

The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study

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Table S1. Evaluation of laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress and in 888 patients with cancer according to anemic status

	Non anemic cancer patients (325)	Anemic cancer patients (563)	P value
Chronic Inflammation			
CRP, mg/l	4.1±0.8	14±1.1	<0.001
Fbg, mg/dl	380±109	452±169	0.020
IL-6, pg/ml	14.0±7.8	25.3±9.0	0.028
TNF- α , pg/ml	20±9	29±12	0.018
IL-1 β , pg/ml	18±8	37±18	0.009
Iron metabolism			
Serum observed EPO, mUI/ml	22±12	38.7±18	0.008
Observed/expected EPO ratio	0.9±0.8	0.4±0.3	0.020
Serum iron, g/dl	71±55	53±41	0.048
Transferrin, mg/dl	239±77	214±57	<0.001
Transferrin saturation,%	27±11	24±6	0.182
Ferritin, ng/ml	228±58	436±177	<0.001
Hepcidin, ng/ml	56±19	109±47	0.033
Nutritional status			
Leptin, ng/ml	0.7±0.3	0.4±0.1	0.026
Albumin, g/dl	4.1±0.6	3.5±0.5	<0.001
Cholesterol, mg/dl	194±63	170±46	0.015
HDL, mg/dl	55±15	41±19	0.001
LDL, mg/dl	107±39	100±30	0.063
Triglycerides, mg/dl	145.6±27	125±69	<0.001
Oxidative stress			
ROS, FORT U	370±180	410±113	0.036
SOD, U/ml	118±59.4	88±42	<0.001
GPx, U/l	8670±2350	7210±1228	<0.001

Results are considered significant for P<0.05 as calculated by Student's t test in comparison to non anemic patients. Abbreviations: CRP, C-reactive Protein; Fbg, Fibrinogen; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S2. Evaluation of laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress and in 888 patients with cancer according to stage of disease

	Stage I-II	Stage III-IV
Chronic Inflammation		
CRP, mg/l	1.2±0.8	13.5±1.3§
Fbg, mg/dl	327±68	439±142§
IL-6, pg/ml	5.9±3.8	28.9±20.5§
TNF- α , pg/ml	10.1±4.8	40.2±21.4§
IL-1 β , pg/ml	10.8±5.3	30±17§
Iron metabolism		
Serum observed EPO, mUI/ml	13.7±5.3	37.2±11.1
Observed/expected EPO ratio	1.01±0.6	0.44±0.39
Serum iron, g/dl	73.4±28.8	57.8±38.5
Transferrin, mg/dl	228±44.9	212±73
Transferrin saturation,%	28±14	23±5
Ferritin, ng/ml	325±253	485±354§
Hepcidin, ng/ml	55±6	105±51§
Nutritional status		
Leptin, ng/ml	0.4±0.5	0.2±0.03§
Albumin, g/dl	4.1±0.63	3.7±0.7
Cholesterol, mg/dl	196±56.8	176±45.2
HDL, mg/dl	55±12.6	47.2±19.5
LDL, mg/dl	113.3±22.7	103.8±37.1
Triglycerides, mg/dl	213.2±88.3	129.1±61.7§
Oxidative stress		
ROS, FORT U	345±38	403±113§
SOD, U/ml	138±59.4	88±42
GPx, U/l	9560±2435	7019±2928§

§ $P < 0.05$ in comparison to stage I-II cancer patients. Abbreviations: CRP, C-reactive Protein; Fbg, Fibrinogen; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S3. Evaluation of laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress and in 888 patients with cancer according to stage of disease and anemic status

	Stage I		Stage II		Stage III		Stage IV	
	No anemia (13)	Anemia (2)	No anemia (105)	Anemia (25)	No anemia (76)	Anemia (37)	No anemia (131)	Anemia (499)
Chronic Inflammation								
CRP, mg/l	1.1±0.04	1.2±0.1	1.1±0.8	1.3±0.7	5.6±1	10±2.1*	13±2.7	20±4.2*
Fbg, mg/dl	318±156	345±174	339±47	352±122	394±125	425±230	429±132	490±155*
IL-6, pg/ml	2.1±0.4	2.6±0.5	5.6±2.8	6.8±3.5	12.4±7.6	18±8.1*	22±5.7	35±11*
TNF-α, pg/ml	9.8±1.4	10.2±1.9	9.7±5.6	12±6.7	16.1±7.9	18±11	38±9	45±21*
IL-1 β, pg/ml	9±4.1	10±3.2	11.8±3.4	14±6.9	21±6.4	22±5.6	31±14	35±16*
Iron metabolism								
Serum observed EPO, mUI/ml	16±6	10±8	18±8	16±14	20±8	38.9±10*	31.2±7	51±15*
Observed/expected EPO ratio	1.1±0.4	0.9±0.3	1.0±0.6	0.8±0.6	0.9±0.8	0.5±0.3*	0.7 ±0.5	0.3±0.1*
Serum iron, g/dl	80.7±32	63±20	89±38	73±31*	66±37	50±24*	58±26	42±25*
Transferrin, mg/dl	250±32	250±44	251±136	260±57	230±91	205±84	220±63	190±61
Transferrin saturation,%	30±6	25±5	35±7	28±3	29±2	24±9	26±6	22±5
Ferritin, ng/ml	196±53	208±44	349±153	280±1*65	340±218	386±245	434±264	518±285*
Hepcidin, ng/ml	44±12	49±17	51±19	55±23	67±15	90.8±29*	87.7±25	138±24*
Nutritional status								
Leptin, ng/ml	0.7±0.2	0.6±0.04	0.7±0.2	0.5±0.2*	0.47±0.2	0.36±0.3*	0.4±0.2	0.2±0.05*
Albumin, g/dl	4.3±0.5	3.8±0.9	4.4±0.2	3.7±0.5*	4±0.6	3.6±0.4	3.7±0.8	3.1±0.7*
Cholesterol, mg/dl	185±37	161±25	261±37	163±43*	193±37	180±47	181±52	151±38*
HDL, mg/dl	54±11	51±16	64±22.6	48±21*	58±14	47±18	51±18	35±19*
LDL, mg/dl	111±14	100±25	121±34	113±45	108±27	99±61	98±40	95±33
Triglycerides, mg/dl	218±32	214±52	219±137	203±61	123±66	113±31	110±65	108±53
Oxidative stress								
ROS, FORT U	310±33	340±54	345±58	365±76	390±125	370±134	410±160	480±123*
SOD, U/ml	125±35	133±41	146±49	126±79	108±41	92±37	88±22	78±42
GPx, U/l	9750±3240	9320±2890	9890±2560	9230±3190	8960±1130	7580±1260	8450±2170	6210±1328*

**p*<0.05 as assessed by ANOVA test. Abbreviations: CRP, C-reactive Protein; Fbg, Fibrinogen; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S4. Evaluation of laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress and in 888 patients with cancer according to tumor site

	Ovary (178)	Breast (133)	Lung (178)	Prostate (53)	Upper GI (142)	Lower GI (37 (115)	Head and neck (62)	Bladder (27)
Chronic Inflammation								
CRP, mg/l	13.6±2.4	6.2±1.3	10.3±1.5	8.5±1.6	6.3±1.2	6.1±1	8.9±3.5	7.5±1.2*
Fbg, mg/dl	466±155	390±80	483±158	424±160	386±163	390±100	433±197	450±135
IL-6, pg/ml	37±16	25±10	52±23	22.5±1.4	26±5	26±7.5	18±3	25±5*
TNF-α, pg/ml	33±6	25±8	27±9	26±6.7	33±11	17±5.3	19±4	23±16
IL-1 β, pg/ml	21±9.9	18±8	39±11	19±9.8	25±6	15±7	16.9±3	12±3.9
Iron metabolism								
Serum observed EPO, mIU/ml	40.3±18	23.8±14	33.3±16	30.3±13	31±12	37±17	20.7±5.6	28±11
Observed/expected EPO ratio	0.3±0.1	0.8±0.4	0.5±0.36	0.9±0.4	0.4±0.3	1.1±0.6	1.1±0.4	0.4±0.1
Serum iron, g/dl	66±19	74±34	55±15	71±12	51±36	52±37	84±47	54±25*
Transferrin, mg/dl	202±67	259±67	181±47	286±39	45±62	252±63	246±41	189±45
Transferrin saturation,%	23±3	27±3	30±5	25±3	21±7	20±6	29±12	28±2
Ferritin, ng/ml	420±157	262±129	418±182	339±97	137±62	102±65	334±113	302±162*
Hepcidin, ng/ml	68±39	38±16	62±29	44±13	38±19	34±12	40±18	55±28*
Nutritional status								
Leptin, ng/ml	0.4±0.3	0.7±0.4	0.5±0.3	0.4±0.3	0.2±0.1	0.6±0.3	0.2±0.06	0.2±0.08
Albumin, g/dl	3.6±0.8	4.2±0.5	3.5±0.8	4.1±0.7	3.8±0.6	3.6±0.9	4.3±0.1	3.7±0.8
Cholesterol, mg/dl	178±46	200±45	177±55	185±22	160±33	175±59	162±24	173±48
HDL, mg/dl	48±15	56±12	48±23	60±17	39±14	34±16	48±10	44±18
LDL, mg/dl	91±40	125±26	107±49	101±23	96±22	114±45	95±32	94±23
Triglycerides, mg/dl	126±51	158±32	116±35	111±63	135±87	159±76	125±82	115±86
Oxidative stress								
ROS, FORT U	429±109	377±98	409±124	430±113	351±100	352±113	425±126	336±85
SOD, U/ml	98±35	133±41	89±29	116±79	94±36	124±61	78±32	98±42
GPx, U/l	8450±324	9420±290	6980±2610	9830±2190	7190±1870	10540±2305	6800±1230	9219±1280

* $p < 0.05$ as assessed by ANOVA test. Abbreviations: CRP, C-reactive Protein; Fbg, Fibrinogen; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S5. Correlation of Hb levels with markers of chronic inflammation, iron metabolism, nutritional status and oxidative stress among cancer patients at different stage of disease

Parameters	Stage I-II		Stage III-IV	
	Pearson	<i>P</i>	Pearson	<i>P</i>
Chronic inflammation				
CRP	-0.164	0.631	-0.338	<0.001
Fbg	-0.250	0.369	-0.250	0.001
IL-6	-0.118	0.145	-0.410	<0.001
TNF- α	-0.177	0.717	-0.264	0.026
IL1 β	-0.266	0.169	-0.266	0.036
Iron metabolism				
Serum observed EPO	-0.981	<0.001	-0.364	0.011
Serum iron	0.414	0.012	0.494	<0.001
Transferrin	0.116	0.087	0.316	0.010
Transferrin saturation	0.418	0.022	0.318	0.012
Ferritin	0.294	0.041	-0.384	0.016
Hepcidin	-0.159	0.121	-0.309	0.001
Nutritional status				
Leptin	0.540	0.021	0.479	0.021
Albumin	0.414	0.002	0.371	0.002
Total Cholesterol	0.547	0.001	0.368	0.001
HDL	0.397	0.041	0.359	0.011
LDL	0.162	0.701	0.150	0.342
Triglycerides	0.164	0.238	0.113	0.317
Oxidative stress				
ROS	-0.140	0.070	-0.340	0.006
SOD	0.268	0.230	0.268	0.036
GPx	0.155	0.130	0.355	0.002

Results are considered significant for $P < 0.05$. Abbreviations: Fbg, Fibrinogen; CRP, C-reactive Protein; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin, ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S6. Correlation of Hb levels with markers of chronic inflammation, iron metabolism, nutritional status and oxidative stress according to performance status

Parameters	KPS 100-70		KPS 40-0	
	Pearson	<i>P</i>	Pearson	<i>P</i>
Chronic inflammation				
CRP	-0.393	0.015	-0.420	<0.001
Fbg	-0.350	0.010	-0.380	0.003
IL-6	-0.609	<0.001	-0.584	<0.001
TNF- α	-0.223	0.038	-0.496	0.043
IL1 β	-0.296	0.016	-0.266	0.022
Iron metabolism				
Serum observed EPO	-0.318	0.018	-0.284	0.021
Serum iron	0.575	<0.001	0.334	0.033
Transferrin	0.260	0.047	0.216	0.018
Transferrin saturation	0.318	0.012	0.395	0.002
Ferritin	0.464	<0.001	-0.385	0.001
Hepcidin	-0.545	<0.001	-0.409	<0.001
Nutritional status				
Leptin	0.428	<0.001	0.490	<0.001
Albumin	0.492	0.001	0.352	0.033
Total Cholesterol	0.422	0.001	0.364	0.018
HDL	0.486	0.003	0.307	0.044
LDL	0.052	0.779	0.181	0.065
Triglycerides	0.167	0.206	0.164	0.084
Oxidative stress				
ROS	-0.304	0.007	-0.340	0.005
SOD	0.368	0.030	0.289	0.016
GPx	0.355	0.034	0.355	0.004

Results are considered significant for $P < 0.05$. Abbreviations: KPS, Karnofsky Performance Status; Fbg, Fibrinogen; CRP, C-reactive Protein; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin, ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S7. Correlation of Hb levels with markers of chronic inflammation, iron metabolism, nutritional status and oxidative stress according to tumor site

	Ovary	Breast	Lung	Prostate	Upper GI	Lower GI	Head and neck	Bladder
Chronic Inflammation								
CRP, mg/l	-0.636*	-0.391*	-0.379*	-0.585*	-0.371*	-0.321*	-0.468*	-0.399*
Fbg, mg/dl	-0.367*	-0.311*	-0.285*	0.532*	0.154	-0.166	-0.271	-0.110
IL-6, pg/ml	-0.418*	-0.360*	-0.560*	0.682*	-0.388*	-0.419*	-0.767*	-0.354*
TNF- α , pg/ml	-0.342*	-0.222	-0.509*	0.604*	-0.140	-0.620*	-0.406*	-0.074
IL-1 β , pg/ml	-0.373*	0.108	-0.362*	0.558*	-0.250	-0.350*	-0.340*	-0.284*
Iron metabolism								
Serum observed EPO, mIU/ml	-0.957*	-0.959*	-0.650*	-0.540*	-0.670*	-0.261*	-0.371*	-0.410*
Observed/expected EPO ratio	0.452*	0.812*	0.673*	0.420*	0.638*	0.501*	0.961*	0.520*
Serum iron, g/dl	0.326*	0.373*	0.378*	0.394*	0.278*	0.474*	0.326*	0.210*
Transferrin, mg/dl	0.168	0.062	0.483*	0.127	0.356*	0.221	0.336*	0.140
Transferrin saturation,%	0.198	0.145	0.250*	0.150	0.450*	0.341*	0.633*	0.310*
Ferritin, ng/ml	-0.431*	0.023	-0.315*	-0.256*	0.711*	0.596*	-0.736*	-0.478*
Hepcidin, ng/ml	-0.601*	-0.300*	-0.443*	-0.340*	0.281	-0.367*	0.159	-0.370*
Nutritional status								
Leptin, ng/ml	0.335*	-0.298	0.452*	0.520*	0.324*	0.140	0.450*	0.382*
Albumin, g/dl	0.651*	0.513*	0.698*	0.434*	0.380*	0.201	0.587*	0.387*
Cholesterol, mg/dl	0.454*	0.560*	0.396*	0.116	0.525*	0.098	0.472*	0.240*
HDL, mg/dl	0.505*	0.311*	0.509*	0.119	0.096	0.065	0.380*	0.326*
LDL, mg/dl	0.373*	0.045	0.076	0.056	0.094	0.049	0.048	0.122
Triglycerides, mg/dl	0.026	0.207	0.104	0.098	0.007	0.010	0.101	0.010
Oxidative stress								
ROS, FORT U	-0.306*	-0.320*	-0.540*	-0.374*	-0.265*	0.320*	-0.570*	-0.349*
SOD, U/ml	0.240*	0.080	0.245*	0.155	0.024	0.150	0.250*	0.364*
GPx, U/l	0.354*	0.350*	0.386*	0.350*	0.550*	0.320*	0.382*	0.507*

* $P < 0.05$ calculated with Spearman correlation test. Abbreviations: CRP, C-reactive Protein; Fbg, Fibrinogen; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S8. Correlation of observed/expected EPO ratio with markers of chronic inflammation, and oxidative stress in patients with cancer at different sites

Parameters	Pearson	P
Chronic inflammation		
CRP	-0.500	0.035*
Fbg	-0.500	0.035*
IL-6	-0.357	0.045*
TNF- α	-0.223	0.052
IL1 β	-0.266	0.060
Oxidative stress		
ROS	-0.440	0.007**
SOD	0.368	0.002**
GPx	0.455	0.003*

Results are considered significant for $P < 0.05^*$ and highly significant for $p < 0.01^{**}$. Abbreviations: Fbg, Fibrinogen; CRP, C-reactive Protein; IL, Interleukin; TNF, Tumor Necrosis Factor; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S9. Evaluation of laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress in the population of anemic cancer patients according to Hb levels (Hb \geq 10 g/dl vs Hb $<$ 10 g/dl)

Parameters	Hb categories		p value
	Hb \geq 10.0 gr/dl	Hb $<$ 10.0 gr/dl	
Chronic inflammation			
CRP	6.2 \pm 10.5	17 \pm 18.4	<0.001
Fbg	422 \pm 132	492 \pm 170	<0.001
IL-6	16.7 \pm 10.5	26.6 \pm 13.2	0.013
TNF- α	17.3 \pm 9.5	24.1 \pm 14.4	0.066
IL-1 β	21.5 \pm 16.4	27.7 \pm 17.2	0.310
Iron metabolism			
Serum EPO	23.1 \pm 7.8	38 \pm 14.3	0.035
Serum iron	63.1 \pm 38.1	39.9 \pm 34.7	0.075
Transferrin	220.4 \pm 65.3	183 \pm 55.4	0.883
Transferrin saturation	21 \pm 6	24 \pm 5	0.051
Ferritin	444.2 \pm 359.55	637.0 \pm 680.5	<0.001
Hepcidin	84.33 \pm 38.54	121.1 \pm 53.77	0.032
Nutritional status			
Albumin	3.9 \pm 0.7	2.9 \pm 0.8	0.001
Leptin	0.6 \pm 0.2	0.4 \pm 0.3	0.019
HDL	51.7 \pm 17.6	31.6 \pm 11.94	0.003
LDL	107.3 \pm 35.1	85.8 \pm 16.9	0.148
Total cholesterol	185.5 \pm 46.7	141.7 \pm 18.8	<0.001
Triglycerides	135.2 \pm 89.9	125.9 \pm 54.9	0.691
Oxidative stress			
ROS	381.2 \pm 103.5	474 \pm 126.2	<0.001
SOD	106.1 \pm 45.5	92.6 \pm 46	0.666
GPx	7402 \pm 3003	5447 \pm 1925	0.002

Abbreviations: BMI, body mass index; Fbg, Fibrinogen; CRP, C-reactive Protein; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.

Table S10. Evaluation of Hb levels in the population of anemic cancer patients according to quartiles of the laboratory parameters of chronic inflammation, iron metabolism, nutritional status and oxidative stress

Hb mean levels (g/dl) according to quartiles of different parameters (from the lowest to the highest value)						
	1	2	3	4	<i>P</i>	<i>Test for trend</i>
Chronic Inflammation						
CRP	11.1±0.9	10.9±1.1	10.5±1.4	10.1±1.1	<0.001	<0.001
Fibrinogen	10.9±1.1	10.4±1.4	10.8±1.2	10.5±1.2	0.031	0.125
IL-6	10.9±0.8	10.7±1.2	10.5±1.3	10.2±1.3	0.019	0.019
TNF- α	10.7±1.4	10.6±1.2	10.7±1.1	10.3±1	0.290	0.176
IL1 β	11.1±1.1	10.4±1.1	10.3±1.0	10.2±1.1	0.033	0.011
Iron Metabolism						
Serum EPO	11.3±0.6	10.8±1.2	10.5±1.3	10.2±1.3	0.029	0.021
Serum iron	10.1±1.3	10.6±1.3	10.8±1.3	11.1±1.0	0.001	<0.001
Transferrin	10.2±1.2	10.4±1.3	11.3±1.3	10.6±1.1	0.006	0.055
Transferrin saturation	9.5±0.2	10.1±0.6	10.7±1.1	11.3±1.5	0.003	0.034
Ferritine	10.4±1.1	10.7±1.3	11.2±1.1	10.7±1.2	0.195	0.250
Hepcidin	10.8±0.7	10.5±0.9	10.6±0.5	10.1±0.3	0.046	0.036
Nutritional status						
Leptin	10.0±1.2	10.7±0.9	10.7±1.3	10.9±0.7	0.012	0.023
Albumin	9.9±1.3	10.8±1.2	10.4±1.6	11±1.1	0.243	0.119
Total cholesterol	10.2±1.3	10.4±1.4	10.6±1.3	11.6±0.7	0.007	0.001
HDL	9.8±1.5	10.9±1.0	10.6±1.4	11.6±1.0	0.054	0.015
LDL	11.1±1.2	10.0±1.1	11±1.3	11.3±1.2	0.183	0.470
Triglycerides	11±1.4	10.8±1.3	9.9±1.1	11±1.2	0.049	0.625
Oxidative stress						
ROS	10.8±0.8	11.1±1.3	10.2±0.9	10.4±1.1	0.035	0.035
SOD	10.6±1.2	10.0±1.2	10.9±0.9	11.1±1.2	0.017	0.050
GPx	10.5±1.1	10.0±1.1	10.7±1.0	11.4±0.9	<0.001	<0.001

Groups are compared by ANOVA test. Results are considered significant for $p \leq 0.05$. Significant p-values are reported in bold. Abbreviations: CRP, C-reactive protein; IL, Interleukin; TNF, Tumor Necrosis Factor; EPO, erythropoietin; ROS, reactive oxygen species; SOD, superoxide dismutase; GPx, Glutathione Peroxidase.