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Abrupt ferritin increases as a marker of cancer in transfusion-dependent thalassemia

Elena Chatzikalil[1,2*], Polyxeni Delaporta[1,2*], Ilona Binenbaum[2], Vasiliki Chouliara[1,2], Dimitra Kyriakopoulou[1,2], Sofirela Berdalli[1,2], Konstantinos Bistas[1,2], Maria-Ioanna Chatzieleftheriou[1,2], Euthalia-Faidra Agiomavriti-Stefanopoulou[1,2], Antonis Kattamis[1,2]

[1]Thalassemia Unit, First Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece

[2]'Aghia Sophia' Children's Hospital, ERN-EuroBloodNet Center, Athens, Greece

*Equal contribution

Correspondence: Antonis Kattamis, ankatt@med.uoa.gr

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Current therapeutic strategies in the treatment of transfusion-dependent β-thalassemia (TDT), have resulted in significant improvement in life expectancy. Along with increased survival, cancer became a leading cause of morbidity and mortality[1–4]. Neoplasia is generally associated with increased ferritin levels, which has been attributed to the role of ferritin as a reactive protein and to the dysregulation of iron metabolism during carcinogenesis[5,6]. On the other hand, ferritin levels have been used for longitudinal evaluation of iron overload (IO) in TDT patients[7]. The aim of this retrospective cohort study is to evaluate ferritin changes in TDT patients with IO, during the occurrence of a neoplastic event.

This study has been approved by the Hospitals Ethical Committee per National Guidelines for retrospective (observational) clinical studies. All TDT patients followed in our unit during the study period extending from 1st January 2013 till 31st December 2024 were included. Our thalassemia unit is the largest one in Greece with the number of patients attending the unit corresponding approximately to 15% of the total TDT population nationwide. Demographic-epidemiological data, and clinical course of our TDT patients, in terms of age distribution, disease complications, survival and morbidity causes are representative of the reference population. All patients are regularly transfused and receive iron chelation therapy with different schemas which include any of the available iron chelators either in monotherapy or combination, according to the Thalassemia International Federation (TIF) guidelines.

For TDT patients who developed cancer (c-TDT), data on the type of cancer, age at diagnosis, survival status, and IO indices [serum ferritin, liver iron concentration (LIC) and cardiac iron concentration (cardiac T2*) assessed by MRI], were recorded and analyzed. The mean (SD) ferritin levels were assessed for the following time intervals prior to cancer diagnosis: 0-6 months, 12–24 months and 1-3 years. All 21 patients who developed cancer were regularly transfused with no significant differences regarding transfusion burden the year prior to cancer diagnosis and were under a stable chelation schema prior to the abrupt ferritin elevation. For TDT patients who did not develop cancer (nc-TDT), longitudinal ferritin levels for the last 3 years prior to last observation were captured as above. nc-TDT patients for whom ferritin and LIC values were available for the last 3 years were used as a control group. Other causes of chronic inflammation were excluded as per standard of care, using different diagnostic parameters (C-reactive protein, transaminases, autoimmune markers).

All analyses were performed using RStudio version 3.6.2. (Integrated Development Environment for R. Posit Software, PBC, Boston, MA.). Comparisons were performed, using t-test for independent samples and paired t-test and Mann-Whitney U test for continuous variables and chi squared and Fisher's exact test for categorical. Receiver operating characteristic (ROC) curve analysis was completed to evaluate sensitivity and specificity of ferritin increase as a screening tool for malignancy, while area under the curve (AUC) values were estimated with 95% confidence intervals. Longitudinal trajectories of ferritin over time were evaluated with a linear mixed effects model accounting for confounders. Stratified sensitivity analyses were performed based on baseline ferritin levels, and when necessary, Holm correction for multiple comparisons was applied. Complete data was available for all variables of interest. A two-tailed p-value of less than 0.05 was considered statistically significant.

Three hundred seventy-six TDT patients (192 males, 184 females) have been followed in our Unit during the study period, with a median age 44 years (range 1-66) as of December 2024.

During the study period, 21 patients (10 males, 11 females) were diagnosed with cancer at a median age of 45 year **(Table 1)** which corresponds to cancer prevalence of 5.6%. For the reference Greek population, cancer prevalence is estimated at 0.5%, while median age at cancer diagnosis at 66 years[8]. Eight distinct types of cancer were diagnosed, with hepatocellular carcinoma (HCC) being the most frequent. Ten patients (2.7% of our cohort) developed HCC with none of them having active hepatitis C or B. This corresponds to a significant higher prevalence compared to general population, which is estimated at 0.0073%[9]. Gender distribution (4 males, 6 females) also differs from the one at the general population where HCC is more common in males[9]. All c-TDT patients were regularly transfused at a fixed rate, and all were under chelation treatment at a stable dose prior to ferritin elevation. When ferritin increase was noted, intensification of chelation therapy was applied in 12/21 patients without affecting serum ferritin levels.

Ferritin levels, while they were no different between 1 year and 3 years prior to cancer diagnosis (p=0.13), rose sharply for 0-6 months prior, with a mean increase of 933±1728 (129% of baseline) to all patients except two (**Figure 1**). Ferritin levels 0-6 months prior to cancer diagnosis (median 2116 ng/ml, range: 412-9582 ng/ml) significantly differed compared to levels both at 12-24 months (median 1180 ng/ml, range: 244.3-5950 ng/ml) (p=0.00014) and 1-3 years (median 707 ng/ml, range: 128-4900 ng/ml) (p=0.009) prior to cancer diagnosis. At the same period, other indicators of IO (LIC and cardiac T2*), have remained stable (p>0.05) (mean change: 0.39±4.09 mg Fe/g.d.w. and 0.76±6.48 msec, respectively). There was no statistical difference in ferritin for patients developing HCC compared to other malignancies (p=0.347). However, this comparison is underpowered due to small sample size (power of two sample t test: 0.144). Of note is, that a female patient presented a notable increase in ferritin levels 0-6 months prior to the diagnosis of HCC, which resolved when remission was achieved, with a similar increase in ferritin levels occurring 4 years later upon relapse.

Two patients (patients 1 and 16) did not exhibit these changes in ferritin kinetics. Patient 1 had thyroid carcinoma with low IO (ferritin levels 230-454 ng/ml, LIC 1.1mg Fe/g.d.w.) and presented a 10% increase in chelation treatment dose. Patient 16 was diagnosed with HCC with mild IO (ferritin levels 2000-2750 ng/ml, LIC 4.4 mg Fe/g.d.w.) and had hepatic lesions under a 2-year close evaluation prior HCC diagnosis. Different explanations for the different kinetics in ferritin levels in these two patients are hypothesized; ferritin elevation may not be observed in cases of low-grade neoplasia with slow evolution, while the over-6-month extent of the period of malignant development prior to cancer diagnosis may cause difficulties in establishing the baseline ferritin values.

None of the patients had active hepatitis, although 8 patients had previously received treatment for HCV infection. There was no significant association between history of HCV exposure and development of HCC or other malignancies. Mean change in serum ferritin over time did not differ significantly between patients with positive vs negative HCV exposure (p=0.942).

The sensitivity and specificity for changes of serum ferritin as a prognostic marker for malignancy were calculated by evaluating data on serum ferritin, LIC and heart T2* for all 376 patients followed in our unit. Thirty-two out of these patients, none of whom had cancer, showed significant increase in iron load, as demonstrated by increased LIC > 50% and were excluded from the ROC analysis. The nc-TDT patients, that were included in the analysis, had stable iron load, as reflected by minimal variations in their ferritin levels and MRI-

assessed cardiac and hepatic iron load. c-TDT patients were at a stable chelation schema prior to abrupt ferritin elevation. ROC analysis showed that the sensitivity and specificity of the changes in ferritin levels as a marker of malignancy were estimated at 90.48% and 100%, respectively, for increase more than 70.55% from baseline, and 96.9% and 85.7%, respectively, for absolute increase more than 442.4 ng/ml from baseline (**Figure 2**). Positive prognostic values were estimated at 100%, for relative ferritin increase more than 70.55% and at 64.29%, for absolute increase more than 442.4 ng/ml while negative prognostic value is 99.38% and 99.05% respectively.

Sensitivity stratified ROC analysis based on baseline ferritin levels in 2 groups: (i) </=1000 ng/ml, and (ii) >1000 ng/ml, revealed similar results. Specifically, regarding sensitivity and specificity of changes in ferritin levels as a marker of malignancy for the aforementioned two groups were estimated as follows: (i) for the </=1000 ng/ml baseline ferritin group, 86% and 81% respectively (cut off: 33.28%), and (ii) for the >1000 ng/ml baseline ferritin group, 57.1% and 91.0% respectively (cut off: 31.20%), indicating that this marker performs best for the lower baseline ferritin group.

The limitations of this study include its retrospective nature and being from a single institution. On the other hand, as a single-institution cohort study, patients were treated uniformly by the same medical team, even though there is heterogeneity in transfusion and iron chelation schemas which are individualized according to the needs of the patients. The study population is limited, thus, perspective investigation in larger cohorts is needed to confirm our findings.

In conclusion, this study investigated the clinical significance of serum ferritin as a prognostic factor for cancer development in TDT patients. Sharp increases in ferritin levels were shown to be indicative of malignant processes, with a high specificity and sensitivity, even in the light of secondary IO. Thus, sustained unexplained ferritin increases in TDT patients should prompt for timely evaluation for an underlying malignancy.

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Patient	Gender	Age at diagnosis (years)	Age at L.O. (years)	Type of cancer	Baseline ferritin** (ng/ml)	Ferritin levels* (ng/ml)	Chelation treatment	Outcome
1	Male	44	55	Thyroid carcinoma	556	230	DFX	In remission
2	Female	42	49	Renal cell carcinoma	223	873	DXF	In remission
3	Male	42	45	Renal cell carcinoma	599	2100	DFO+DFX	In remission
4	Female	48	56	Renal cell carcinoma	558	760	DFX	In remission
5	Female	48	48	Non-Hodgkin lymphoma	691	1520	DFX	In remission
6	Female	49	57	Hepatocellular carcinoma	144	389	DFO	Deceased
7	Female	45	57	Colorectal cancer	1785	3100	DFP+DFO	In remission
8	Female	45	46	Hepatocellular carcinoma	787	1700	DFP+DFO	Deceased
9	Male	46	47	Non-small cell lung carcinoma	601	2250	DFP+DFO	Deceased
10	Male	50	52	Hepatocellular carcinoma	1201	9550	DFX	Deceased
11	Male	48	48	Pancreatic carcinoma	757	3000	DFX+DFP	Deceased
12	Male	46	47	Cholangiocarcinoma	843	1800	DFX	Deceased
13	Female	41	43	Hepatocellular carcinoma	664	1515	DFP	Deceased
14	Male	54	56	Hepatocellular carcinoma	235	506	DFP	Deceased
15	Male	44	44	Hepatocellular carcinoma	1749	4600	DFP	Deceased
16	Female	43	43	Hepatocellular carcinoma	2096	2200	DFX	Deceased
17	Female	50	54	Hepatocellular carcinoma	236	1680	DFP+DFO	Deceased
18	Female	46	48	Hepatocellular carcinoma	3401	4150	DFX	Deceased

19	Female	45	47	Colorectal cancer	6335	7600	DFP+DFO	Deceased
20	Male	45	46	Hepatocellular carcinoma	1679	2850	DFP+DFO	Deceased
21	Male	39	52	Non-Hodgkin lymphoma	1612	2100	DFP+DFO	In remission
Median	n/a	45	48			1800		

Table 1. Characteristics of transfusion-dependent thalassemic patients with malignancy.
[DFO: desferrioxamine; DFP: deferiprone; DFX: deferoxamine; LO: Last observation corresponds to time of death or 31/12/2024; *: at time of cancer diagnosis; **: mean ferritin 3 years prior until 6 months prior to cancer diagnosis].

Figure 1.

Trends of serum ferritin levels during the 3 years prior to the diagnosis of cancer in 21 transfusion-dependent thalassemic patients who developed cancer.

(A) Individual trends

(B) Combined trend of ferritin level trajectories, assessed by a mixed effects model

Figure 2.

ROC curves for the changes of ferritin levels as a marker of cancer in transfusion-dependent thalassemic patients.

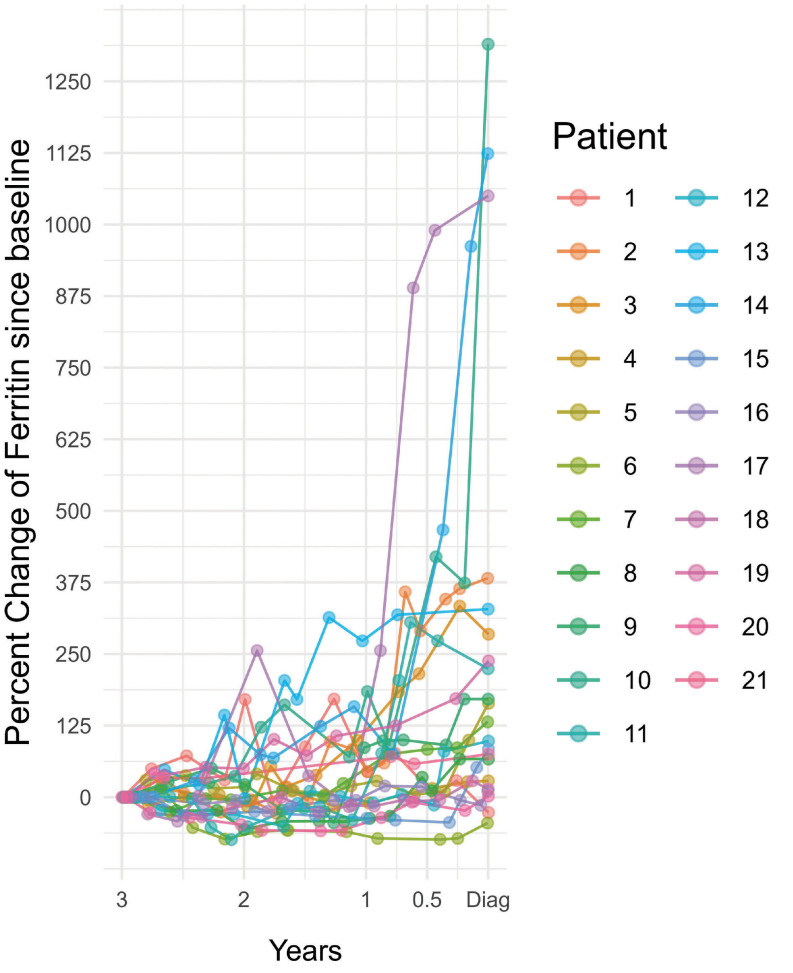
(A) model of relative (%) changes compared to previous levels observed 1-3 year prior to cancer diagnosis

(B) model of absolute changes (in ng/ml) compared to previous levels observed 1-3 year prior to cancer diagnosis

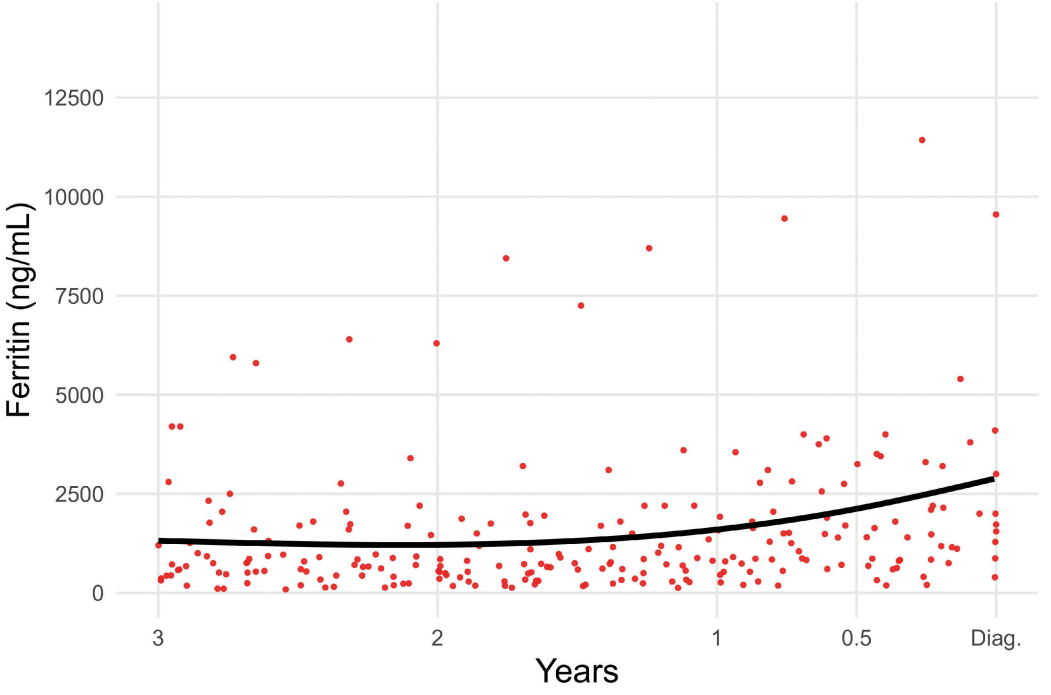
Sensitivity and specificity of the changes in ferritin levels as a marker of malignancy were estimated at 90.5% and 100%, respectively, for increase more than 71% from baseline, and 96.9% and 85.7%, respectively, for absolute increase more than 442 ng/ml from baseline.

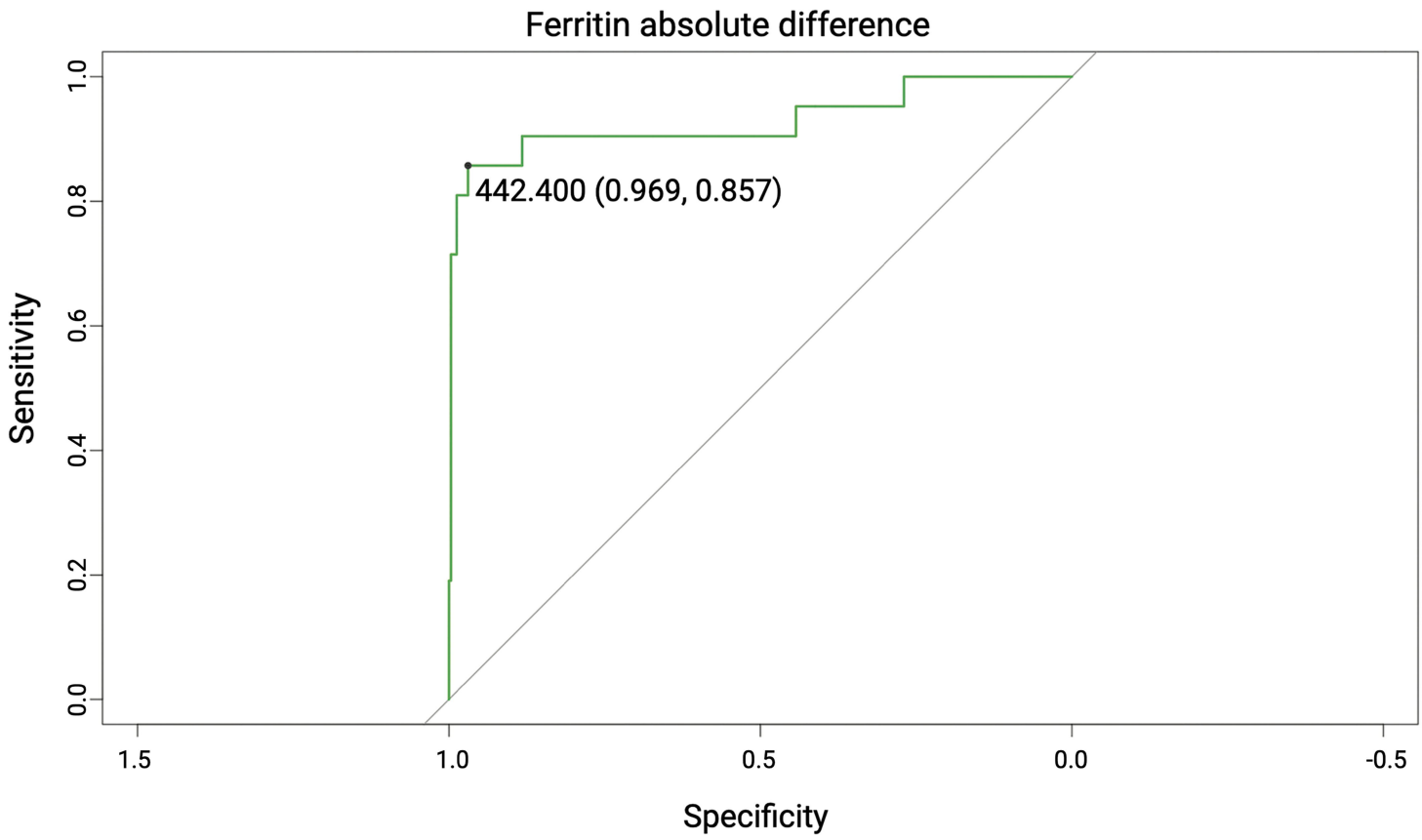
Patient ΔFerritin(%) Trajectories

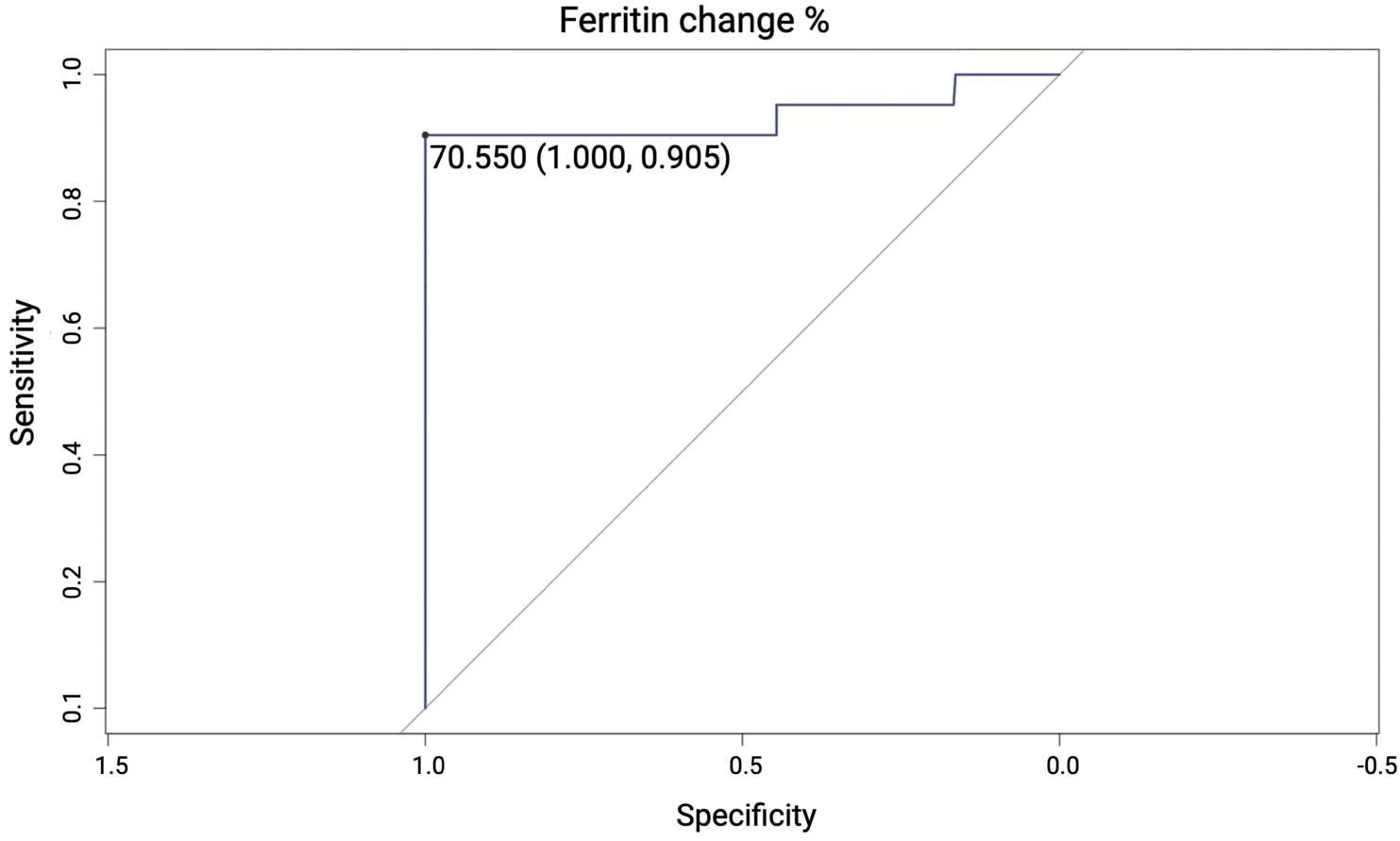
Up to cancer diagnosis timepoint



Combined Patient Ferritin Trajectory




Ferritin absolute difference
442.400 (0.969, 0.857)
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
1.5
1.0
0.5
0.0
-0.5


Ferritin change %
70.550 (1.000, 0.905)
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.1
1.5
1.0
0.5
0.0
-0.5