Treating ID in medical and surgical condition

Jun Ho Jang

Hematology-Oncology

Samsung Medical Center

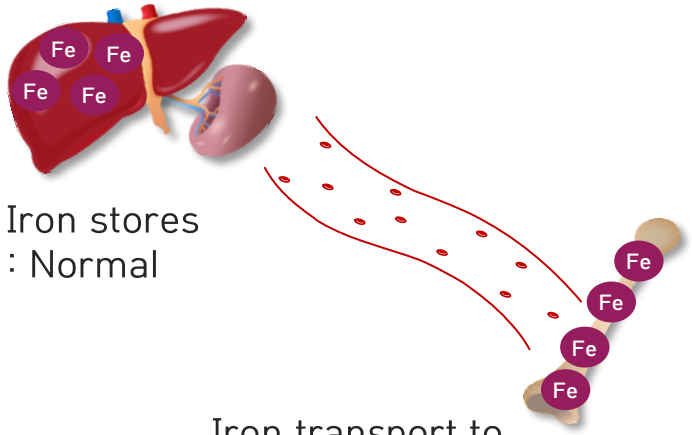
Sungkyunkhan University School of Medicine

Contents

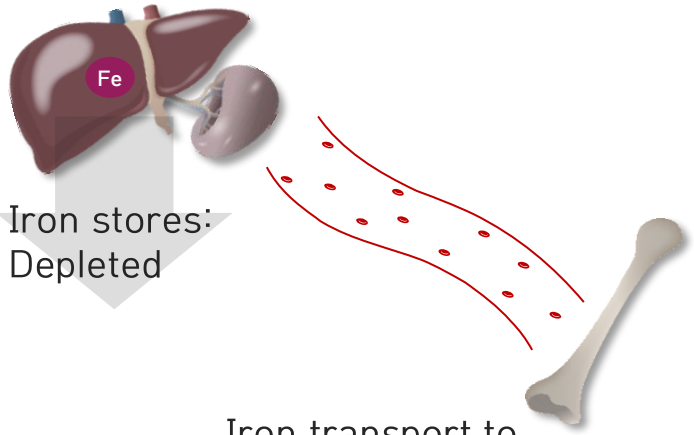
1. Medical conditions
2. Surgical conditions
3. Cancer patients

Iron Deficiency

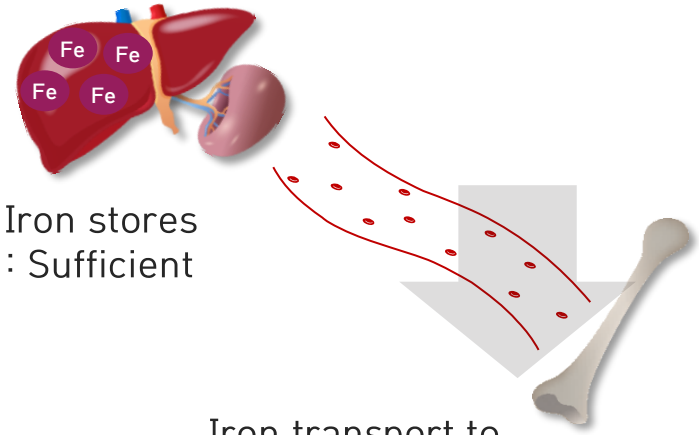
Normal



Absolute Iron Deficiency(AID)

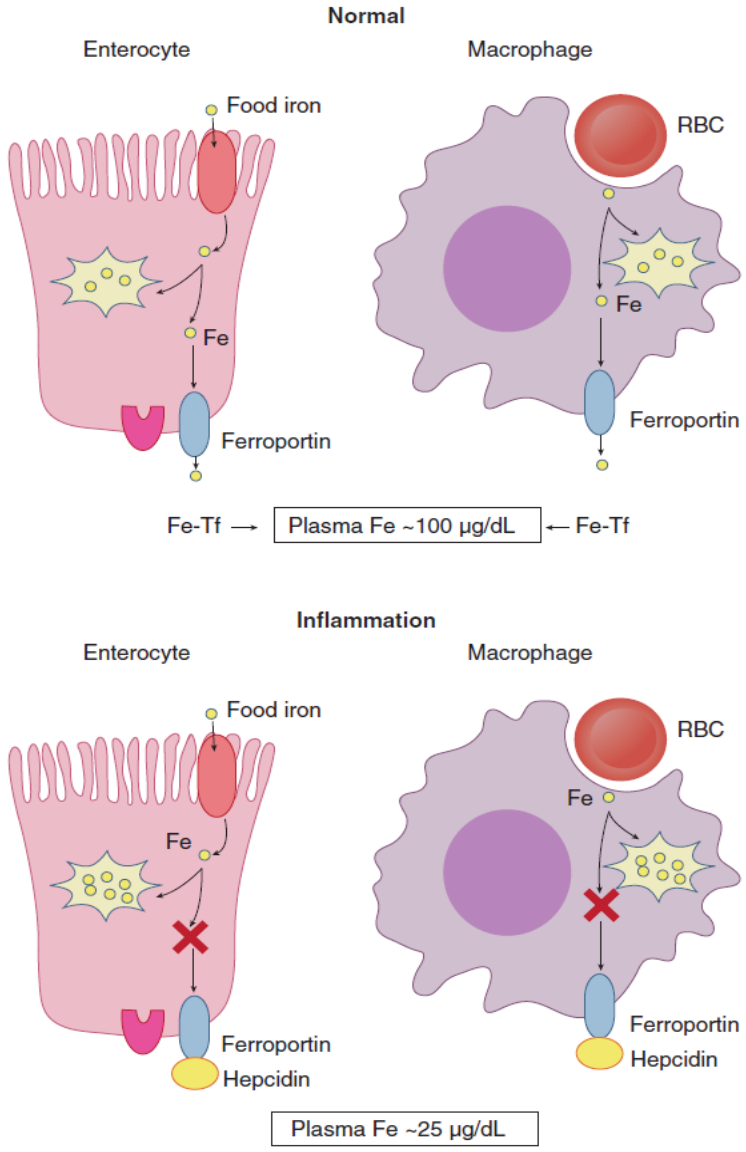


Functional Iron Deficiency(FID)



Condition	Iron stores are **actually depleted**	Iron stores are apparently adequate, but there is **insufficient iron supply** for erythropoiesis
Cause	Nutritional deficiencies, blood losses	Upregulated **hepcidin** by cytokines release or CKD
Ferritin	<30ng/mL	30-500ng/mL
TSAT (Iron/TIBC x 100%)	**<20%**	**<50%**

Anemia of inflammation or chronic illness (AOI)



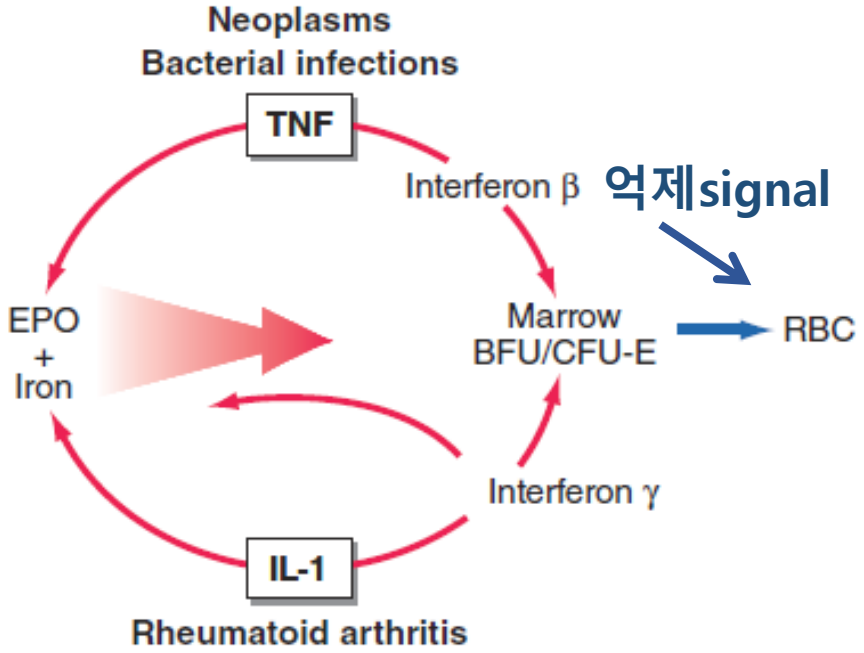


TABLE 93-4 Diagnosis of Microcytic Anemia

TESTS	IRON DEFICIENCY	INFLAMMATION
Smear	Micro/hypo	Normal micro/hypo
Serum iron (µg/dL)	<30	<50
TIBC (µg/dL)	>360	<300
Percent saturation	<10	10–20
Ferritin (µg/L)	<15	30–200
Hemoglobin pattern on electrophoresis	Normal	Normal

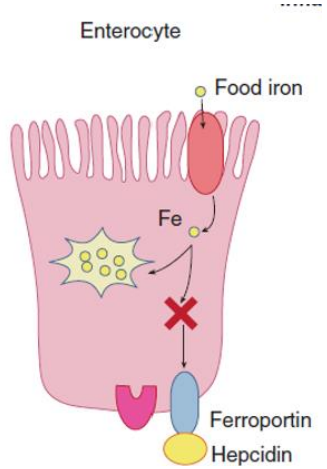
Abbreviation: TIBC, total iron-binding capacity.

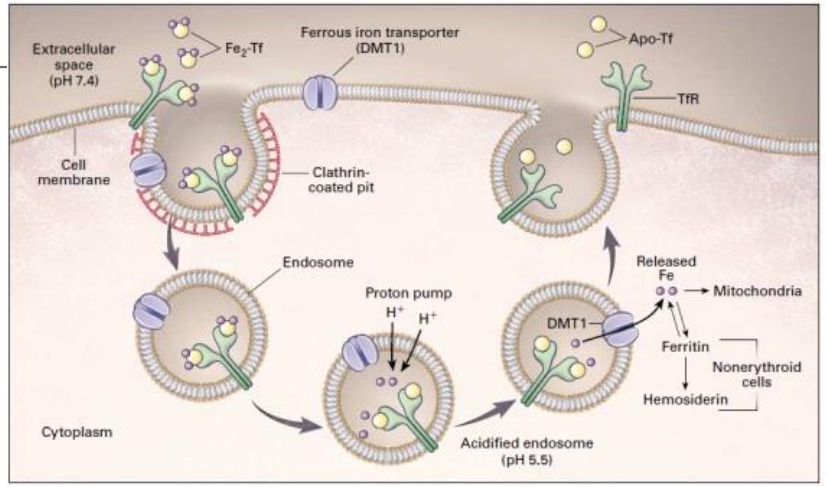
Goldman's Cecil of Medicine, 24th ed

Biomarkers in inflammatory condition

Table 2. Effects of cytokines on iron metabolism and erythropoiesis

Cytokines	Effects on red cell dynamics
TNF-α inhibition of erythropoietin production	Stimulation of ferritin synthesis Enhances degradation and phagocytosis of effete red cells Direct inhibition of erythropoiesis
IFN-γ inhibits production of erythropoietin	Increases intracellular iron by stimulation of DMT-1 and inhibition of ferroportin Increased nitric oxide production and inducible nitric oxide synthase mRNA expression
IL-6 increases iron uptake via DMT-1 activation	Reduces TfR by decreasing TfR RNA expression Downregulates expression of SLC4a1 in erythroid precursors
IL-4 and -10 increase ferritin via action on iron regulatory elements/proteins	





- **Ferritin**
  - **염증 시 상승** (acute-phase reactant)

- **TSAT**: Iron/TIBC x 100 (%)
  - **Serum iron**
    - **염증 시 hepcidin 상승** → **serum iron 감소**
  - **TIBC** (Total Iron Binding Capacity)
    - 혈액 내 모든 transferrin이 **결합 가능한 철의 총량 (잠재적 철 결합 능력)**
    - **TIBC (μg/dL) ≈ Transferrin (mg/dL) × 1.25**
    - **Transferrin**은 negative acute-phase reactant → **염증 시 감소**

ADC ⇒ AOI ≠ FID

Functional iron deficiency는 AOI 및 Chronic disease나 Cancer anemia의 중요한 mechanism중 하나,

AOI에는 Functional iron deficiency 이외에도 다양한 기전이 작용.
(조혈감소, 적혈구 생존 감소, EPO 반응성 감소, 골수 침윤 등..)

FID 감별을 통한 parenteral iron therapy의 적용은 일부 AOI 및 Cancer anemia개선에 도움

Special situations in the context of FID

HF - CKD - IBD

- 심장 자체에도 철이 필요: Mitochondrial function, ATP 생성에 필수 → 철 결핍 시 심근 수축력 저하
- 심부전시 골격근, 심근의 철 수요 ↑ : 철 결핍이 있으면 산소 이용 효율 ↓, 운동능력 저하
- 심부전 → 전신 염증 → IL-6 증가 → Hepcidin 증가 → FID 유발
- Anemia는 HF 예후를 악화시킴, 그러나 Anemia가 없어도 iron deficiency 자체가 HF 예후를 악화
- Anemia 여부와 무관하게 FID 집단에서 IV iron 유용성 (심장 연관 outcome 개선)이 입증되었음

1. 철결핍 상태로 평가되면
- Ferritin < 100 µg/L or
- Ferritin 100–299 µg/L when TSAT<20%

2. (Hb 15 초과하지 않는다면) 빈혈여부와 상관없이 고용량 iv iron 제제를 투약

Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] 12,41,47–49	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.[c] 12,41,43–46	IIa	A

1. McDonagh TA, et al. Eur Heart J. 2021;42(36):3599-3726; 2. McDonagh TA, et al. Eur Heart J. 2023 Aug 25; doi: 10.1093/eurheartj/ehad195.

Special situations in the context of FID

HF - CKD - IBD

- 신부전 → 요독증, 만성 염증 → IL-6 및 염증상 사이토카인 증가 → Hepcidin 증가 → FID 유발
- Erythropoietin (EPO) 생성 감소 → ESA 치료 필요
- FID 상태에서는 ESA 단독 치료 효과 떨어짐 (ESA 반응하려면 충분한 기능적 철 공급이 전제조건이 되어야함)
- 경구 대비 IV iron 사용을 권고하고 있음.

- Several Guidelines

1. NKF-Kidney Disease Outcomes Quality Initiative (KDOQI)
2. National Institute for Clinical Excellence (NICE)
3. KDIGO 2012
4. European Best Practice

① Guideline 별로 ID 치료를 권고하는 ferritin, TSAT 수치가 상이 (Ferritin <100, <200, <300, not exceeding 500 or 800, **TSAT 20-30%)**
② ESA 사용 여부에 따라서도 상이
(ID 평가 기준으로서 TSAT, ferritin 수치가 상향)
③ 투석 여부에 따라서도 상이
(투석을 하면 ID 평가 기준으로서 ferritin 수치가 상향)

1. KDOQI. *Am J Kidney Dis.* 2006;47(5 Suppl 3): S58-70; 2. NICE guideline [NG203] Published: 25 August 2021 Available at https://www.nice.org.uk/guidance/ng203. assessed May 2023; 3. KDIGO Clinical practice guideline for anemia in chronic kidney disease Kidney Inter Suppl. 2012;2:279-335; 4. Locatelli F et al. *Nephrol Dial Transplant*. 2013;28:1346–1359; 5. Babitt J, et al . *Kidney International.* 2021;99, 1280–1295.

Special situations in the context of FID

HF - CKD - IBD

- 위장관 출혈, 장 점막의 흡수장애, 염증 상태 등의 IBD 병태생리상 경구 iron의 흡수 제한
- 경구 iron에 대한 내약성 낮음: 복통, 설사, 악화된 장 증상 유발 가능성 있음.
- 철 결핍성 빈혈 교정에서 IV iron이 경구 iron보다 효과적

Clinical Gastroenterology and Hepatology 2024;22:1575–1583

CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review

Check for updates

There is some controversy about the best route to supplement iron in patients with IBD. Many studies have demonstrated that IV iron appears to be superior to oral iron in patients with IBD.[59–61] In a systematic

oral iron. In fact, current consensus recommendations by the European Crohn's and Colitis Organization recommend IV over oral iron as first-line therapy for patients with a hemoglobin level <10 g/dL.[62]

References: PMID 38864796

ECCO

ECCO anaemia statement 2C:

- IV iron should be considered as first line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with Hb below 10 g/dl, and in patients who need ESAs [EL1]

Prevention of iron deficiency anaemia

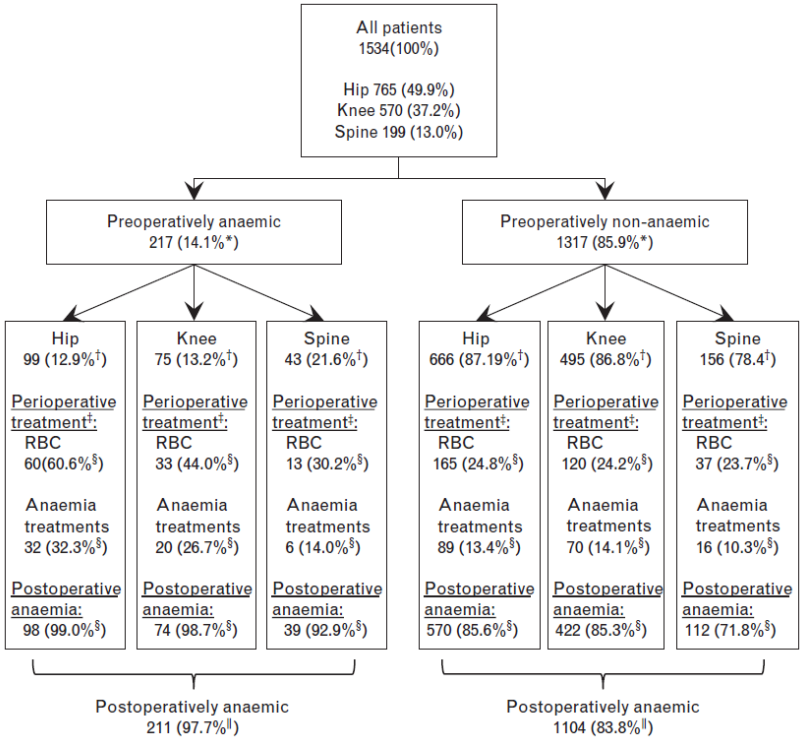
ECCO anaemia statement 3A:

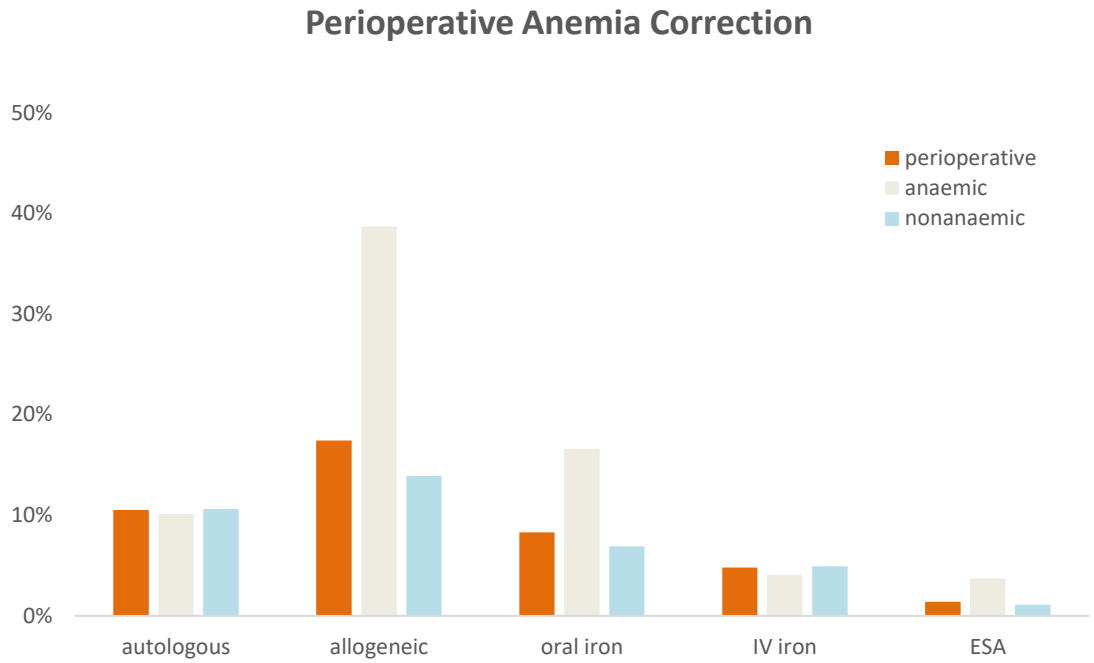
- Patients with IBD should be monitored for recurrent iron deficiency every 3 months for at least a year after correction and between 6 and 12 months thereafter [EL4]

Dignass AU et al. J Crohns Colitis. 2015;9:211-22

PREPARE: the prevalence of perioperative anaemia and need for PBM in elective orthopedic surgery

- Anaemia prevalence increased from 14.1% preoperatively to **85.8%** postoperatively.
- Perioperative anaemia correction (mainly **transfusion**) was given to **34.3%.**

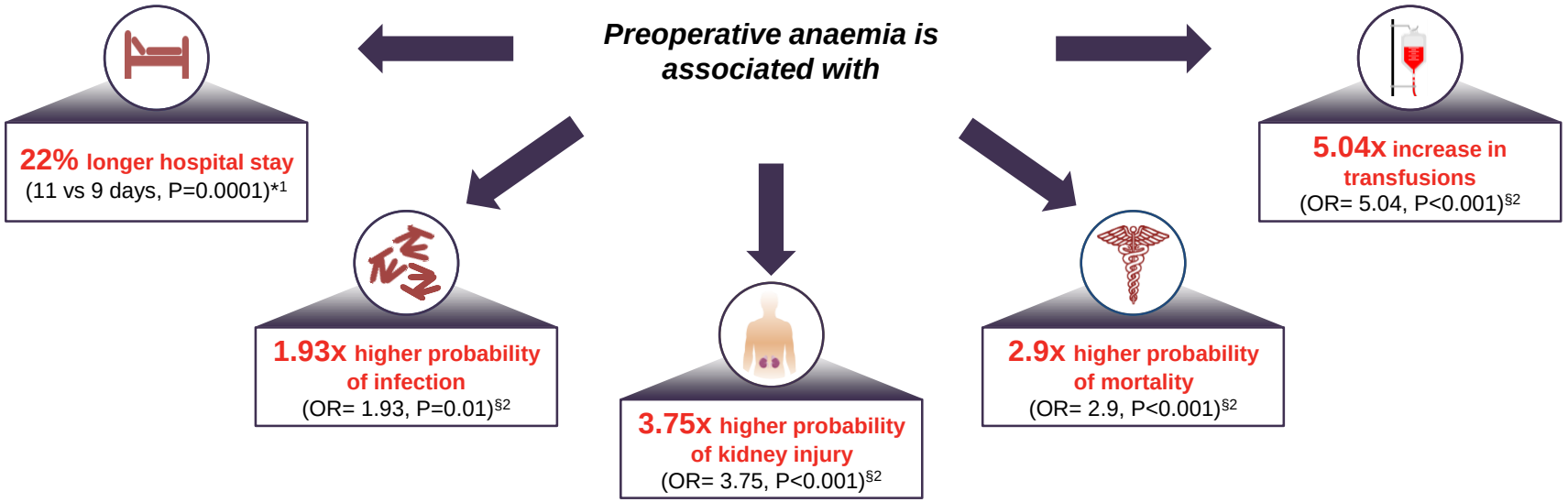




- **1534 patients undergoing major elective hip, knee or spine surgery [49.9% hip, 37.2% knee, 13.0% spine] Prevalence of preoperative (primary endpoint) and postoperative anaemia [haemoglobin (Hb) <13 g dl1 (male), Hb <12 g dl1 (female)], perioperative anaemia management, time to first blood transfusion and number of transfused units**

Eur J Anaesthesiol. 2015 Mar;32(3):160-7

Preoperative anaemia has a negative impact on patient outcomes[1,2]

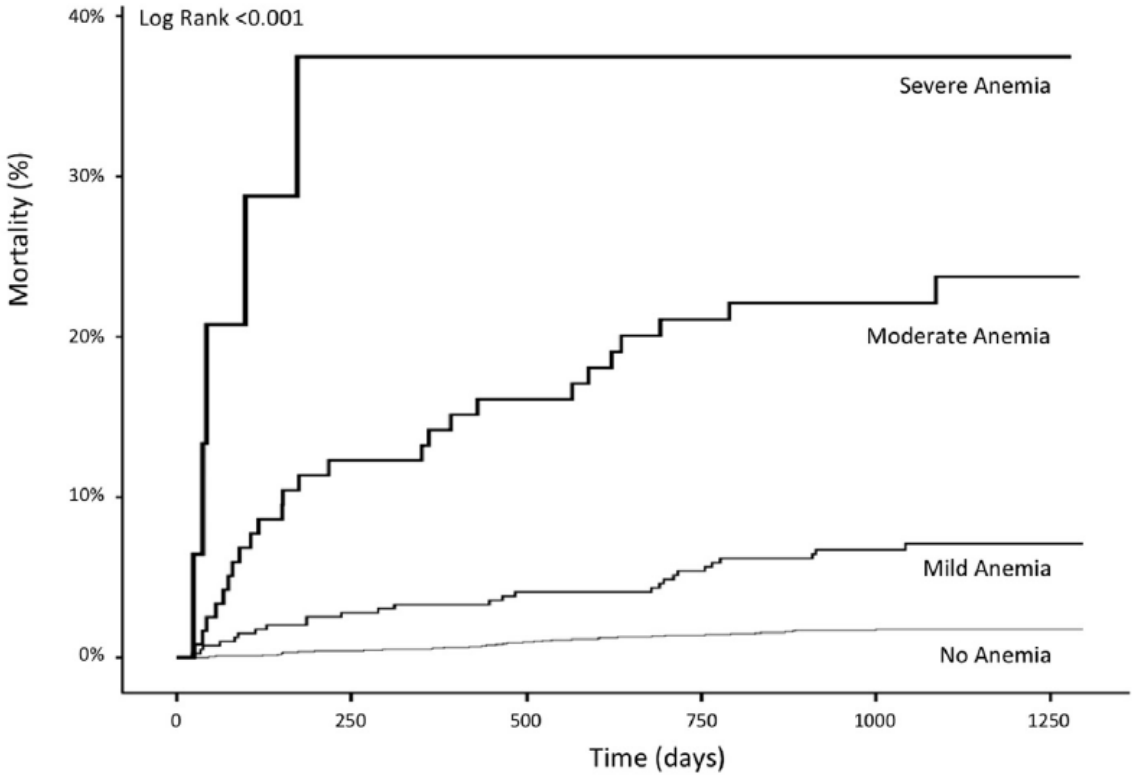


* Retrospective single-centre cohort study of consecutive patients >18 years undergoing non-cardiac surgery between March 2003 and June 2006 (N= 7,759). Shown are the propensity-matched values for variables that are potential confounders in the relationship between anaemia and postoperative mortality (N=2,090).1
§ Systematic review and meta-analysis of observational studies exploring associations between preoperative anaemia and postoperative outcomes (24 studies N=949,445).2
† Retrospective cohort study of major non-cardiac surgery in 2008 (a prospective validated outcomes registry from 211 hospitals worldwide, N=227,425). OR presented had an extended adjustment for a large number of clinically relevant variables.3

1. Beattie WS et al. Anesthesiology. 2009;110(3):574–81
2. Fowler AJ et al. Br J Surg. 2015;102(11):1314–24

Preoperative anaemia, even to a mild degree, is independently and significantly associated with long-term mortality

3050 patients underwent hip, knee and spinal surgery in a single centre in the USA between 2008 and 2009



Long-term mortality increases with incre ased severity of pre operative anaemia*

*Anaemia defined as Hb <13 g/dL (males) and Hb <12 g/dL (females); P<0.001 versus no anaemia
Hb, haemoglobin

Smilowitz NR et al. Am J Med 2016;129:315–323

Preoperative anaemia is significantly associated with adverse surgical outcomes – 2010 literature review

49 studies examining the effect of preoperative anaemia on patients who underwent total hip or knee arthroplasty and hip fracture surgery were included

Reference	Type of Surgery	Study Design	Definition of Anemia (Hb Level in g/dl)	No.	Mean Age, yr	Predefined Clinical Outcomes Associated with Anemia vs. No Anemia				
						Quality of Life	Physical Function	Infections	LOS	Mortality
Foss *et al.*[16]	Hip fracture	Prospective	MF < 10	487	82	NR	Poorer (cumulated ambulatory score)	NR	13 vs. 8 days (P < 0.001)	12.6 vs. 6.3% at 30 days (P < 0.05)
Su *et al.*[18]	Hip fracture	Retrospective	M < 13; F < 12	844	80	NR	No difference (activities of daily living)	NR	NR	No difference
Halm *et al.*[23]	Hip fracture	Prospective	MF < 12	550	82	NR	No difference after adjustment (functional independence motor score)	NR	Higher preoperative hemoglobin levels associated with shorter LOS (OR = 0.67, P < 0.001)	Higher preoperative hemoglobin levels associated with lower risk for death (OR = 0.69, P < 0.05)
Dharmarajan *et al.*[19]	Hip fracture	Retrospective	M < 13; F < 12	145	82	NR	NR	NR	NR	NR
Lawrence *et al.*[29]	Hip fracture	Retrospective		5,793	79	NR	Poorer (distance walked at discharge)	NR	NR	NR
Gruson *et al.*[20]	Hip fracture	Prospective	M < 13; F < 12	395	65–84: 74% ≥ 85: 26%	NR	No difference (activities of daily living)	NR	Not quantified, P < 0.01	OR = 5.0, P = 0.01 if Hb level < 10 g/dl
Myers *et al.*[22]	THA	Prospective		225	64	NR	NR	Increased urinary tract infection rate (28 vs. 14%, P = 0.039)	18 vs. 11 days, no P value published	NR

F, female; Hb, haemoglobin; M, male; Los, length of stay; NR, not reported; OR, odds ratio; THA, total hip arthroplasty

Preoperative anaemia was associated with infections, poorer physical functioning and recovery, and increased hospital LoS and mortality

Preoperative anaemia was **highly prevalent** in total hip or knee arthroplasty and hip fracture surgery (24–44%)

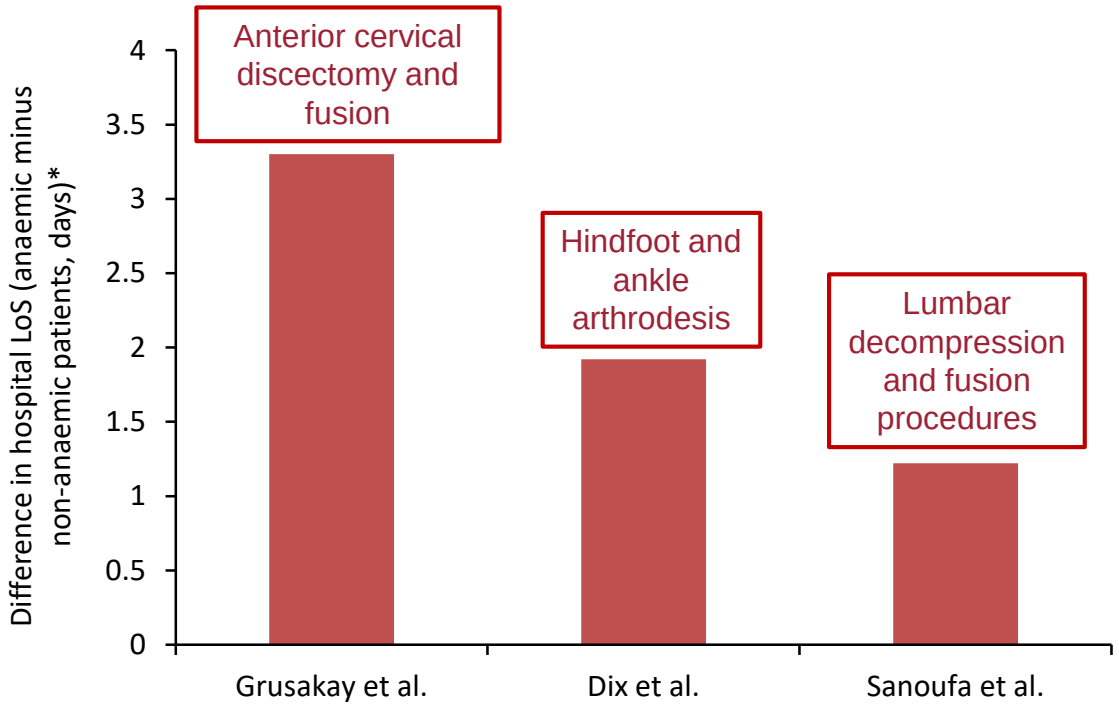
Preoperative anaemia was associated with **high blood transfusion rate** ~45%

Treatment of preoperative anaemia **decreased the need for blood transfusion** and may contribute to improved patient outcomes

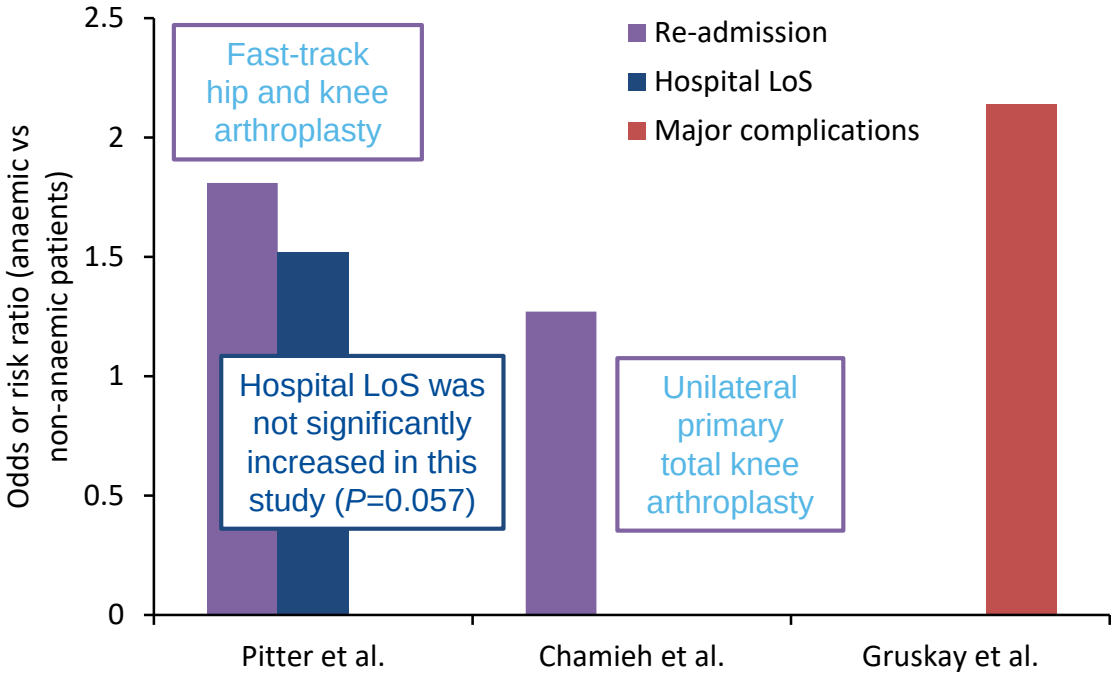
Spahn DR. Anesthesiology 2010;113:482–495

Several publications have shown that preoperative anaemia is significantly associated with other adverse surgical outcomes

Hospital LoS was significantly increased in patients with preoperative anaemia versus non-anaemic patients



Re-admissions and major complications were significantly increased in patients with preoperative anaemia



*Positive values indicate greater risk with anaemia. LoS, length of stay

1. Gruskay JA et al. Clin Spine Surg 2016;29:E34–E42; 2. Dix B et al. Foot Ankle Spec 2017 Apr;10(2):109-115 3. Sanoufa M et al. J Perioper Pract 2015;25:267–271;
4. Pitter FT et al. Anesth Analg 2016;122:1807–1815; 5. Chamieh JS et al. J Arthroplasty 2016;31:766–770 7. Khanna R et al. Clin Spine Surg 2016 Jul 14. [Epub ahead of print];

Preoperative anaemia is independently associated with mortality, complications and increased hospital LoS after revision total joint arthroplasty

Retrospective analysis from the ACS-NSQIP database of 9480 patients who underwent revision total joint arthroplasty (n=6830 aseptic revision [50% with anaemia]; n=2650 septic revision [50% with anaemia]) between 2006 and 2014

Multivariable regression analysis assessing anaemia* as a risk factor for complications

Multivariate logistic regression	Aseptic revisions, aOR (95% CI)	*P* value	Septic revisions, aOR (95% CI)	*P* value
Any complication	1.45 (1.24–1.70)	<0.001	2.16 (1.83–2.56)	<0.001
Deep infection	1.68 (1.19–2.38)	0.003	1.44 (1.06–1.94)	0.018
Mortality	2.18 (1.09–4.36)	0.028	3.16 (1.03–9.74)	0.045
Increased hospital LoS (days)	1.02 (0.73–1.31)	<0.001	2.04 (1.53–2.55)	<0.001

In patients undergoing total joint arthroplasty, preoperative anaemia was independently associated with postoperative complications, mortality and increased hospital LoS versus no anaemia

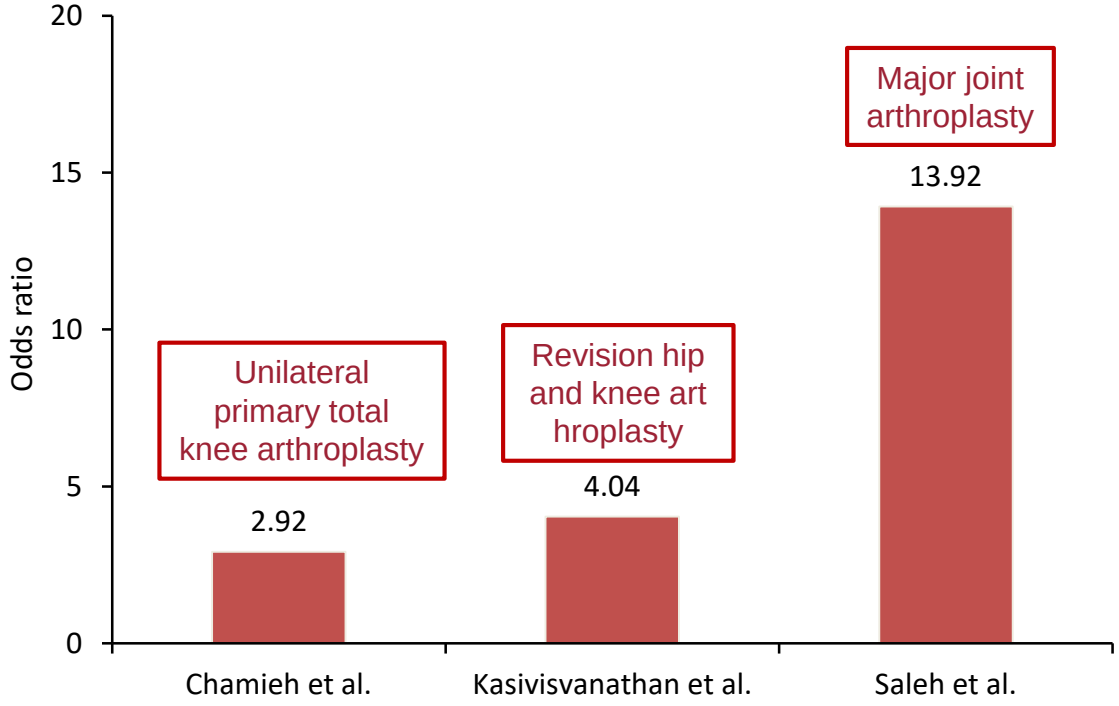
*Haematocrit <39% for males and <36% for females

ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; aOR, adjusted odds ratio; CI, confidence interval; LoS, length of stay

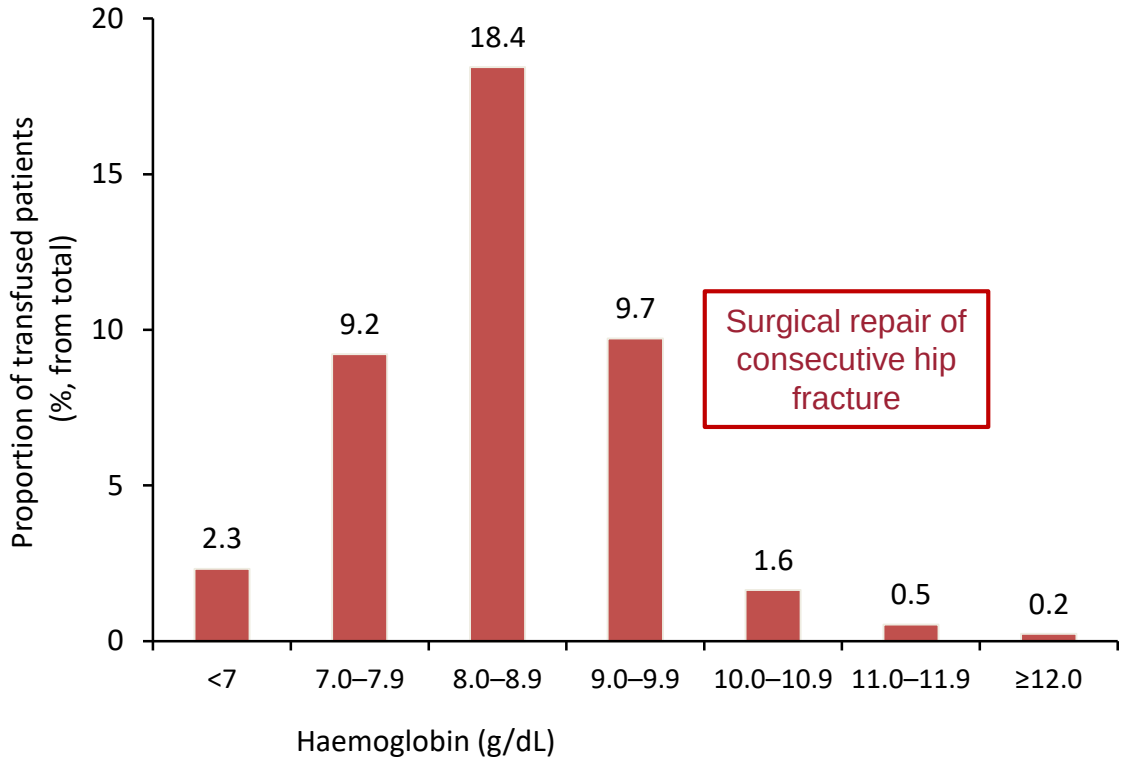
Lu M et al. J Arthroplasty 2017;32:S197–S201

Preoperative anaemia is associated with an increased requirement for transfusion, leading to increased risk of morbidity and mortality

Transfusion requirement was significantly increased in patients with preoperative anaemia versus non-anaemic patients



The **Hb 8.0–10.0 g/dL** and **Hb <8.0 g/dL** groups had a particularly high proportion of patients who required transfusion (**55.6%** and **90.5%**, respectively)



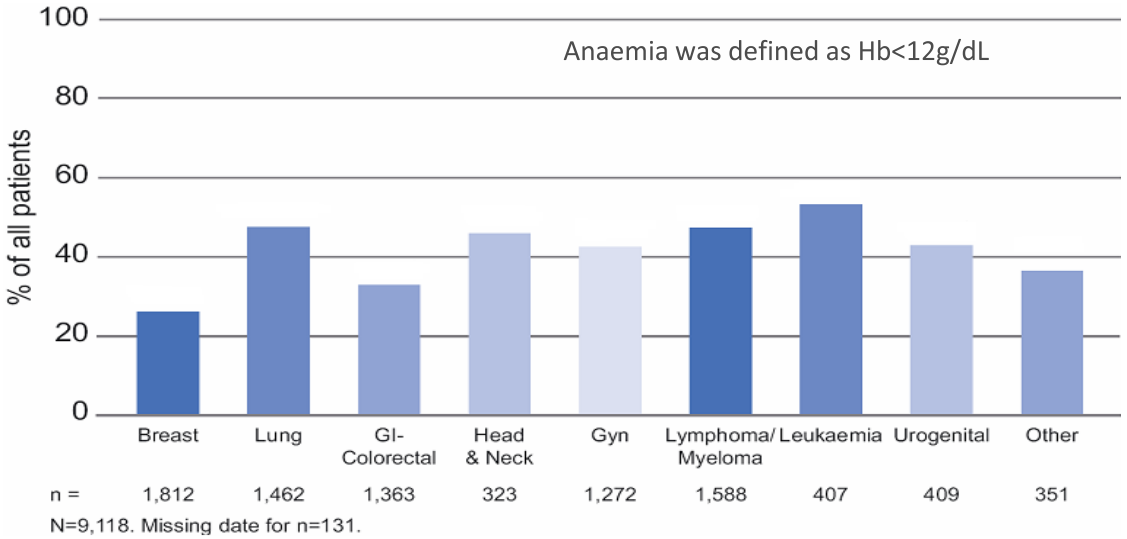
Hb, haemoglobin

1. Chamieh JS et al. J Arthroplasty 2016;31:766–770; 2. Kasivisvanathan R et al. Transfusion Med 2016;26:271–277; 3. Saleh E et al. Br J Anaesth 2007;99:801–808; 4. Carson JL et al. JAMA 1998;279:199–205

Prevalence of Anemia in Cancer

- **Anemia occurred more than 30% of cancer patients at diagnosis before the initiation of antineoplastic therapy, rising to 67% once treatment is initiated.**
- **CIA (Cancer-and-chemotherapy induced anemia) prevalence differs among cancer types, with the highest percentage of anemic patients reported in lung cancer, gynecologic or genitourinary, and gastrointestinal tumors**

[Anaemia prevalence in different cancer types]



[Incidence of anemia in patients receiving chemotherapy]

Table 2 Proportion of patients developing CIA by CIA severity and type

	Total (N=4,426)	Breast (N=2,348)	Colorectal (N=678)	Gastric (N=193)	Lung (N=888)	Ovary (N=319)
Incidence proportion (%, 95% confidence interval)						
Anemia, any grade	89.5 (88.6–90.4)	86.3 (84.9–87.7)	91.7 (89.7–93.8)	98.4 (96.7–100)	93.1 (91.5–94.8)	93.1 (90.3–95.9)
Percentage of CIA[a]						
Anemia severity[a]						
Grade 1	57.8	61.0	71.4	41.1	51.3	36.4
Grade 2	33.7	33.3	24.1	44.7	35.3	45.5
Grade 3	7.6	5.3	4.2	11.1	12.0	16.2
Grade 4	0.9	0.4	0.3	3.2	1.5	2.0
Anemia type[a]						
Microcytic	5.3	4.0	11.4	7.4	4.0	3.1
Normocytic	84.9	89.3	75.9	76.7	84.6	79.6
Macrocytic	9.8	6.7	12.7	15.9	11.4	17.3
Anemia type[a]						
Hypochromic	8.7	7.1	16.6	10.1	7.5	5.4
Normochromic	46.9	50.7	41.8	48.1	42.8	42.5
Hyperchromic	44.4	42.2	41.6	41.8	49.8	52.0

Note: [a]Using the most severe CIA episode for patients with multiple CIA episodes.
Abbreviation: CIA, chemotherapy-induced anemia.

Kristof Verraes et al., Annals of Gastroenterology 2015;28, 19-24; Ludwig H, 2004;
Ludwig et al. Annals of Oncology. 2013 May 29; Hairong Xu et al., Clinical Epidemiology 2016:8 61–71

KOREA: Prevalence of anemia in cancer


www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

Iron deficient erythropoiesis might play key role in development of anemia in cancer patients

Silvia Park[1], Chul Won Jung[1], Kihyun Kim[1], Seok Jin Kim[1], Won Seog Kim[1], Jun Ho Jang[1]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence to:
Jun Ho Jang, **e-mail:** smcjunhojang@gmail.com

Keywords: *cancer, anemia, soluble transferrin receptor, hepcidine*

Received: *July 19, 2015* **Accepted:** *October 13, 2015* **Published:** *October 26, 2015*

- **49/345 (14.2%)** had **anemia** at their initial diagnosis of cancer
- But, number of patients with anemia **during 1st line anti-cancer treatment increased to 129/345 (37.4%)**

The incidence of anemia at diagnosis and during 1st-line anti-cancer treatment among 4 major cancers in Korea

Cancer type	Total N	Anemia at diagnosis, (%)	Anemia during treatment, n(%)
Gastric cancer	101	14 (20.3%)	40 (39.6%)
Colorectal caner	69	14 (13.9%)	15 (21.7%)
Hepatocellular carcinoma	23	2 (8.7%)	6 (26.1%)
Lung cancer	152	19 (12.5%)	68 (44.7%)

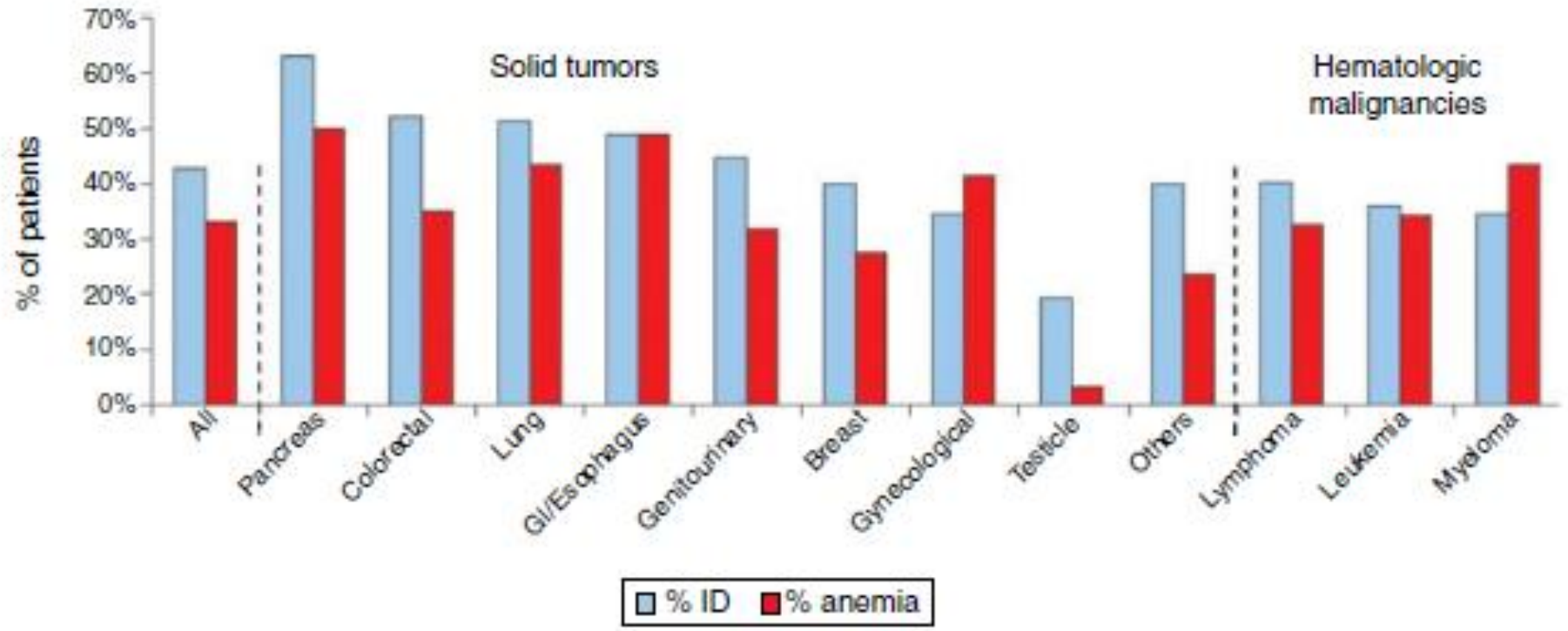
The incidence of anemia among 4 major cancers (gastric, colorectal, lung cancer and hepatocellular carcinoma), and biochemical features of anemia using ferritin, CRP, hepcidin and soluble transferrin receptor (sTfR) were assessed. Anemia was defined either by Hb≤11g/dL or a drop of Hb 2g/dL or more during anticancer treatment.

1st- line anti-cancer treatment: Chemotherapy (215, 62.3%), chemo-radiation (75, 21.7%) and target agents (55, 15.9%)
34 patients (26.4%) were treated for their anemia: RBC transfusion, n = 28; oral iron replacement, n = 5; ESA, n = 1
Definition of anemia: less than Hb level of 11 g/dL or a drop of 2 g/dL or more from baseline

Silvia Park et al., oncotarget 2015

Prevalence of iron deficiency & anemia in Cancer patients

- **They reported that a high prevalence of ID across different tumor types and ID correlated with anemia.**



Iron Deficiency(ID): TSAT < 20%
Anemia: Hb ≤ 12g/dL

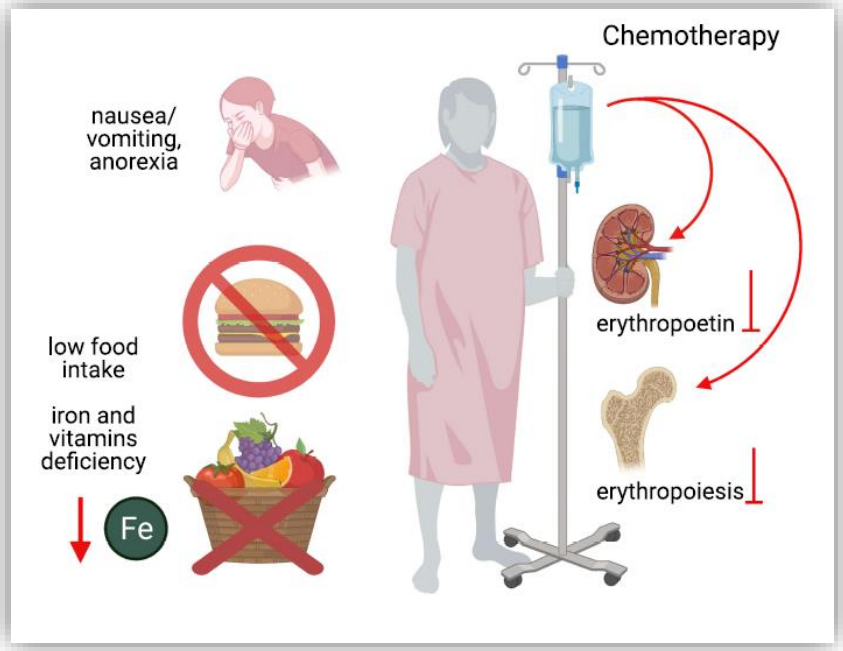
Iron Deficiency 42.6%, Anemia 33.3%[3]

Ludwig et al. Annals of Oncology. 2013 May 29

Pathogenesis of chemotherapy-induced anemia[1,2]

- **Chemotherapy-induced anemia is related to the toxic effect of anticancer treatments on bone marrow or to a nephrotoxic effect, which negatively influence EPO production.** [1,2]
  - the condition is often induced by platinum-based regimens. Indeed, beyond the direct toxic effect on erythropoiesis, platinum-based chemotherapy may cause nephrotoxicity with a subsequent drop in EPO production.[1]

- **Anticancer treatments can induce gastro-enteric side effects, such as anorexia, nausea, and vomiting, and diarrhea**[1]
  - These side effects objectively decrease food intake or lead to a loss of nutrients, vitamins, and minerals, ultimately affecting erythropoiesis

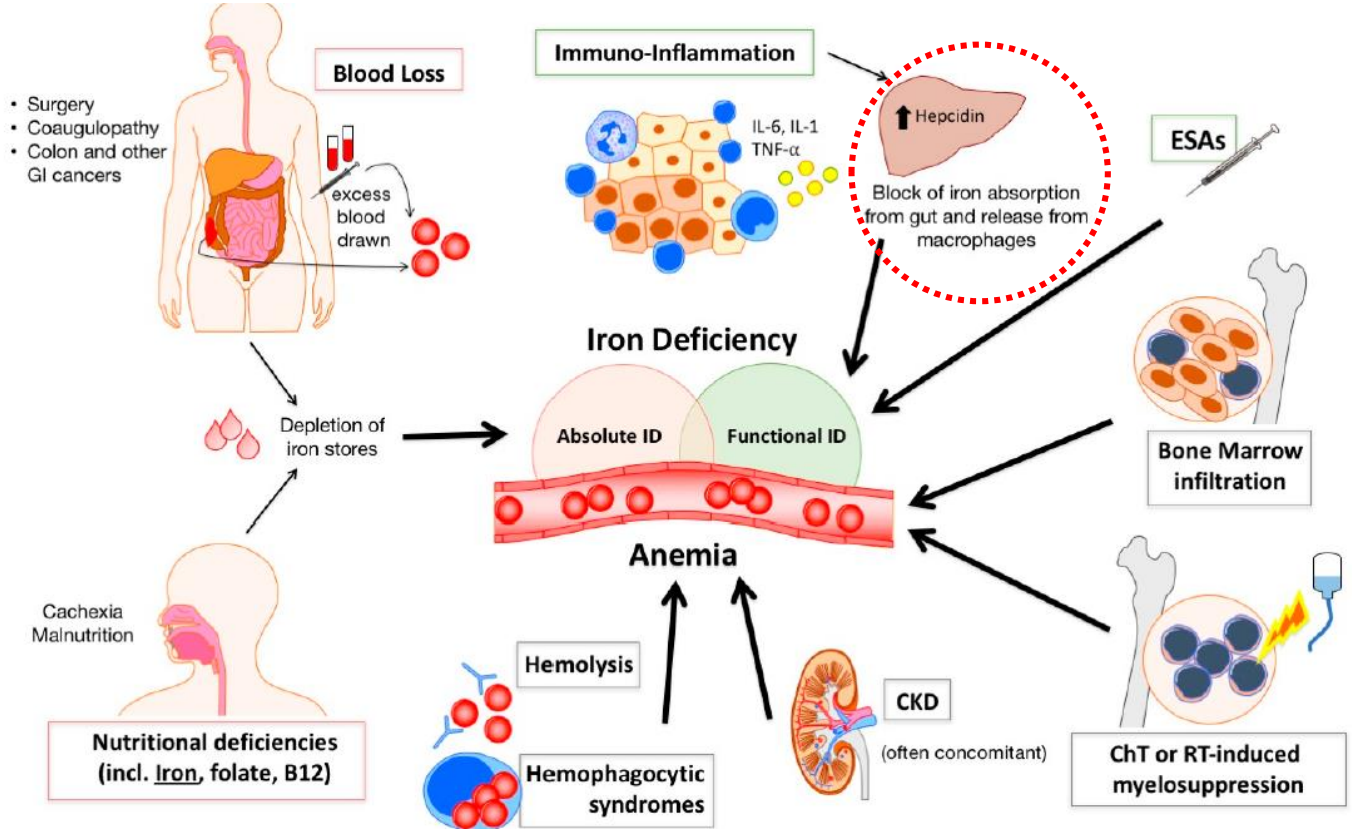


CIA is often precipitated by platinum-based therapies.[20] Factors that are associated with the development of platinum-induced anemia include early decrease in hemoglobin following treatment, cumulative platinum dose, advanced age, failure to respond to chemotherapy, and high concentration of residual platinum in the bloodstream following administration.[16,21] Mechanisms of CIA by platinum-based regimens involve direct suppression of erythroid progenitor cells within the bone marrow as well as nephrotoxic effects on erythropoietin-producing cells within the kidney.[22,23] States of inherent erythropoietin deficiency secondary to cisplatin-induced renal tubular damage can be prevented or treated by replacement with recombinant hormone.[24] Nonplatinum-based chemotherapy regimens, including antimicrotubular agents, campothecins, and biologics, can also be particularly myelosuppressive.[25,26]

1. Madeddu C et al. J Exp Pharmacol. 2021 Jun 24;13:593-611.
2. Bryer and Henry. International Journal of Clinical Transfusion Medicine 2018:6 21–31

Multifactorial pathogenesis of Cancer-related Anemia

- ID in cancer patients can be due to multiple concurring mechanisms, including **bleeding** (e.g., in gastrointestinal cancers or after surgery), **malnutrition, medications, and hepcidin-driven iron sequestration into macrophages with subsequent iron-restricted erythropoiesis**

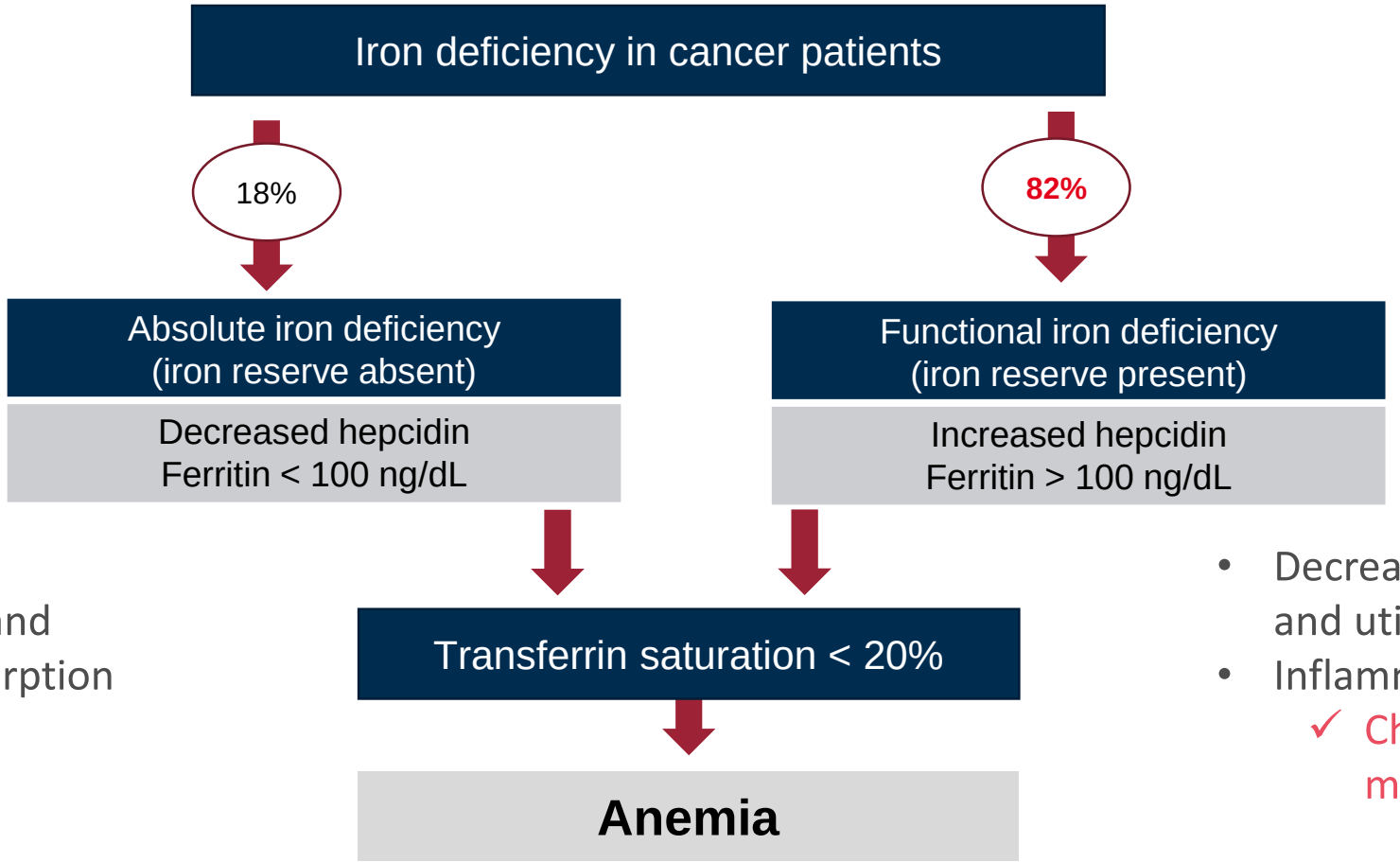


ID, Iron Deficiency; ChT, Chemotherapy; RT, Radiotherapy;
ESA, Erythropoietic Stimulating Agents; CKD, Chronic Kidney Disease

Busti F. et al. Pharmaceuticals (Basel). 2018 Sep 30;11(4):94.

Absolute and functional iron deficiency in cancer patients

- **Of the 409 iron-deficient patients in whom serum ferritin levels were available additionally to TSAT, 335 (81.9%) presented with functional ID (FID) (TSAT < 20%, serum ferritin ≥30 ng/ml) and 74 (18.1%) with absolute ID.**



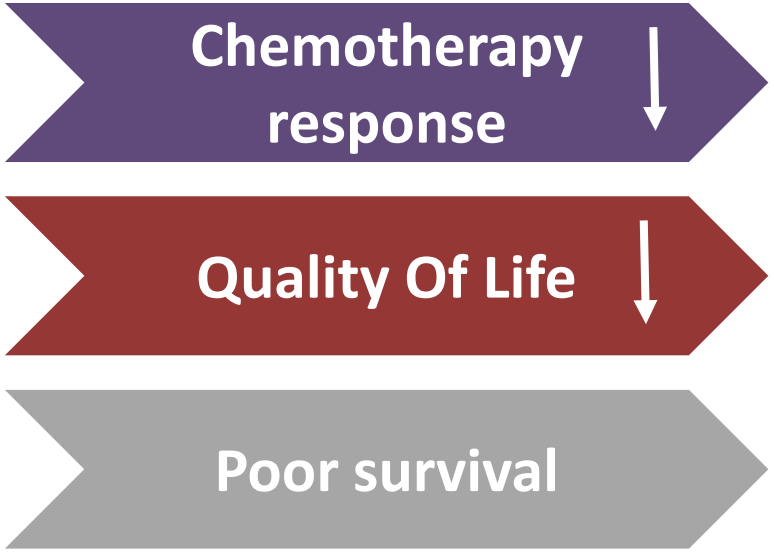
- Blood loss
- Increase iron demand
- Decrease iron absorption

- Decreased iron absorption and utilization/release
- Inflammatory bowel disease
  - ✓ Chronic inflammatory or malignant diseases

Ludwig H. et al. Annals of Oncology 24: 1886–1892, 2013
Flavio Augusto Naoum. Rev Bras Hematol Hemoter. Oct-Dec 2016;38(4):325-330

Clinical relevance of CIA

- **Anaemia and iron deficiency (ID) are frequent complications in patients with solid tumours or haematological malignancies, particularly in patients treated with chemotherapeutic agents. Frequently, anaemia is associated with fatigue, impaired physical function and reduced quality of life (QoL).**



ESMO

Annals of Oncology 0: 1–15, 2018
doi:10.1093/annonc/mdx758

CLINICAL PRACTICE GUIDELINES

Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines†

M. Aapro[1], Y. Beguin[2,3], C. Bokemeyer[4], M. Dicato[5], P. Gascón[6], J. Glaspy[7], A. Hofmann[8], H. Link[9], T. Littlewood[10], H. Ludwig[11], A. Österborg[12], P. Pronzato[13], V. Santini[14], D. Schrijvers[15], R. Stauder[16], K. Jordan[17] & J. Herrstedt[18,19], on behalf of the ESMO Guidelines Committee*

[1]Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland; [2]University of Liège, Liège; [3]CHU of Liège, Liège, Belgium; [4]Department of Oncology, Hematology and BMT with Section Pneumology, University of Hamburg, Hamburg, Germany; [5]Hématologie-Oncologie, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg; [6]Department of Haematology-Oncology, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain; [7]Division of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, USA; [8]Medical Society for Blood Management, Luxemburg, Austria; [9]Klinik für Innere Medizin I, Westpfalz-Klinikum, Kaiserslautern, Germany; [10]Department of Haematology, John Radcliffe Hospital, Oxford, UK; [11]Wilhelminen Cancer Research Institute, Wilhelminenspital, Vienna, Austria; [12]Karolinska Institute and Karolinska Hospital, Stockholm, Sweden; [13]Medical Oncology, IRCCS Ariana Pediatter Universitaria San Martino – IST, Instituto Nazionale per la Ricerca sol Chancre, Genova; [14]Department of Experimental and Clinical Medicine, Haematology, University of Florence, Florence, Italy; [15]Department of Medical Oncology, Zielenhuisnetwerk Antwerpen, Antwerp, Belgium; [16]Department of Internal Medicine V (Haematology and Oncology), Innsbruck Medical University, Innsbruck, Austria; [17]Department of Medicine V, University of Heidelberg, Heidelberg, Germany; [18]Department of Oncology, Zealand University Hospital Roskilde, Roskilde; [19]University of Copenhagen, Copenhagen, Denmark

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: October 2017.

Anaemia and iron deficiency (ID) are frequent complications in patients with solid tumours or haematological malignancies, particularly in patients treated with chemotherapeutic agents [1–3]. Frequently, anaemia is associated with fatigue, impaired physical function and reduced quality of life (QoL) [4–7]. Consequences of anaemia may include impaired response to cancer treatment and reduced overall survival (OS), even though a causal direct relationship has not yet been established [8, 9].

These new ESMO Clinical Practice Guidelines provide tools to evaluate anaemia, also in patients with myelodysplastic syndromes (MDS), and include recommendations on how to safely manage chemotherapy-induced anaemia (CIA) with intravenous (i.v.) or oral administration, red blood cell (RBC) transfusions and combinations of these treatments [10–13]. The major aims of anaemia management are the reduction or resolution of anaemia symptoms, particularly fatigue, and an improved QoL with the minimum invasive treatment that corrects the underlying causes and proves to be safe. Underlying causes of anaemia, mainly impaired erythropoietic activity and disturbed iron homeostasis, can be consequences of increased release of inflammatory cytokines due to the underlying cancer and/or toxicity of cancer therapy. Furthermore, vitamin B12 and folate deficiency are relatively rare causes of anaemia in cancer patients.

Notably, also more than half of patients with MDS are characterised by a haemoglobin (Hb) level < 10 g/dL, resulting in reduced functional capacities and health-related QoL, and > 80% of these patients require RBC transfusions [14–17]. However, ESAs were not approved by the European Medicines Agency (EMA) for use in MDS patients despite being used effectively in MDS for at least 20 years; their activity has been demonstrated in numerous clinical trials, with published evidence existing for more than 2500 ESA-treated MDS patients [14]. Randomised clinical trials are ongoing.

Since the publication of the European Society of Medical Oncology (ESMO) anaemia Clinical Practice Guidelines in 2010 [18] and the last review of the European Organisation for Research and Treatment of Cancer (EORTC) anaemia treatment guidelines in 2006 [19] (last update in 2007 [20]), clinical experience with ESAs and iron preparations and the understanding of iron homeostasis have markedly increased [10, 21]. Furthermore, specific safety aspects of the different treatment options have been addressed by several analyses and reviews in recent years, although data on the use of blood transfusions in cancer patients are sparse. Therefore, new ESMO guidelines for the diagnosis and treatment of anaemia and ID in cancer patients were deemed necessary. In addition, these guidelines include aspects related to anaemia management in patients with MDS and update the most recent ESMO and European LeukemiaNet (ELN) treatment guidelines for MDS [15, 22].

Questions addressed by these guidelines and respective recommendations including levels of evidence and grades of recommendations [23] are summarised in Table 1 for the management

Aapro M, et al. Ann Oncol 2018;29(Suppl 4):iv96–iv110. (ESMO guidelines)

Treatment & Treatment Options

F/43

2021-04-22 검사코드 처방일 前제외 Abnormal Only 전체선택

검사명 (* :중간보고)	결과	단위	수정	Min	Max	검체	접수일시	검사일시	보고일시	Img	구분
WBC Count, Blood	4.09	x10³/μL		3.15	8.63	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
RBC Count, Blood	3.82	x10^6/μL		3.68	4.83	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Hemoglobin, Blood	▼7.8	g/dL		11.2	14.8	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Hematocrit, Blood	▼28.7	%		31.8	43.8	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
MCV (Mean Corpuscular Volum...	▼75.1	fL		83.9	98.1	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
MCH (Mean Corpuscular Hemo...	▼20.4	pg		27.8	33.2	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
MCHC (Mean Corpuscular Hem...	▼27.2	g/dL		31.9	34.6	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
RDW	▲18.4	%		12.0	14.7	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Platelet Count, Blood	253	x10³/μL		138	347	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
PDW	▲16.8	fL		8.9	15.5	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
MPV	11.2	fL				WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Blast	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Promyelocyte	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Myelocyte	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Metamyelocyte	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Band neutrophil	0	%		0	5	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Segmented neutrophil	58.9	%		40.6	73.5	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Eosinophil	1.0	%		0	8.6	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Basophil	1.0	%		0	1.6	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Lymphocyte	31.8	%		20.0	50.8	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Monocyte	7.3	%		1.7	8.0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Atypical Lymphocyte	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Immature cell	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Plasma cell	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Nucleated RBC	0	/100WBC		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
ANC (Absolute Neutrophil Cou...	2.41	x10³/μL		1.57	8.30	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
ALC (Absolute Lymphocyte Cou...	1.30	x10³/μL		1.00	4.80	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진
Abnormal Lymphoid cell	0	%		0	0	WHOLE B...	2021-04-22 11:00	2021-04-22 11:00	2021-04-22 14:07		건진

페린젝트 투여 2달 후

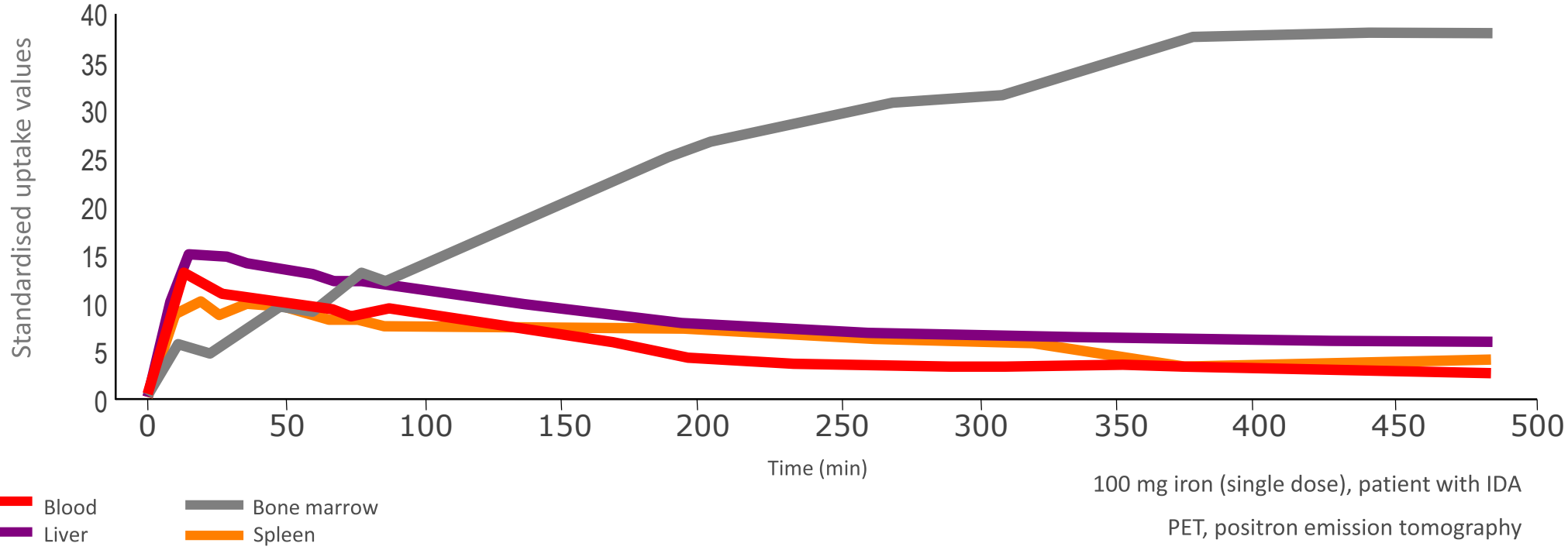
2021-06-10 ☐ 검사코드 ☐ 처방일 전체선택
☐ 前제외 ☐ Abnormal Only

검사명 (*:중간보고)	결과	단위	수정	Min	Max	검체	접수일시	검사일시	보고일시	Img	구분	UVPACS
WBC Count, Blood	5.24	x10³/μL		3.15	8.63	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
RBC Count, Blood	4.10	x10^6/...		3.68	4.83	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
Hemoglobin, Blood	11.9	g/dL		11.2	14.8	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
Hematocrit, Blood	37.1	%		31.8	43.8	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
MCV (Mean Corpuscular Volu...	90.5	fL		83.9	98.1	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
MCH (Mean Corpuscular Hem...	29.0	pg		27.8	33.2	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
MCHC (Mean Corpuscular He...	32.1	g/dL		31.9	34.6	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	
Platelet Count, Blood	215	x10³/μL		138	347	WHOLE B...	2021-06-10 09:20	2021-06-10 09:20	2021-06-10 09:54		외래	

Iron uptake and distribution after FCM administration – PET study

Rapid uptake of radiolabelled iron from FCM in the bone marrow

- The iron from FCM is distributed in the liver and spleen and taken up predominantly by the bone marrow from within 60 minutes after administration while levels in the liver and spleen fall steadily after about 30 minutes.



100 mg iron (single dose), patient with IDA

PET, positron emission tomography

Beshara S et al. Br J Haematol 2003;120:853–9

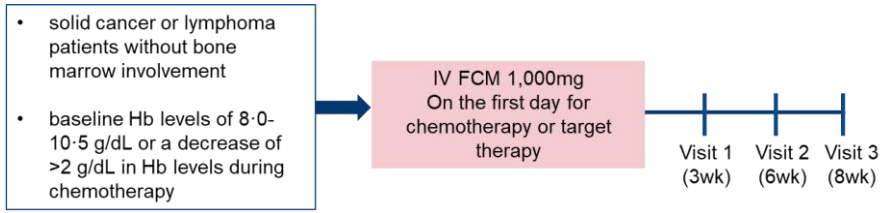
THE EFFICACY OF FERINJECT IN CIA

- **Efficacy of intravenous iron replacement for chemotherapy-induced anemia: A prospective phase II pilot study**

- **Objectives:** to evaluate the efficacy of IV iron administration without erythropoiesis-stimulating agents for anemia in cancer patients and to identify biomarkers for hemoglobin (Hb) response to predict the need for iron supplementation.
- **Methods:** This was a prospective single-arm phase II study conducted between April 2015 and July 2017 with an observation period of 8 weeks. (The cut-off for data collection was February 2018)

- **Primary End Point**
  - **Hemoglobin response (Increase of ≥1.0g/dL Hb or Hb correction ≥11g/dL*) during follow-up period**

- **Secondary End Point**
  - Change of Mean hemoglobin
  - Change of anemia related biochemical variables
    : iron, ferritin, total iron binding capacity (TIBC), TSAT, soluble, transferrin receptor (sTFR), hepcidin, erythropoietin (EPO), interleukin-6 (IL-6)



*only if baseline Hb level was 8·0- 10·5 g/dL

Jun Ho Jang et al., Plos Medicine 2020

66% PATIENTS SHOWED HEMOGLOBIN RESPONSE WITH FERINJECT

- Over time, a greater Hb change was observed after IV iron injection. 36 (39.1%), 56 (60.9%), and 61 (66.3%) responders were observed at weeks 3, 6, and 8, respectively.
- In the PP population, mean increase in Hb levels from baseline to the end of treatment was 1.77±1.30g/dL.

[Hemoglobin response*]

Total ,n(%)		**92 (100)**
Hemoglobin Response at visit 3	Responder	61(66.30)
	Non responder	31(33.70)
Hemoglobin Response by visit		
Hemoglobin Response at visit 1	Responder	36(39.13)
	Non responder	56(60.87)
Hemoglobin Response at visit 2	Responder	53(57.61)
	Non responder	39(42.39)

Table 2: **Hemoglobin level according to visit and mean change from baseline**

Visit		3th week		6th week		8th week	
Hb response, *n*(%)	Responders[a]	36	(39·1)	53	(57·6)	61	(66·3)
	Non-responders	56	(60·9)	39	(42·4)	31	(33·7)
Hb level	Mean ±SD	9·85	±1·31	10·72	±1·26	11·15	±1·35
[b]Hb change	Mean ±SD	0·55	±1·16	1·35	±1·17	1·77	±1·30

*Hemoglobin response: Without transfusion or ESA, increase of Hb ≥1.0g/dL or correction of Hb ≥ 11.0 g/dL
Visit 1, 2, 3: From baseline, approximately week 3, 6, 8 after

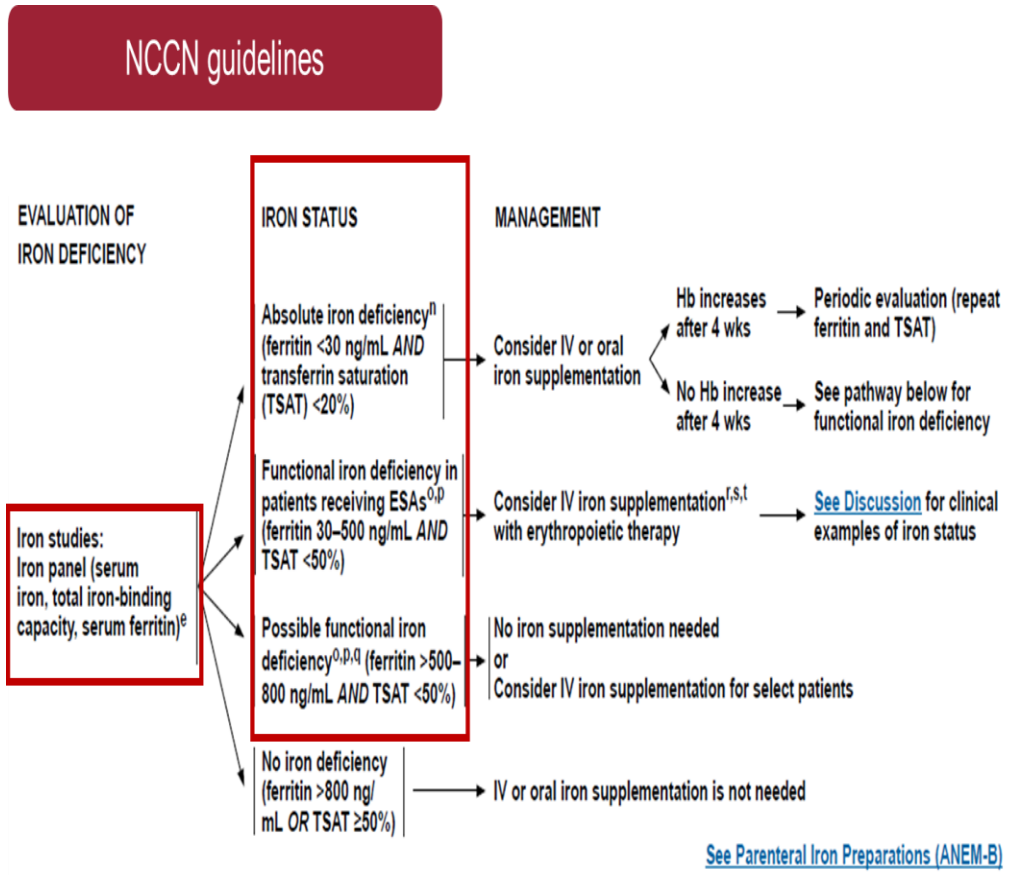
Jun Ho Jang et al., Plos Medicine 2020

FERINJECT IS ALSO EFFECTIVE IN FUNCTIONAL ID

- Without absolute IDA, Functional IDA patients showed Hb response.

[Hemoglobin response in functional ID]

		Responder/ total (%)
Absolute ID	Ferritin <30ng/mL or TAST < 20%	19/20 (95%)
Functional ID		**42/72 (58.3%)**
NCCN criteria	Ferritin 30-500ng/mL and TAST < 50%	34/56 (60.7%)
	Ferritin >500-800ng/mL and TSAT < 50%	3/6 (50%)
	Ferritin >800ng/mL or TSAT ≥ 50%	5/10 (50%)



Jun Ho Jang et al., Plos Medicine 2020

TREATMENT OF ANEMIA IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY WITH IV FCM WITHOUT ESA

Table 2: **Hemoglobin level according to visit and mean change from baseline**

Visit		3th week	6th week	8th week
Hb response, *n*(%)	Responders[a]	36 (39·1)	53 (57·6)	61 (66·3)
	Non-responders	56 (60·9)	39 (42·4)	31 (33·7)
Hb level	Mean ±SD	9·85 ±1·31	10·72 ±1·26	11·15 ±1·35
[b]Hb change	Mean ±SD	0·55 ±1·16	1·35 ±1·17	1·77 ±1·30

Hikmat Abdel-Razeq et al., Therapeutic Advances in Medical Oncology 2020 (Impact factor 2019: 5.70)

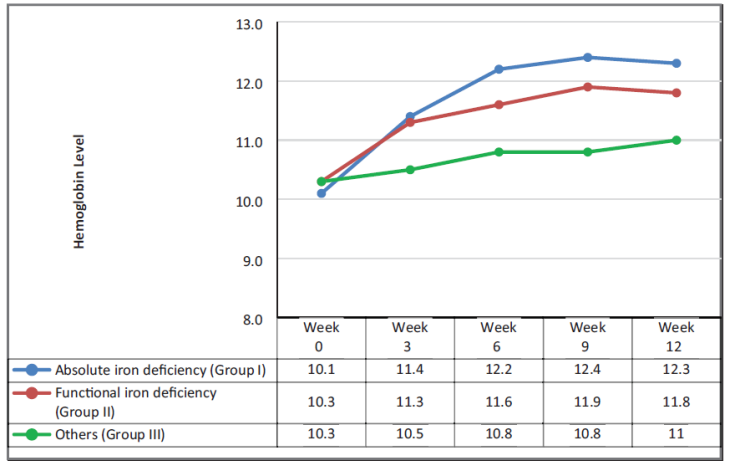
Results: Response

- Among the whole study population, a total of 50 (59.5%) patients had an increment in Hb ⩾ 1.0 gm/dL (responders) at week-12.
- Response rate was the highest among the patients with AIDA (80.8%). However, patients with FIDA had also a high repose rate (70.8%) and both were significantly higher than group III, with a response rate of 35.3% (p = 0.00027; Table 5).
- A total of 6 (7.1%) patients received blood transfusions.

Table 5. Response rates per patient subgroup*.

Groups	Number of patients	Response *n* (%)	*p*-value
Group I Absolute iron deficiency	26	21 (80.8%)	0.00027**
Group II Functional iron deficiency	24	17 (70.8%)	
Group III Others	34	12 (35.5%)	
Total	84	50 (59.5%)	

*Response defined as a Hb increment ⩾1.0 gm/dL at week 12.
**Group I and II *versus* group III.



Summary

- Anemia is common in patients in various medical and surgical conditions.
- All patients with iron deficiency anemia (Hb: male <13g/dL, female <12g/dL) and most patients with iron deficiency without anemia, should be treated, regardless of the presence of symptoms
- Pre/Post-operative anemia has a negative impact on quality and safety performance indicators for surgeries
- **Anemia occurred more than 30% of cancer patients at diagnosis before the initiation of antineoplastic therapy, rising to 67% once treatment is initiated**
- Consequences of anaemia may include impaired response to cancer treatment and reduced overall survival (OS)
- Iv iron supplement can be the important treatment options for the management of Iron deficiency patients in medical and surgical condition including cancer.