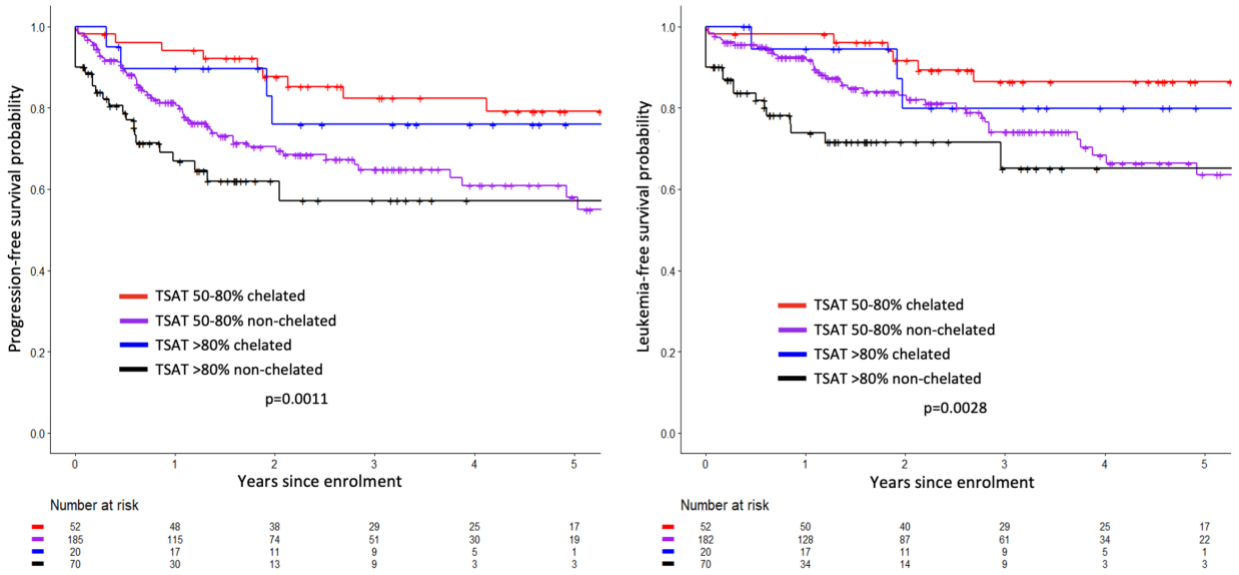



**Figure S6.** Cumulative incidence of death from infection according to three TSAT and three ferritin categories, where mean TSAT and mean ferritin were taken over the entire duration of follow-up.

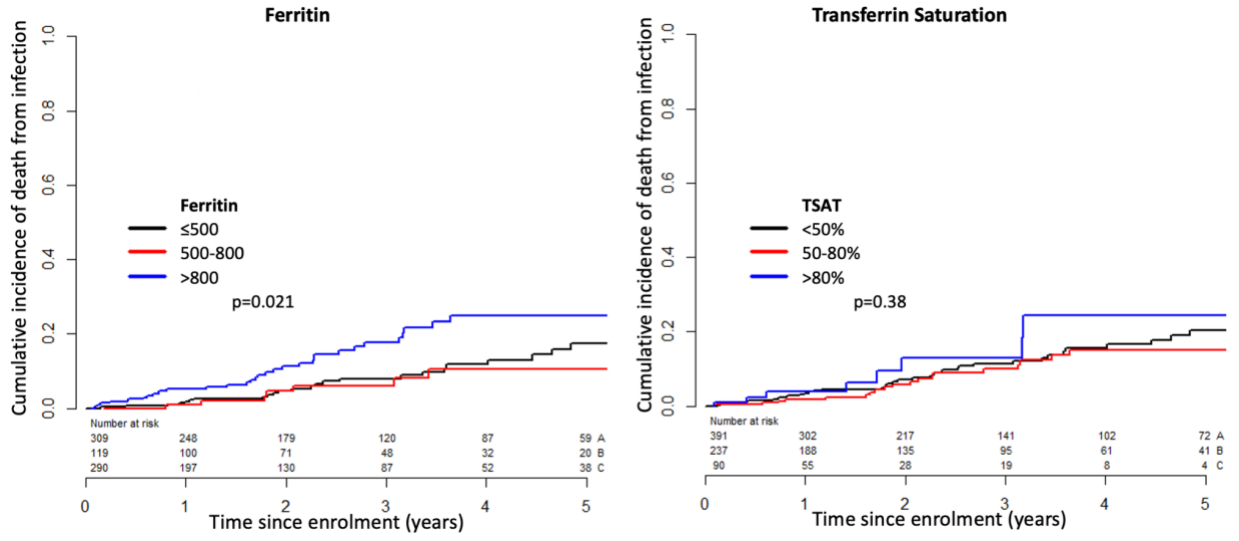


**Table S2.** Univariate Cox proportional hazards analysis of the impact of covariates on overall survival.

| Variable | p-value | HR | 95% CI of HR | | $R^2$ (%) |
|---|---|---|---|---|---|
| **Age at baseline (years)** | **<.0001** | **1.039** | 1.028 | 1.050 | 7.63 |
| **IPSS-R value at baseline** | **<.0001** | **1.369** | 1.303 | 1.438 | 18.88 |
| **Blasts categories at baseline** | **<.0001** | | | | 10.10 |
| **5-9% vs. <5%** | **<.0001** | **1.922** | 1.498 | 2.467 | |
| **≥10% vs. <5%** | **<.0001** | **2.947** | 2.313 | 3.755 | |
| **≥10% vs. 5-9%** | **0.0049** | **1.533** | 1.139 | 2.065 | |
| **ECOG (0-4)** | **<.0001** | **1.557** | 1.362 | 1.780 | 5.37 |
| BMI ($kg/m^2$) | 0.7516 | 1.003 | 0.984 | 1.023 | 0.02 |
| TD vs. TI at anytime | 0.3575 | 1.092 | 0.906 | 1.316 | 0.12 |
| **Frailty value at baseline (continuous)** | **<.0001** | **1.510** | 1.383 | 1.649 | 12.85 |
| **Charlson Comorbidity value at baseline (continuous) *** | **<.0001** | **1.502** | 1.269 | 1.777 | 3.66 |
| **Iron chelation (Yes vs. No)** | **0.0144** | **0.708** | 0.537 | 0.934 | 0.90 |
| **Iron saturation averaged value from all measurements** | **0.0012** | **1.007** | 1.003 | 1.012 | 1.42 |
| **Iron saturation averaged value categories** | **<.0001** | | | | 3.21 |
| 50-80% vs. <50% | 0.7049 | 1.041 | 0.845 | 1.282 | |
| **>80% vs. <50%** | **<.0001** | **2.031** | 1.546 | 2.667 | |
| **>80% vs. 50-80%** | **<.0001** | **1.951** | 1.460 | 2.605 | |
| **Iron saturation averaged value >80% (Yes vs. No)** | **<.0001** | **1.999** | 1.541 | 2.593 | 3.19 |
| **Ferritin averaged value from all measurements *** | **<.0001** | **1.264** | 1.164 | 1.372 | 4.44 |
| **Ferritin averaged value categories** | **<.0001** | | | | 4.66 |
| 501-800 vs. ≤500 | 0.9316 | 1.013 | 0.757 | 1.355 | |
| **>800 vs. ≤500** | **<.0001** | **1.764** | 1.438 | 2.163 | |
| **>800 vs. 501-800** | **0.0001** | **1.742** | 1.315 | 2.307 | |
| **Ferritin averaged value >800 (Yes vs. No)** | **<.0001** | **1.758** | 1.458 | 2.119 | 4.66 |
| **Ferritin averaged value >1000 (Yes vs. No)** | **<.0001** | **1.678** | 1.389 | 2.027 | 3.82 |
| **Transfusion density (>2.7 units/months) categories** | **<.0001** | | | | 6.48 |
| **High vs. No** | **<.0001** | **1.955** | 1.587 | 2.410 | |
| Low vs. No | 0.5198 | 0.919 | 0.710 | 1.189 | |
| **High vs. Low** | **<.0001** | **2.128** | 1.641 | 2.760 | |

*Natural log transformation was applied for some covariates to normalize their distributions. P-values < 0.05 were considered statistically significant (bolded rows). Hazard ratios and 95% confidence intervals (CI) of hazard ratio were also calculated for each covariate. The generalized $R^2$ statistic was calculated based on the likelihood ratio statistic (LRT) for testing the global null hypothesis (see Allison, Paul D. 2010. *Survival Analysis Using the SAS System: A Practical Guide*. Cary, NC: SAS Institute Inc, Second ed. Page 282-283)

**Table S3.** Multivariable cox proportional hazards analysis.

| Model A | p-value | HR | 95% CI of HR | | $R^2$ (%) |
|---|---|---|---|---|---|
| Iron saturation averaged value >80% vs. ≤80% | 0.0071 | 1.584 | 1.133 | 2.215 | **30.30** |
| Ferritin averaged value >800 vs. ≤800 | 0.0056 | 1.480 | 1.122 | 1.953 | |
| Age at baseline (years) | 0.0206 | 1.017 | 1.003 | 1.032 | |
| IPSS-R value at baseline | <.0001 | 1.272 | 1.197 | 1.352 | |
| Frailty value at baseline (continuous) | <.0001 | 1.328 | 1.197 | 1.472 | |
| Charlson Comorbidity value at baseline (log) | 0.0356 | 1.230 | 1.014 | 1.493 | |
| Iron chelation (Yes vs. No) | 0.0022 | 0.581 | 0.410 | 0.822 | |

| Model B | p-value | HR | 95% CI of HR | | $R^2$ (%) |
|---|---|---|---|---|---|
| Iron saturation averaged value >80% vs. ≤80% | 0.0072 | 1.581 | 1.132 | 2.209 | **30.35** |
| Transfusion density (>2.7 units/months) categories | 0.0002 | | | | |
| High vs. No | 0.0092 | 1.516 | 1.108 | 2.075 | |
| Low vs. No | 0.1760 | 0.798 | 0.576 | 1.106 | |
| High vs. Low | <.0001 | 1.899 | 1.386 | 2.603 | |
| Age at baseline (years) | 0.0064 | 1.020 | 1.006 | 1.035 | |
| IPSS-R value at baseline | <.0001 | 1.271 | 1.196 | 1.351 | |
| Frailty value at baseline (continuous) | <.0001 | 1.338 | 1.205 | 1.486 | |
| Charlson Comorbidity value at baseline (log) | 0.0463 | 1.217 | 1.003 | 1.476 | |
| Iron chelation (Yes vs. No) | 0.0092 | 0.636 | 0.452 | 0.894 | |

Potentially significant (p-value <0.10) variables from the univariate analysis were included in the multivariate analysis and backward stepwise selection procedure was used. The above two models emerged with nearly identical $R^2$ values. While age, IPSS-R, frailty, Charlson Comorbidity, ICT and TSAT remained independent predictors in all three models, only one of ferritin or TDD retained significance in each model, suggesting significant co-linearity among these variables.