Comparaison d'une **stratégies transfusionnelle** 'restrictive' vs. 'libérale' associé ou non à une **gestion personnalisée du sang** (fer et EPO) administré en post-opératoire de chirurgie abdominale majeure pour résection tumorale

Etude LIBERTY-2

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AP-HP. Hôpitaux universitaires Paris Seine-Saint-Denis

JAMA Oncology | Original Investigation

Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016

17 millions de cancer / an

JAMA Oncology | Original Investigation

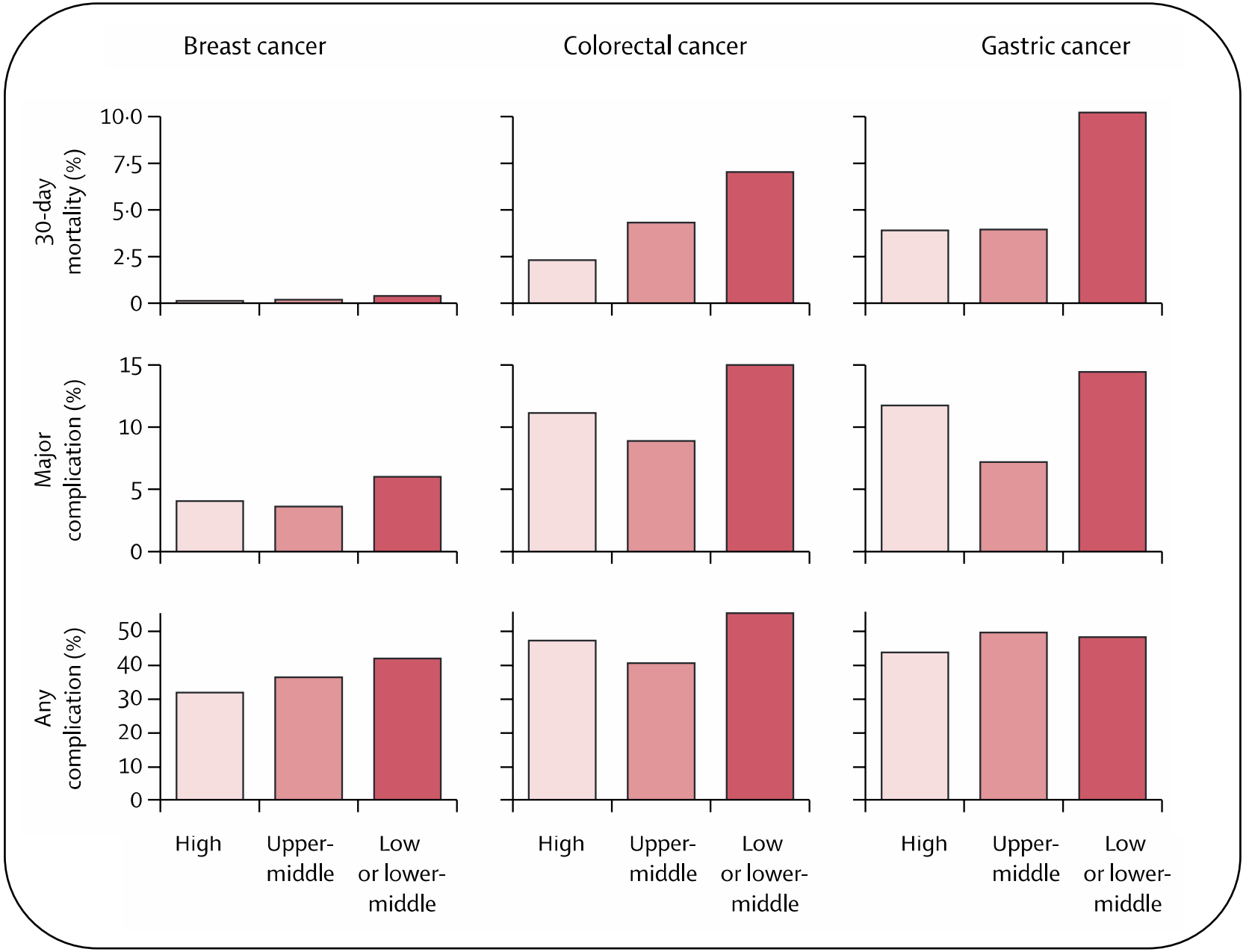
Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050

25000 milliards $/an > 0,5% PIB

Global cancer surgery: delivering safe, affordable, and timely cancer surgery

Richard Sullivan, Olusegun Isaac Alatise, Benjamin O Anderson, Riccardo Audisio, Philippe Autier, Ajay Aggarwal, Charles Balch, Murray F Brennan, Anna Dare, Anil D'Cruz, Alexander M M Eggermont, Kenneth Fleming, Serigne Magueye Gueye, Lars Hagander, Cristian A Herrera, Hampus Holmer, André M Ilbawi, Anton Jarnheimer, Jia-fu Ji, T Peter Kingham, Jonathan Liberman, Andrew J M Leather,

80% des cancers nécessitent une chirurgie

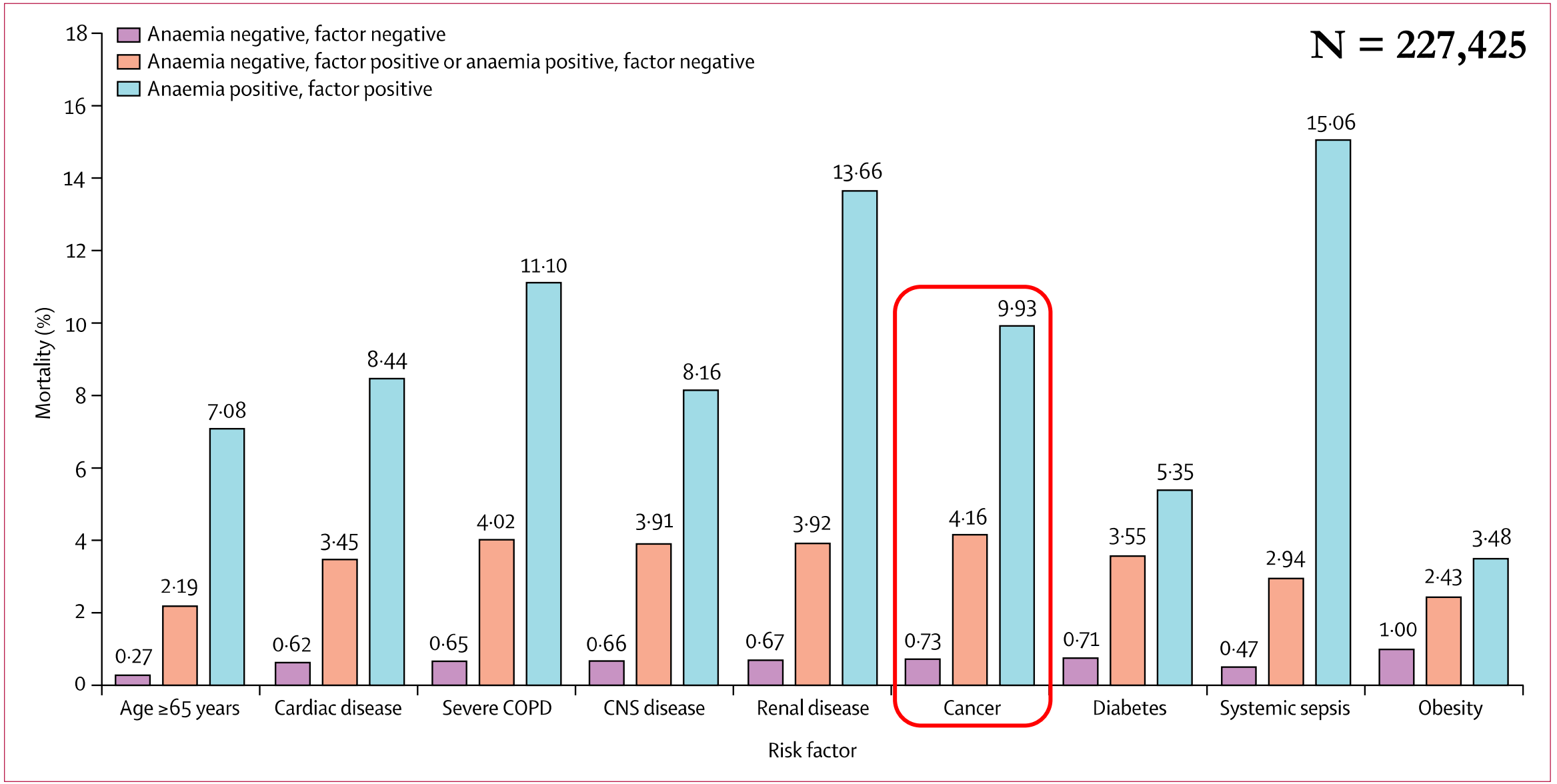


2 - 10%

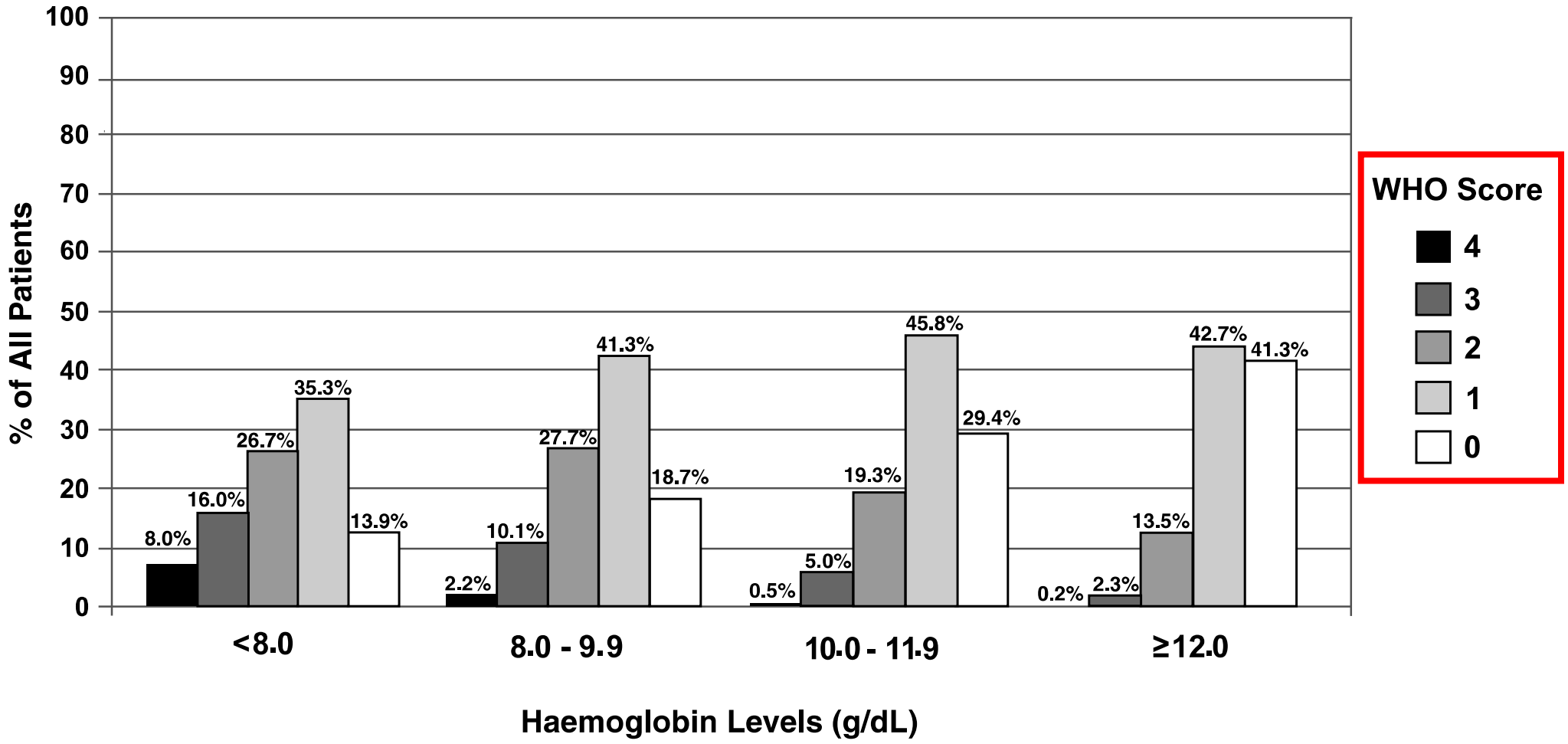
5 - 15%

30 - 40%

GlobalSurg, **Lancet** 2021

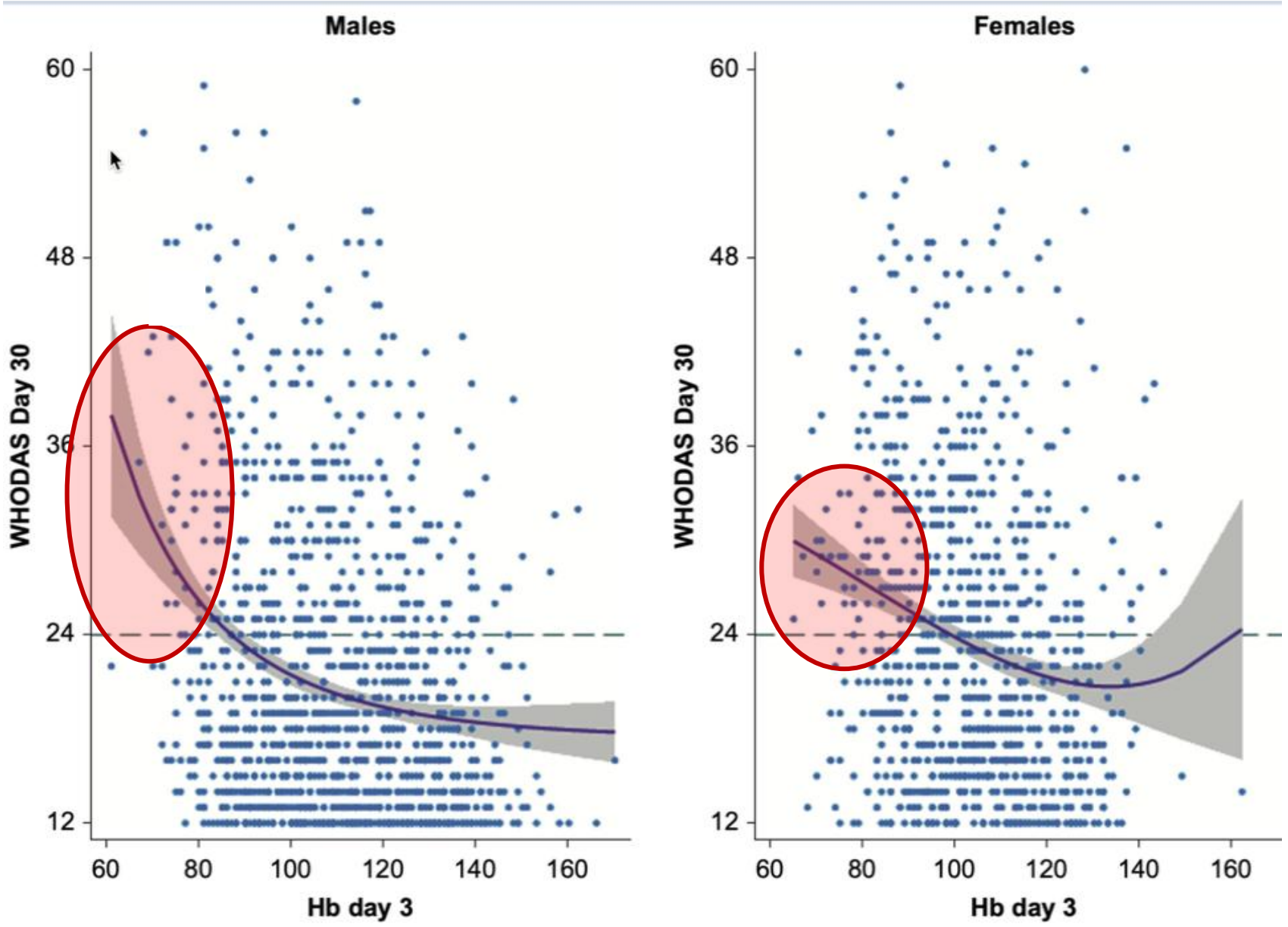


Musallam et al. **Lancet** 2011



n* =	187	1242	4214	8750
Mean (SD) WHO Score	1.7 (1.1)	1.4 (1.0)	1.0 (0.8)	0.8 (0.8)

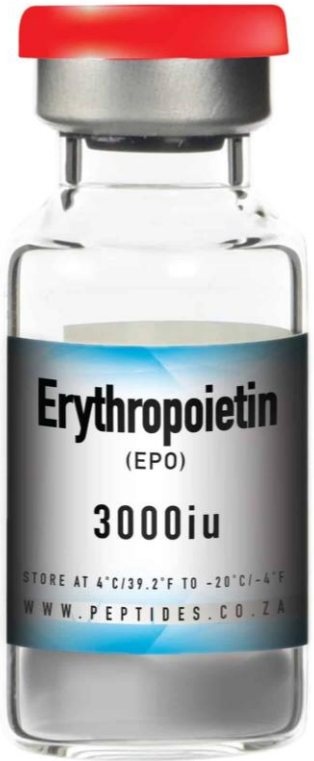
Ludwig et al. **European Journal of Cancer** 2004

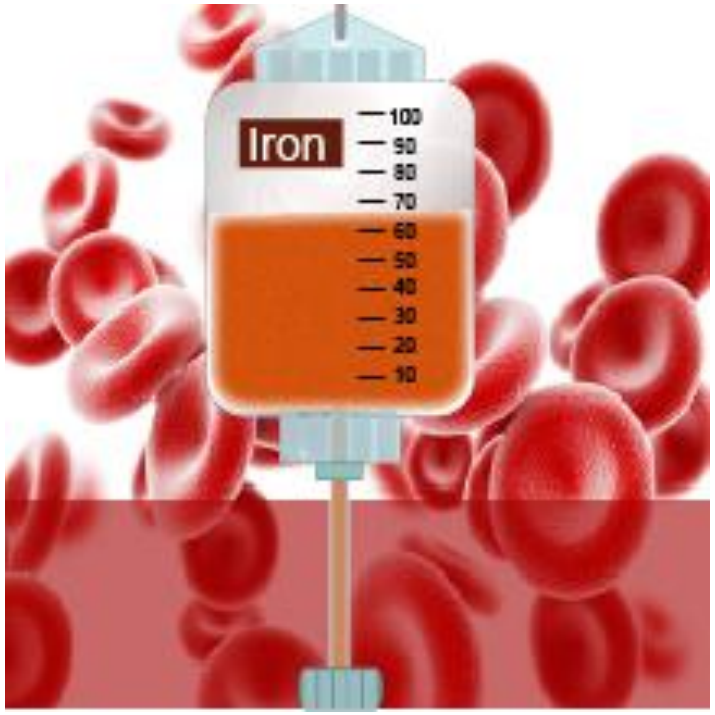


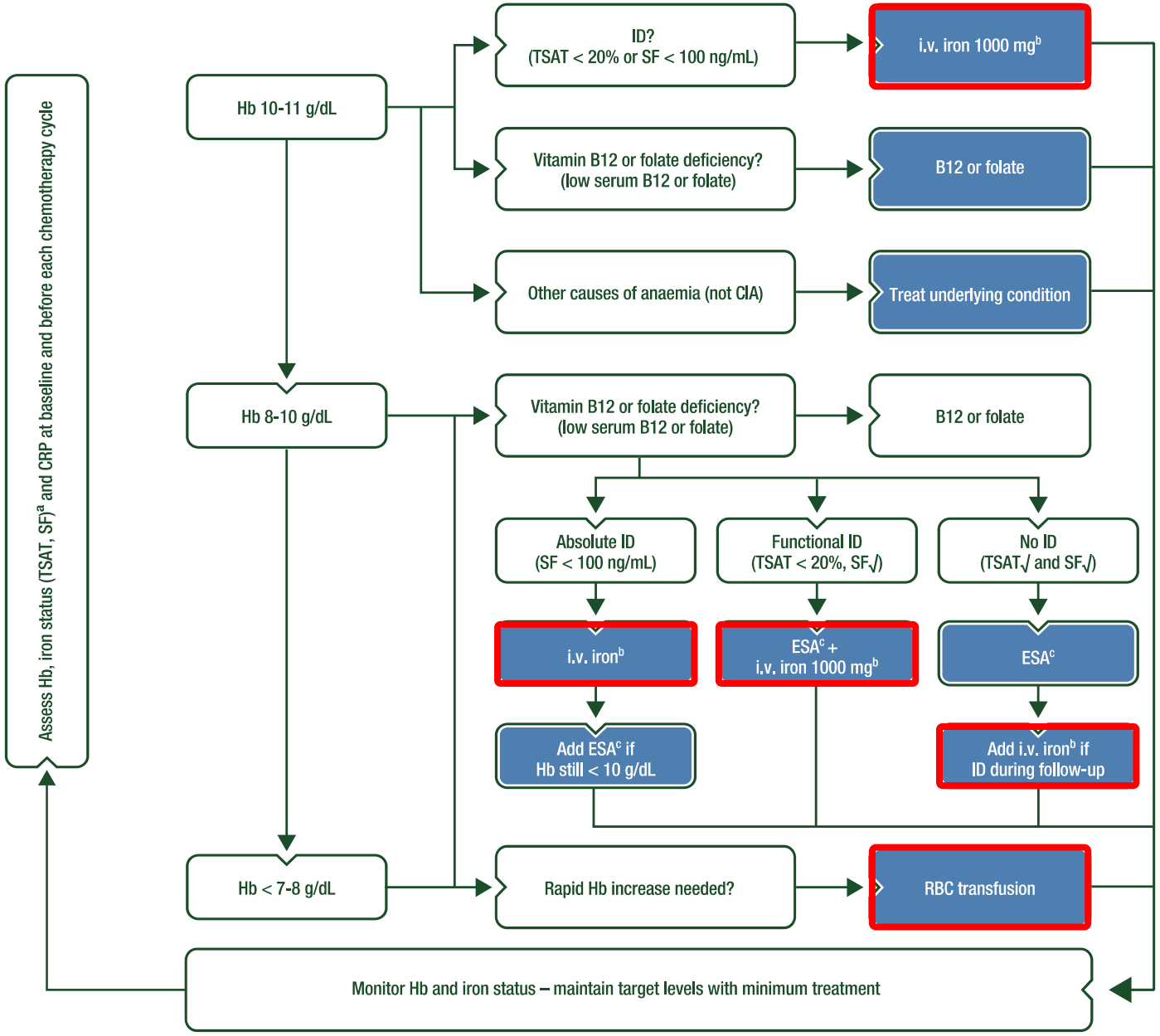
Myles et al. **BJA** 2022

Comment traiter une anémie ?



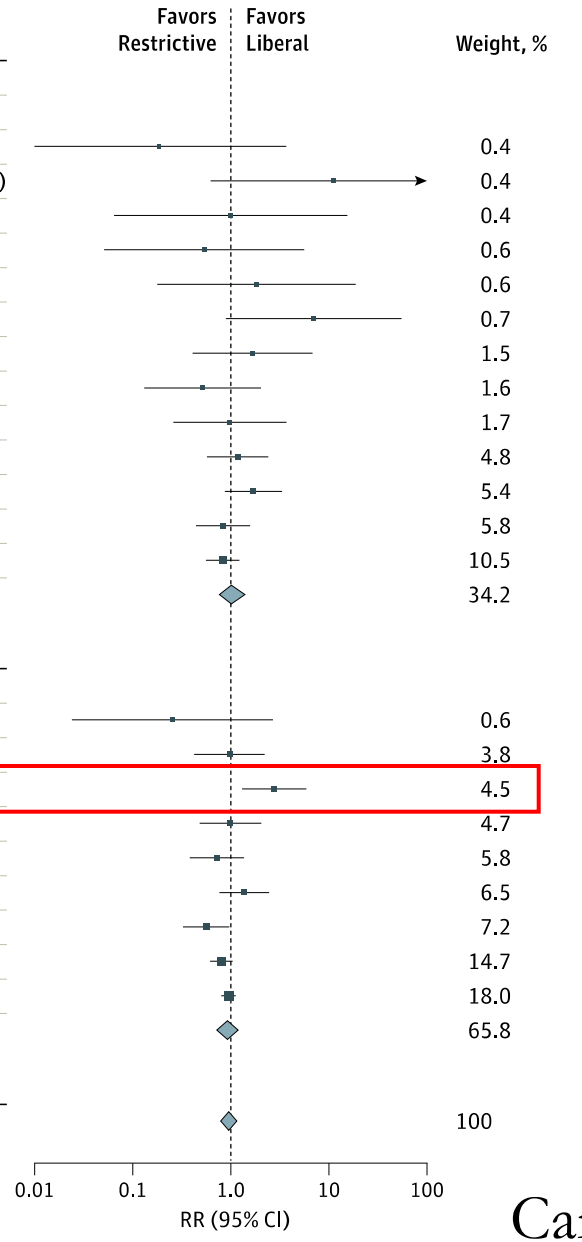





Assess Hb, iron status (TSAT, SF)[a] and CRP at baseline and before each chemotherapy cycle
Hb 10-11 g/dL
ID?
(TSAT < 20% or SF < 100 ng/mL)
i.v. iron 1000 mg[b]
Vitamin B12 or folate deficiency?
(low serum B12 or folate)
B12 or folate
Other causes of anaemia (not CIA)
Treat underlying condition
Hb 8-10 g/dL
Vitamin B12 or folate deficiency?
(low serum B12 or folate)
B12 or folate
Absolute ID
(SF < 100 ng/mL)
Functional ID
(TSAT < 20%, SF√)
No ID
(TSAT√ and SF√)
i.v. iron[b]
ESA[c] +
i.v. iron 1000 mg[b]
ESA[c]
Add ESA[c] if
Hb still < 10 g/dL
Add i.v. iron[b] if
ID during follow-up
Hb < 7-8 g/dL
Rapid Hb increase needed?
RBC transfusion
Monitor Hb and iron status – maintain target levels with minimum treatment



Source	Restrictive Transfusion Threshold: No. of Deaths	Restrictive Transfusion Threshold: Total No.	Liberal Transfusion Threshold: No. of Deaths	Liberal Transfusion Threshold: Total No.	RR (95% CI)	Weight, %
Restrictive threshold, hemoglobin <8 to 9 g/dL						
Lotke et al,[75] 1999	0	62	0	65	Not estimable	
Blair et al,[53] 1986	0	26	2	24	0.19 (0.01-3.67)	0.4
Foss et al,[63] 2009	5	60	0	60	11.00 (0.62-194.63)	0.4
Carson et al,[58] 1998	1	42	1	42	1.00 (0.06-15.47)	0.4
Webert et al,[86] 2008	1	29	2	31	0.53 (0.05-5.58)	0.6
Cooper et al,[61] 2011	2	23	1	21	1.83 (0.18-18.70)	0.6
Carson et al,[56] 2013	7	55	1	55	7.00 (0.89-55.01)	0.7
Parker,[78] 2013	5	100	3	100	1.67 (0.41-6.79)	1.5
Bracey et al,[54] 1999	3	215	6	222	0.52 (0.13-2.04)	1.6
Bush et al,[55] 1997	4	50	4	49	0.98 (0.26-3.70)	1.7
Hajjar et al,[68] 2010	15	249	13	253	1.17 (0.57-2.41)	4.8
Gregersen et al,[64] 2015	21	144	12	140	1.70 (0.87-3.32)	5.4
Jairath et al,[72] 2015	14	257	25	382	0.83 (0.44-1.57)	5.8
Carson et al,[60] 2011	43	1009	52	1007	0.83 (0.56-1.22)	10.5
Subtotal	121	2321	122	2451	1.05 (0.78-1.40)	34.2
Heterogeneity: $\tau^2 = 0.02$; $\chi^2_{12} = 13.14$; $P = .36$; $I^2 = 9\%$						
Tests for overall effect: z score = 0.31; $P = .76$						
Restrictive threshold, hemoglobin <7 g/dL						
DeZern et al,[87] 2016	1	59	2	30	0.25 (0.02-2.69)	0.6
Hébert et al,[70] 1995	8	33	9	36	0.97 (0.42-2.22)	3.8
de Almeida et al,[79] 2015	23	101	8	97	2.76 (1.30-5.87)	4.5
Lacroix et al,[74] 2007	14	320	14	317	0.99 (0.48-2.04)	4.7
Walsh et al,[85] 2013	12	51	16	49	0.72 (0.38-1.36)	5.8
Murphy et al,[76] 2015	26	1000	19	1003	1.37 (0.76-2.46)	6.5
Villanueva et al,[84] 2013	19	416	34	417	0.56 (0.32-0.97)	7.2
Hébert et al,[69] 1999	78	418	98	420	0.80 (0.61-1.04)	14.7
Holst et al,[71] 2014	168	502	175	496	0.95 (0.80-1.13)	18.0
Subtotal	349	2900	375	2865	0.94 (0.74-1.19)	65.8
Heterogeneity: $\tau^2 = 0.05$; $\chi^2_8 = 16.09$; $P = .04$; $I^2 = 50\%$						
Tests for overall effect: z score = 0.53; $P = .59$						
Overall	470	5221	497	5316	0.97 (0.81-1.16)	100
Heterogeneity: $\tau^2 = 0.04$; $\chi^2_{21} = 29.75$; $P = .10$; $I^2 = 29\%$						
Tests for overall effect: z score = 0.29; $P = .77$						
Tests for subgroup differences: $\chi^2_1 = 0.34$; $P = .56$; $I^2 = 0\%$						



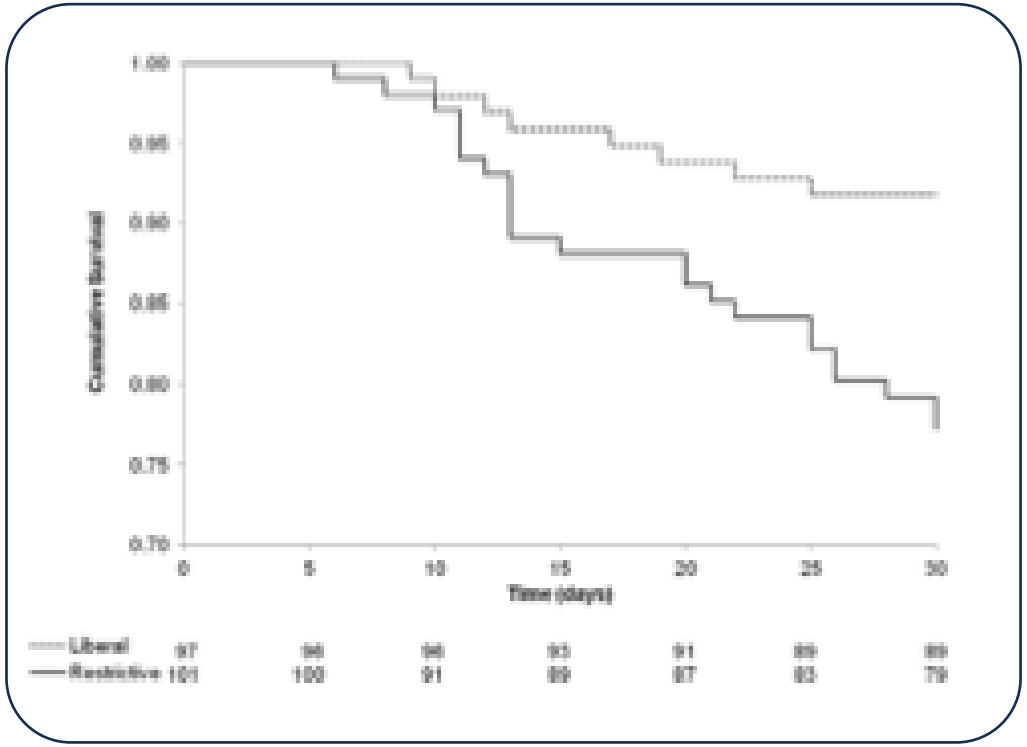
Carson et al. **JAMA** 2016



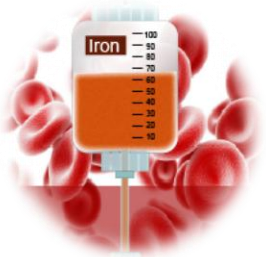
Transfusion Requirements in Surgical Oncology Patients

A Prospective, Randomized Controlled Trial

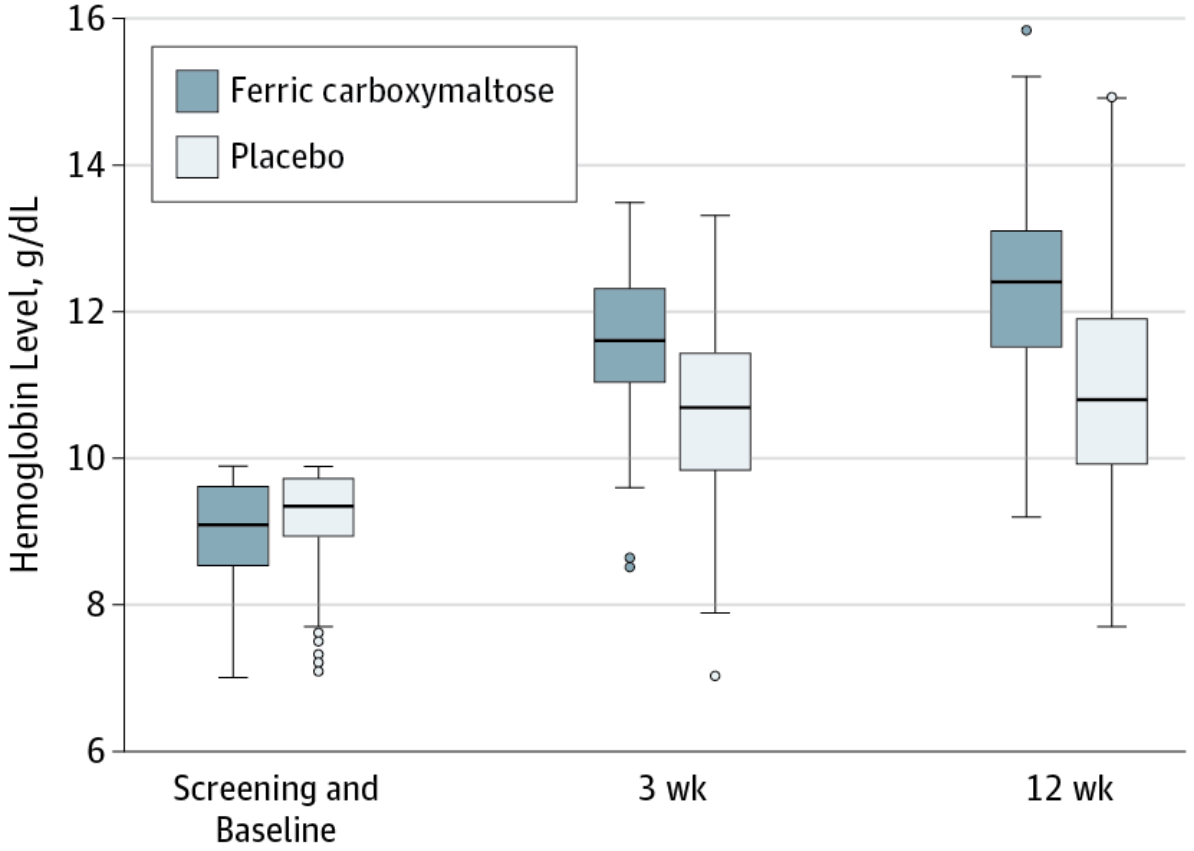
Variables (%)	Liberal Strategy (N = 97)	Restrictive Strategy (N = 101)
Type of tumor		
Upper gastrointestinal	20 (20.6)	20 (19.8)
Lower gastrointestinal	33 (34.0)	45 (44.6)
Pancreas	6 (6.2)	5 (5.0)
Liver and biliary tract	1 (1.0)	3 (3.0)
Urogenital	27 (27.8)	22 (21.8)
Other	11 (11.3)	7 (6.9)
Extent of cancer		
Localized	65 (67.0)	62 (61.4)
Metastatic	32 (33.0)	39 (38.6)



De Almeida et al. **Anesthesiology** 2015

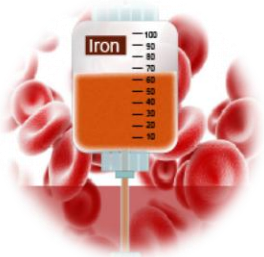


Administration de **1 g ou 500 mg de Fer IV** entre **J5 et J7** Vs. Placebo



No. of participants			
Ferric carboxymaltose	228	217	217
Placebo	226	218	213

Kim et al. **JAMA** 2017



Administration de **1 g de Fer IV** en **pré-opératoire** Vs. Placebo

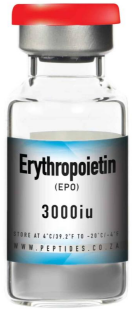
Type of operation		
Abdominal aortic aneurysm	4 (2%)	1 (<1%)
Colorectal	33 (14%)	38 (16%)
General	17 (7%)	21 (9%)
Gynaecological	75 (31%)	63 (26%)
Upper gastrointestinal	77 (32%)	81 (33%)
Urological	22 (9%)	29 (12%)
Anaesthetic time (min)	240 (161–320)	268 (180–376)
Surgery time (min)	145 (98–230)	179 (123–323)

	Placebo (n=243)	Intravenous iron (n=244)	Iron *vs* placebo (95% CI, p value)
Blood transfusion or death			
Combined	67/237 (28%)	69/237 (29%)	1·03 (0·78–1·37, p=0·84)
Transfusion	67/237 (28%)	68/237 (29%)	..
Death	2/237 (1%)	2/237 (1%)	..
Transfusion episodes			
0	170/237 (72%)	169/237 (71%)	..
1	37/237 (16%)	49/237 (21%)	..
2	22/237 (9%)	9/237 (4%)	..
3	5/237 (2%)	5/237 (2%)	..
4	1/237 (<1%)	3/237 (1%)	..
5	1/237 (<1%)	1/237 (<1%)	..
6	1/237 (<1%)	1/237 (<1%)	..
Mean	0·47 (0·9)	0·44 (0·9)	0·98 (0·68–1·43, p=0·93)

Data are n/N (%), mean (SD), and risk or rate ratio (95% CI, p value). A transfusion episode is defined as receiving any volume of 1 unit (or part thereof) or more of packed red blood cells or any other blood product. Treatment effect is a risk ratio for the first coprimary endpoint (number of blood transfusions or deaths) and a rate ratio for the second coprimary endpoint; for the second coprimary endpoint, number of blood transfusions is the number of separate transfusions administered.

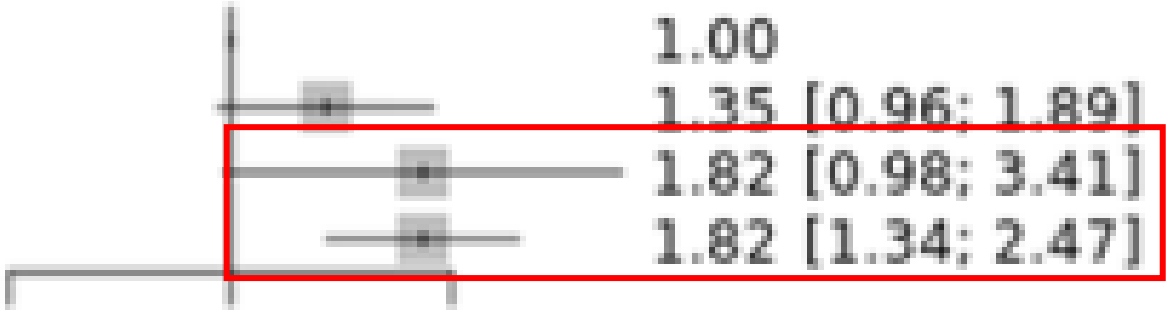
Table 2: **PREVENTT coprimary endpoints from randomisation to 30 days after operation**

Richards et al. **Lancet** 2020



Comparison: other vs 'No treatment'

Contrast to No treatment (Random Effects Model)	RR	95%-CI
No treatment	1.00	
Placebo	1.35	[0.96; 1.89]
ESA + IV iron	1.82	[0.98; 3.41]
ESA + no iron	1.82	[1.34; 2.47]



Effect on thromboembolic events

Adams et al. **Cochrane** 2022

Projet LIBERTY-2

Etudes préliminaires

Is there an optimal trade-off between anaemia and red blood cell transfusion in surgical critically ill patients after oncologic surgery?

Xavier Chapalain,[1] Yves Ozier,[1] Catherine Le Niger,[2] Zoe McQuilten,[3] Olivier Huet[1] & Cécile Aubron[3,4]

86,9%

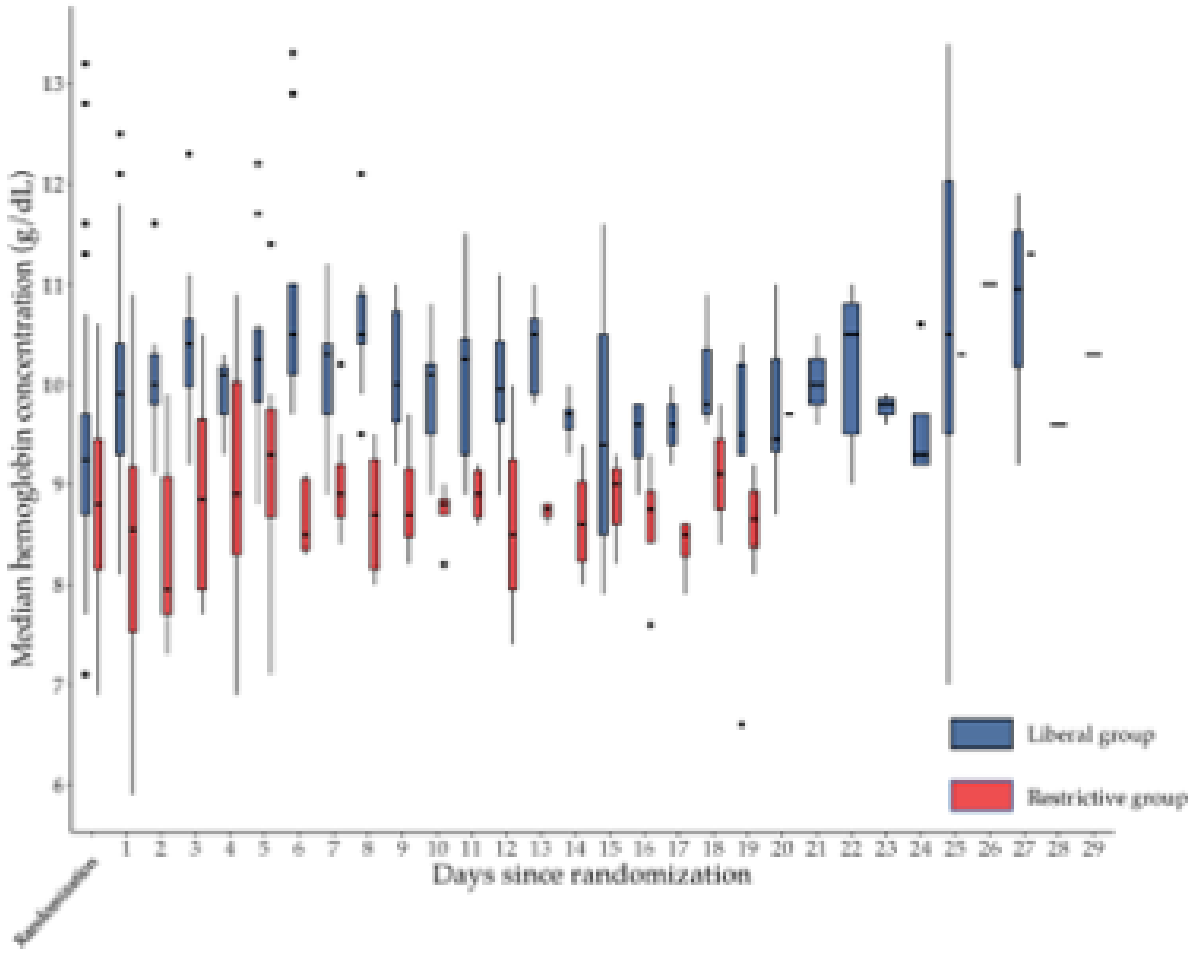
	No anaemia N = 37	Mild anaemia N = 146	Moderate anaemia N = 68	Severe anaemia N = 32	*P*
Age, years (median, IQR)	61 [52–67]	64 [57–71]	68 [62–71]	68 [56–72]	0·05
Surgery (*n*, %)					
Abdominal	4 (11·1)	67 (45·9)	49 (72·1)	25 (78·1)	<0·001
Neurosurgery	28 (77·8)	54 (37)	13 (19·1)	1 (3·1)	<0·001
Thoracic	4 (11·1)	23 (15·8)	5 (7·4)	5 (15·6)	0·44
Comorbidities (*n*, %)					
Arterial hypertension	16 (44·4)	78 (53·4)	36 (52·9)	18 (56·2)	0·74
Coronary artery disease	7 (19·4)	28 (19·2)	12 (17·6)	6 (18·8)	0·99
Arteritis	2 (5·6)	20 (13·7)	11 (16·2)	3 (9·4)	0·53
Arrhythmia	0	7 (4·8)	1 (1·5)	2 (6·2)	0·36
COPD	6 (16·7)	26 (17·8)	11 (16·2)	4 (12·5)	0·95
Cirrhosis	0	5 (3·4)	5 (7·4)	3 (9·4)	0·18
Chronic kidney disease	2 (5·6)	17 (11·6)	8 (11·8)	6 (18·8)	0·49
Diabetes	1 (2·8)	29 (19·9)	14 (20·6)	9 (28·1)	0·03
Estimated blood loss, ml (median, IQR) §	100 [100–325]	300 [200–500]	300 [200–625]	500 [300–1750]	<0·001
Primary outcome (*n*, %)	1 (2·8)	28 (19·2)	27 (39·7)	14 (43·8)	<0·001
Hospital mortality	0	3 (2·1)	8 (11·6)	3 (9·4)	0·01
Postoperative complications	1 (2·8)	28 (19·2)	24 (35·3)	14 (43·8)	<0·001

Chapalain et al. **Vox Sanguinis** 2021

ORIGINAL RESEARCH

TRANSFUSION

Postoperative transfusion hemoglobin threshold and functional recovery after high-risk oncologic surgery: A randomized controlled pilot study



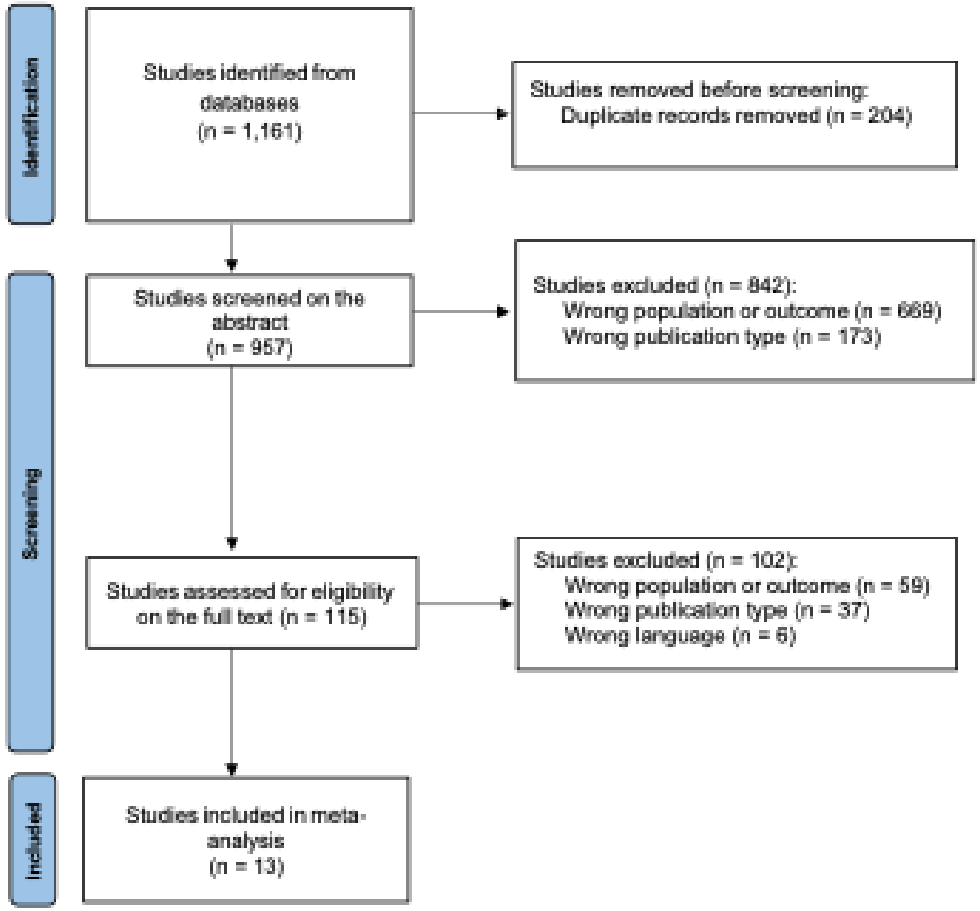
	Transfusion strategy		
	Liberal (n = 15)	Restrictive (n = 15)	p
Functional recovery assessment			
WHODAS 2.0, median (IQR)	19 (7–31)	23 (18–27)	.65
Disability-free survival, n (%)	4 (26.7)	3 (20)	1
QoR-15 at Day 30, median (IQR)	111 (95–129)	123 (84–132)	.54
Postoperative complications			
Medical complications, n (%)			
Respiratory insufficiency	4 (26.7)	1 (6.7)	.33
Acute Kidney Injury (KDIGO 2–3)	8 (53.3)	4 (26.7)	.14
Myocardial infarction	0 (0)	0 (0)	NA
Thromboembolic event	2 (13.3)	2 (13.3)	1
Stroke	0 (0)	0 (0)	NA
Septic shock	2 (13.3)	1 (6.7)	1
Bacteremia	2 (13.3)	2 (13.3)	1
Surgical complications, n (%)			
Surgical site infection	4 (26.7)	3 (20)	1
Hemorrhage at surgical site	2 (13.3)	0 (0)	.48
Length of stay (days), median (IQR)			
In ICU	3 (2–7)	3 (1–6)	.36
In hospital	17 (10–33)	18 (11–23)	.95

Chapalain et al. **Transfusion** 2023

Original article

Perioperative red blood cell transfusion following high-risk oncologic surgery for tumor resection: a systematic review and *meta*-analysis

Xavier Chapalain [a,*], Morgane Zaïna [a], Jean-Philippe Metges [b], Bogdan Badic [c], Rosemary L. Sparrow [d], Zoe McQuilten [d], Olivier Huet [a], Cécile Aubron [d,e]



Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Restrictive transfusion strategy	Risk with Liberal transfusion strategy				
Post-operative mortality	196 per 1 000	**124 per 1 000** (17 to 520)	**OR 0.57** (0.07 to 4.38)	228 (2 RCTs)	⨁◯◯◯ Very low[1,a,b]	
Sepsis	196 per 1 000	**135 per 1 000** (67 to 250)	**OR 0.63** (0.29 to 1.35)	228 (2 RCTs)	⨁◯◯◯ Very low[a,b]	
Acute Kidney Injury	414 per 1 000	**504 per 1 000** (321 to 721)	**OR 1.44** (0.67 to 3.66)	228 (2 RCTs)	⨁◯◯◯ Very low[a,b]	
Thromboembolic event	26 per 1 000	**26 per 1 000** (5 to 126)	**OR 1.01** (0.19 to 5.44)	228 (2 RCTs)	⨁◯◯◯ Very low[c]	
Myocardial infarction	9 per 1 000	**3 per 1 000** (0 to 69)	**OR 0.34** (0.01 to 8.54)	228 (2 RCTs)	⨁◯◯◯ Very low[c]	
Stroke	26 per 1 000	**4 per 1 000** (0 to 70)	**OR 0.14** (0.01 to 2.83)	228 (2 RCTs)	⨁◯◯◯ Very low[c]	
ICU length of stay	The mean ICU length of stay was **3.5** days	MD **0 days** (0.97 fewer to 0.97 more)	-	228 (2 RCTs)	⨁⨁◯◯ Low[b]	
Hospital length of stay	The mean hospital length of stay was **15** days	MD **1 days fewer** (3.2 fewer to 1.2 more)	-	228 (2 RCTs)	⨁⨁◯◯ Low[b]	

Chapalain et al. **TCB** 2025

PHRC inter-régional 2025

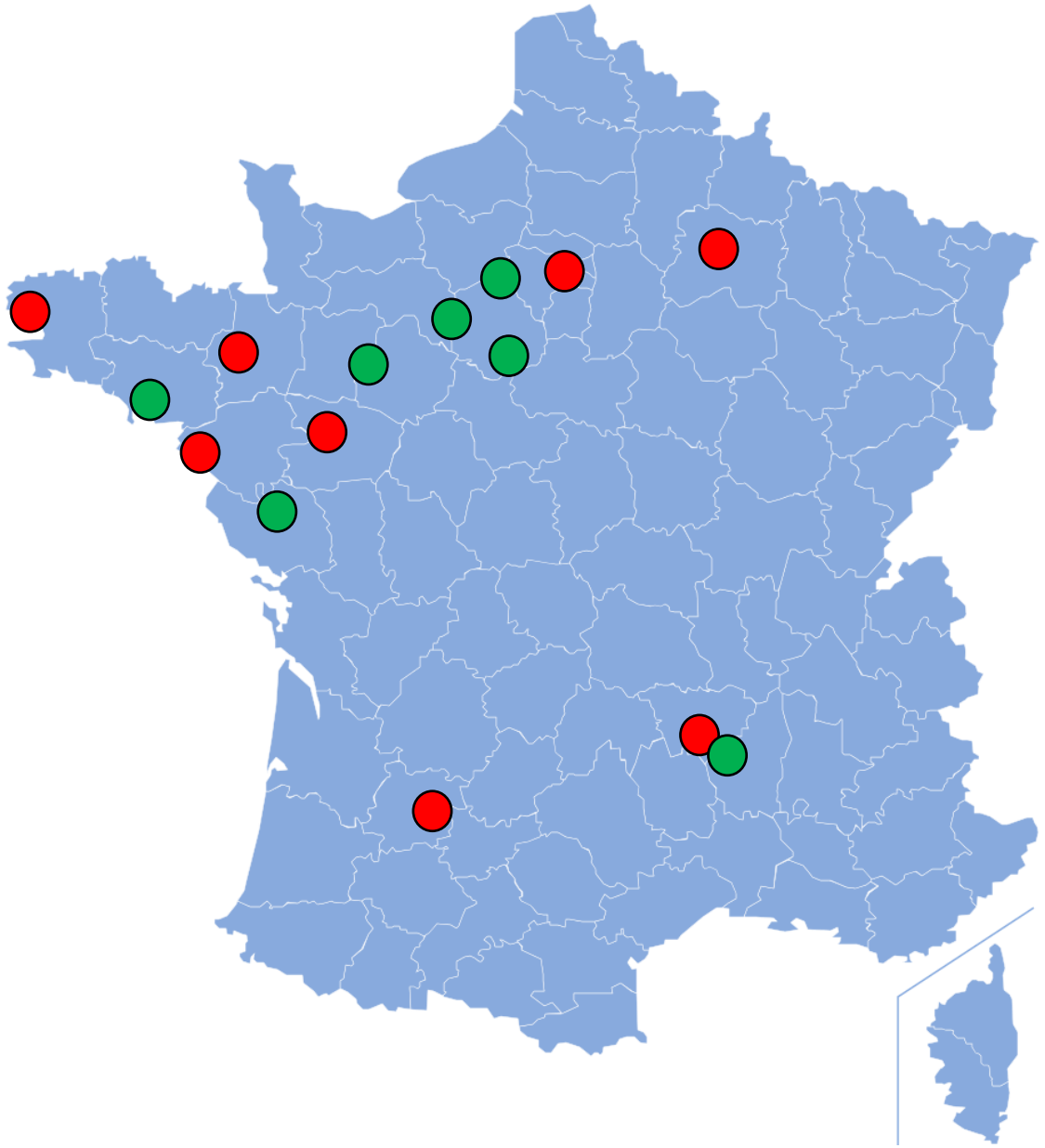
Comparaison d'une **stratégies transfusionnelle** 'restrictive' vs. 'libérale' associé ou non à une **gestion personnalisée du sang** (fer et EPO) administré en post-opératoire de chirurgie abdominale majeure pour résection tumorale

Etude LIBERTY-2



15 centres participants

- 8 CHU
  - Brest
  - Rennes
  - Nantes
  - Angers
  - Avicenne
  - Clermont-Ferrand
  - Toulouse
  - Reims
- 7 CH ou hôpitaux privés
  - Cholet
  - Vannes
  - Dreux
  - Clermont-Ferrand
  - Chartres
  - Trappes
  - Le Mans



Critères d'inclusion



- Age > **18 ans**
- Admission en réanimation / USC après **chirurgie digestive pour résection tumorale** (hépatectomie, duodéno-pancréatectomie, gastrectomie, oesophagectomie, résection intestinale, or colectomie).
- Pertes sanguines péri-opératoires estimées supérieure à **300 ml**
- Anémie post-opératoire modérée à sévères **(Hb < 9.5 g/dl)** survenant dans les 5 premiers jours post-opératoire
- Randomisation dans les **12 heures** suivant la survenue de l'anémie

Critères d'exclusion

- Chirurgie urgente
- Fragilité pré-opératoire (clinical frailty scale > 5)
- Infarctus du myocarde ou angor récent (< 4 mois)
- Patients ayant déjà reçu un CGR avant l'inclusion
- Patients ayant déjà reçu du fer ou de l'EPO dans la période post-opératoire
- Contre indication au fer IV ou à l'EPO
- Patients moribond (espérance de vie estimée < 24 heures)
- Patients bénéficiant de soins palliatifs
- Patients participants à une autre étude concernant la transfusion, le fer ou l'EPO
- Refus de transfusion
- Refus de participation
- Femme enceinte ou allaitante
- Patient sous curatelle ou tutelle

Schéma expérimental (n = 424)

Digestive surgery for tumor resection

Admission in ICU in postoperative period

Anaemia (Hb < 9,5 g/dl)
Blood losses > 300 ml

Randomisation
- Clinical frailty scale (1-3 vs. 4-5)
- Length of surgery (>3 hours: Yes/No)
- Centre
- Ischemic heart disease (Yes/No)

Restrictive transfusion strategy: One RBC if Hb < 7,5 g/dl until Day 45
No post-operative intravenous iron
No post-operative EPO
N = 106

Restrictive transfusion strategy: One RBC if Hb < 7,5 g/dl until Day 45
AND postoperative intravenous iron (**ferric derisomaltose** OR **ferric carboxymaltose**)
AND **EPO alpha**
N = 106

Liberal transfusion strategy: One RBC if Hb < 9,5 g/dl until Day 45
No post-operative intravenous iron
No post-operative EPO
N = 106

Liberal transfusion strategy: One RBC if Hb < 9,5 g/dl until Day 45
AND postoperative intravenous iron (**ferric derisomaltose** OR ferric **carboxymaltose**)
AND **EPO alpha**
N = 106

Interventions

Stratégie transfusionnelle « restrictive » : 1 CGR si Hb < 7,5 g/dl jusqu'à J45
ET **Fer carboxymaltose** ou **Fer dérisomaltose (la veille ou le jour de la sortie)**
ET **EPO** (40,000 UI)



Si Hb < 7.5 g/dl

Fer IV (15-30 mg/kg)
EPO (40 000 UI)

Stratégie transfusionnelle « libérale » : 1 CGR si Hb < 9,5 g/dl jusqu'à J45
ET **Fer carboxymaltose** ou **Fer dérisomaltose (la veille ou le jour de la sortie)**
ET **EPO** (40,000 UI)



Si Hb < 9.5 g/dl

Fer IV (15-30 mg/kg)
EPO (40 000 UI)

Jour de la chirurgie — **< J10** — **J45**

Interventions

Stratégie transfusionnelle « restrictive » : 1 CGR si Hb < 7,5 g/dl jusqu'à J45
Pas de fer IV post-opératoire
Pas d'EPO post-opératoire



Si Hb < 7.5 g/dl

Stratégie transfusionnelle « libérale » : 1 CGR si Hb < 9,5 g/dl jusqu'à J45
Pas de fer IV post-opératoire
Pas d'EPO post-opératoire



Si Hb < 9.5 g/dl

Jour de la chirurgie → **J45**

Critère de jugement principal

Importance de l'incapacité fonctionnelle à J45

- **WHODAS** (**W**orld **H**ealth **O**rganisation **D**isability **A**ssessement **S**cale)
- Questionnaire avec 12 items
- Validé en post-opératoire
- Traduit en Français et Anglais
- Utilisé dans des journaux de rang A+ :
  - RELIEF trial, Myles et al. NEJM 2018

In the past 30 days, how much difficulty did you have in:						
S1	Standing for long periods such as 30 minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
S2	Taking care of your household responsibilities?	None	Mild	Moderate	Severe	Extreme or cannot do
S3	Learning a new task, for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do
S4	How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	None	Mild	Moderate	Severe	Extreme or cannot do
S5	How much have you been emotionally affected by your health problems?	None	Mild	Moderate	Severe	Extreme or cannot do

In the past 30 days, how much difficulty did you have in:						
S6	Concentrating on doing something for ten minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
S7	Walking a long distance such as a kilometre [or equivalent]?	None	Mild	Moderate	Severe	Extreme or cannot do
S8	Washing your whole body?	None	Mild	Moderate	Severe	Extreme or cannot do
S9	Getting dressed?	None	Mild	Moderate	Severe	Extreme or cannot do
S10	Dealing with people you do not know?	None	Mild	Moderate	Severe	Extreme or cannot do
S11	Maintaining a friendship?	None	Mild	Moderate	Severe	Extreme or cannot do
S12	Your day-to-day work?	None	Mild	Moderate	Severe	Extreme or cannot do

Critères de jugement secondaires

- Incapacité fonctionnelle post-opératoire à J45 (WHODAS binaire)
- Durée de séjour en réanimation
- Durée de séjour à l'hôpital
- Complications médico-chirurgicales post-opératoire entre la randomisation and J45
- Traitement adjuvant anti-cancéreux entre la chirurgie et J90
- Temps entre la chirurgie et l'administration du traitement adjuvant
- Qualité de vie (EQ-5D-5L) à J90
- Mortalité à J45 et J90

A venir…

- **Extension à l'international (ANZIC-RC) – Avril 2026**
  - MRFF International Collaboration Clinical Trial grant (+400 patients, 15 centres)



Allison Mo



Zoé McQuilten



Erica Wood

Comparaison d'une **stratégies transfusionnelle** 'restrictive' vs. 'libérale' associé ou non à une **gestion personnalisée du sang** (fer et EPO) administré en post-opératoire de chirurgie abdominale majeure pour résection tumorale



- Etude **pragmatique**, **contrôlée**, **randomisée**
- **Multicentrique** (15 centres)
- **Stratégie intégrée** de la gestion de l'anémie après chirurgie oncologique majeure
- Critère principal centré sur le patient
- Analyse médico-économique

Soumission CPP ✅

Mise en place : Début 2027