Transfusión y pronóstico en los síndromes mielodisplásicos

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SINDROMES MIELODISPLASICOS

- Hemopoyesis displásica.
- Anemia y otras citopenias.
- Marcada propensión a la transformación leucémica.
- Incidencia (>70 años):

  > 200 / millón - año

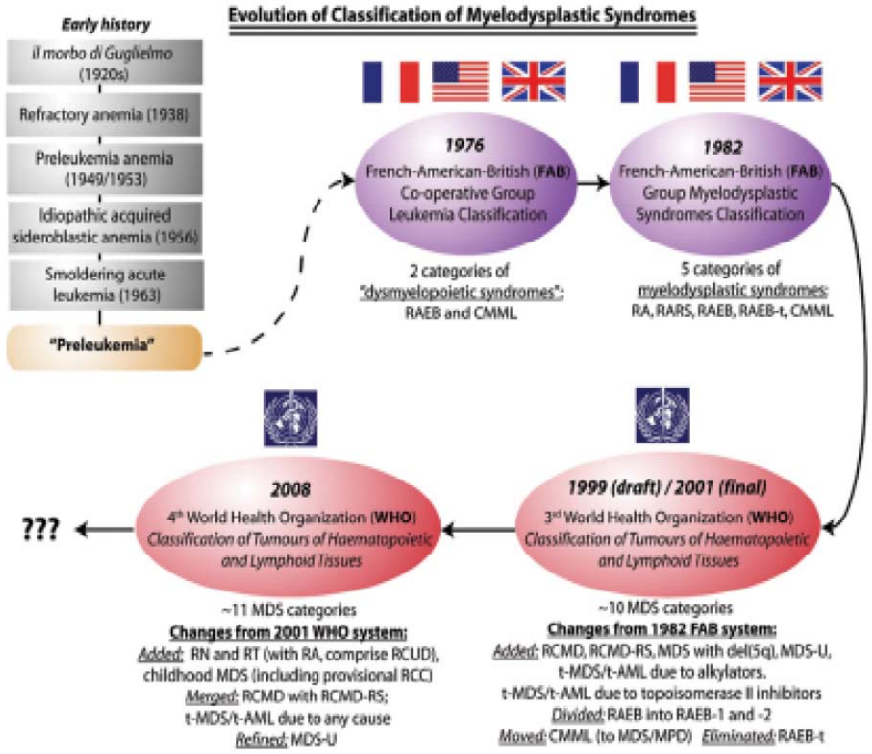


Table 1. Classification of Myeloid Neoplasms, According to World Health Organization Criteria.

Acute myeloid leukemia and related neoplasms*

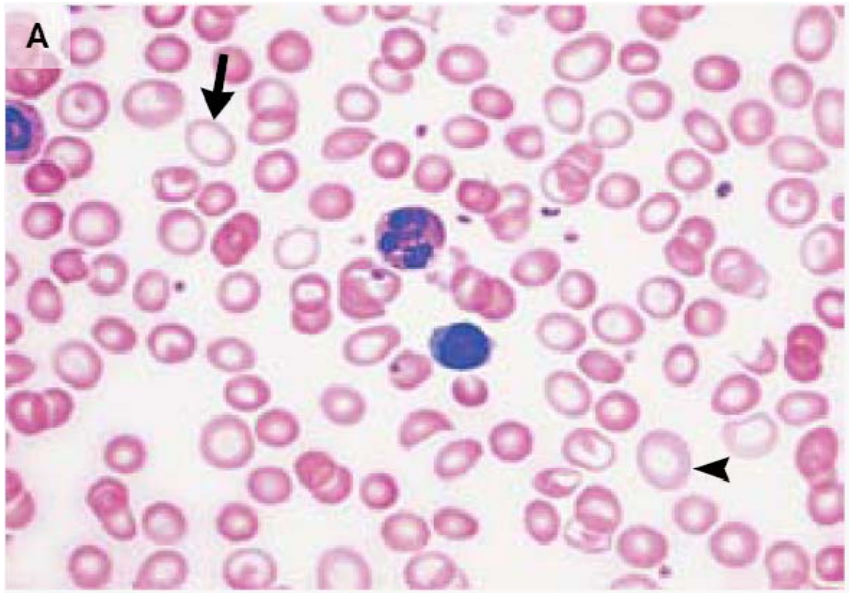
Myelodysplastic syndromes

- Refractory cytopenia with unilineage dysplasia†
  - Refractory anemia (ring sideroblasts <15% of erythroid precursors)
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts (dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow erythroid precursors)
- Refractory cytopenia with multilineage dysplasia (regardless of ring sideroblast count)
- Refractory anemia with excess of blasts (RAEB)
  - RAEB-1 (2–4% circulating blasts or 5–9% marrow blasts)
  - RAEB-2 (5–19% circulating blasts or 10–19% marrow blasts or Auer rods present)
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome (unclassifiable)

Myeloproliferative neoplasms‡

Myelodysplastic–myeloproliferative neoplasms§

Molecularly characterized myeloid or lymphoid neoplasms associated with eosinophilia¶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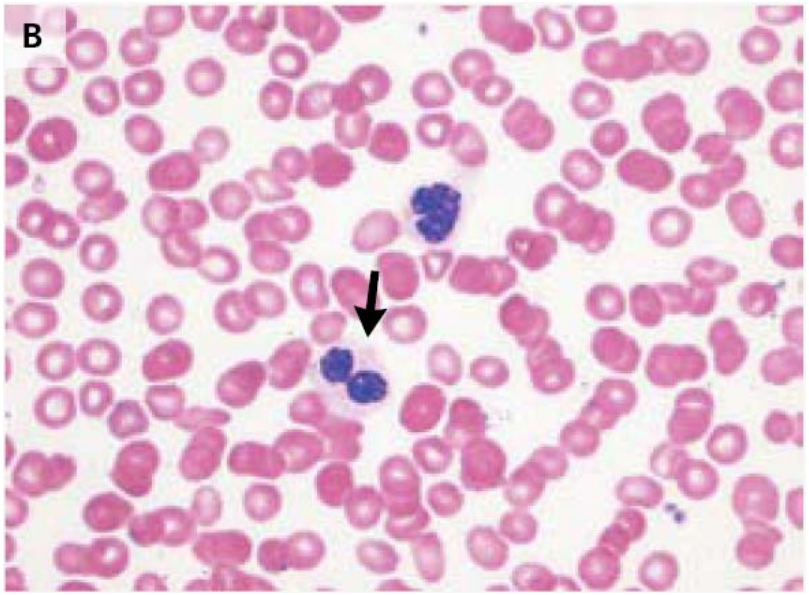
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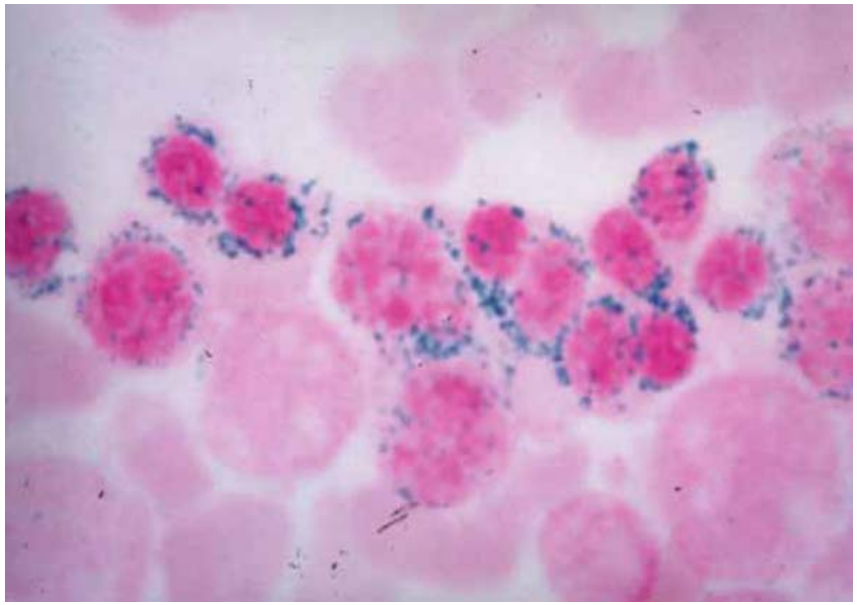
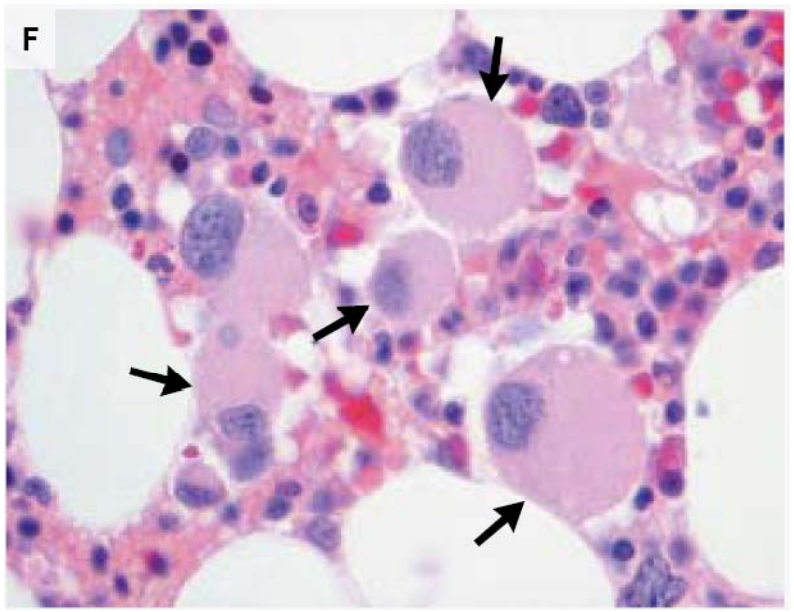


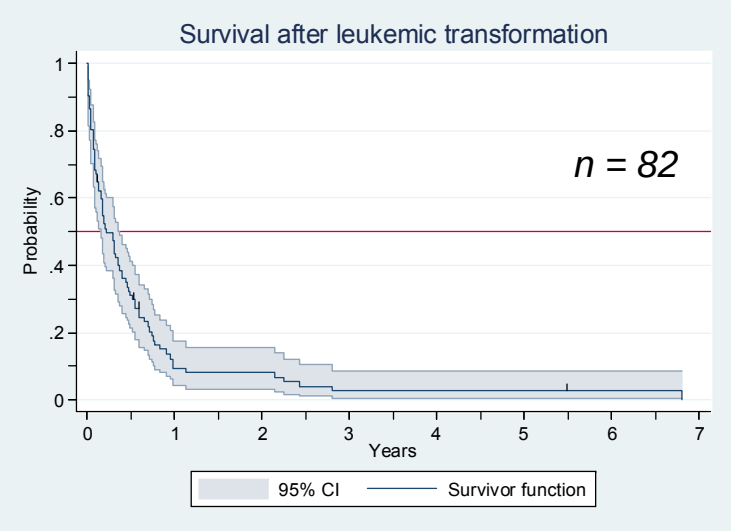

F

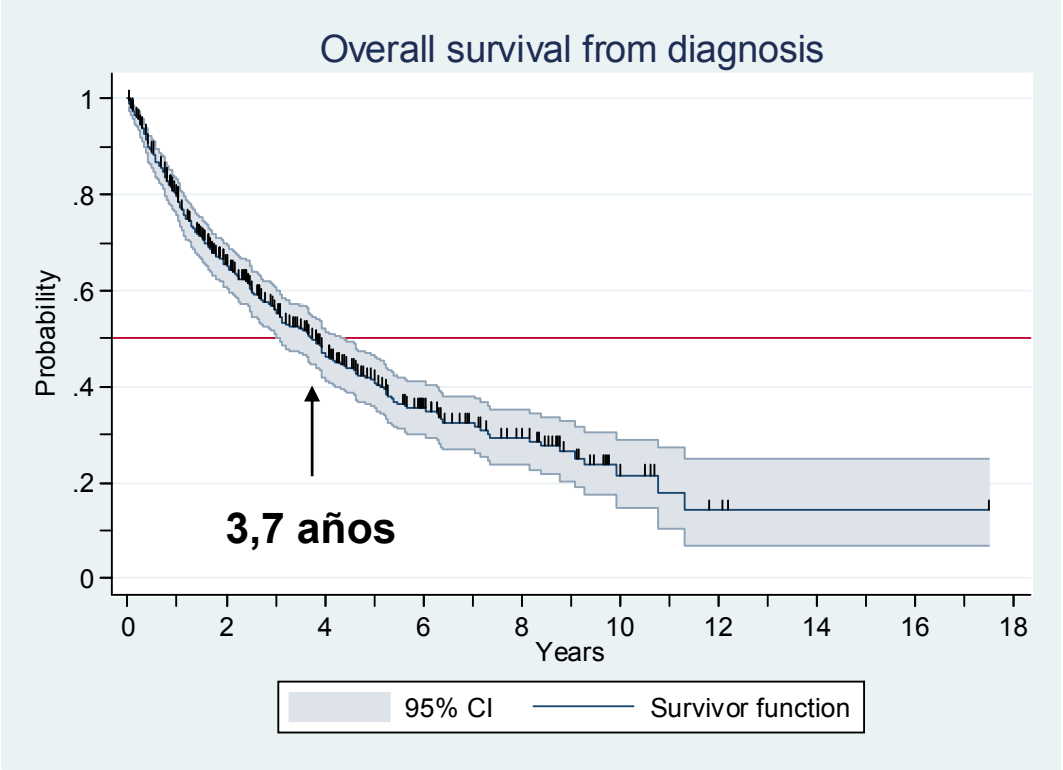
Hospital Clínic (1997 – 2009): 467 pacientes

Tipo OMS	Frecuencia
AR	6 %
ARS	3 %
CRDML	53 %
AREB	20 %
del(5q)	1 %
LMMC (n.p.)	17 %

Edad, mediana (extremos): 74 (16 – 99) años

Mujeres / varones: 204 / 263 (56%)





Anemia

Relevancia clínica:

- ≈ 50% de los pacientes incialmente (Hb < 10 g/dL).
- > 30 % durante la evolución
- Mala respuesta al tratamiento farmacológico.
  - Factores madurativos, andrógenos, ESA, etc.
  - Excepción: lenalidomida en *del*(5q), azacitidina,...
- Muchos, sólo soporte transfusional.
- Afecta a calidad de vida y comorbilidades.

Relevancia logística:

- 2ª causa de transfusión de hematíes en Cataluña.
- ≈ 5% del total (aprox. 13.000 CH /año)

SMD: clasificación pronóstica

International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

By Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti, and John Bennett

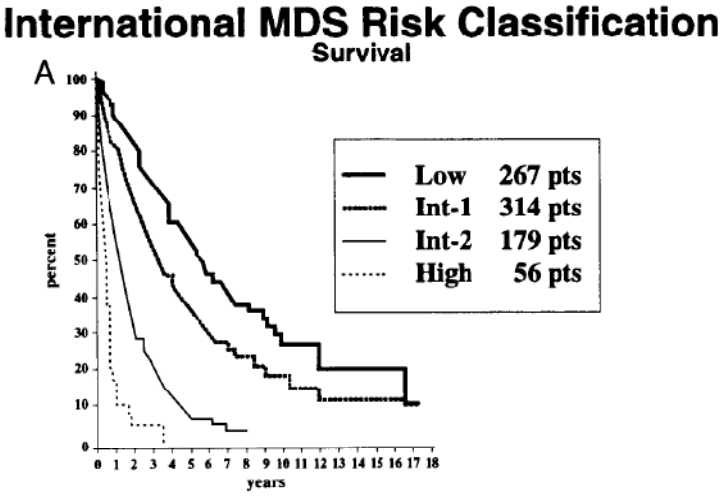
Blood, Vol 89, No 6 (March 15), 1997: pp 2079-2088

Table 3. IPSS for MDS: Survival and AML Evolution

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

* Good, normal, −Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.



Grupo de riesgo	Pacientes	Mediana srv (años)
Bajo	33%	5,7
Intermed.-bajo	38%	3,5
Intermed.-alto	22%	1,2
Alto	7%	0,4

La dependencia transfusional como factor pronóstico

VOLUME 23 · NUMBER 30 · OCTOBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic Factors and Life Expectancy in Myelodysplastic Syndromes Classified According to WHO Criteria: A Basis for Clinical Decision Making

Luca Malcovati, Matteo Giovanni Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Marina Boni, Erica Travaglino, Francesco Passamonti, Luca Arcaini, Margherita Maffioli, Paolo Bernasconi, Mario Lazzarino, and Mario Cazzola

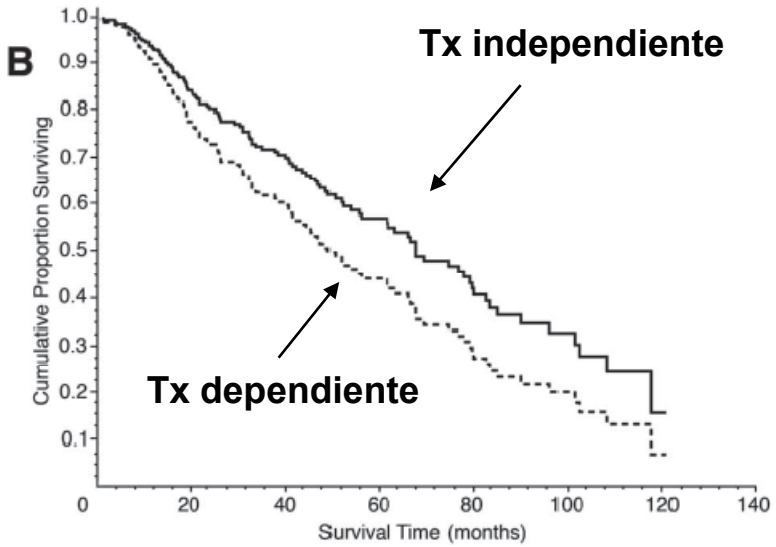
VOLUME 25 · NUMBER 23 · AUGUST 10 2007

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Time-Dependent Prognostic Scoring System for Predicting Survival and Leukemic Evolution in Myelodysplastic Syndromes

Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, and Mario Cazzola

1.



2.

development of secondary iron overload significantly affected the OS ($P < .001$), with an HR of 1.36 every 500 ng/mL of increase in serum ferritin above the threshold. After we added

Conclusión:

have a median survival of about 50 months. On the basis of these results, it seems possible to recommend adequate iron chelation therapy for patients with RA whose transfusion burden exceeds 20 to 25 RBC units.

Table 2. WHO Classification–Based Prognostic Scoring System for MDS

Variable	0	1	2	3
WHO category	RA, RARS, 5q–	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	—
Transfusion requirement†	No	Regular	—	—

NOTE. Risk groups were as follows: very low (score = 0), low (score = 1), intermediate (score = 2), high (score = 3 to 4), and very high (score = 5 to 6).
Abbreviations: MDS, myelodysplastic syndrome; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; 5q–, myelodysplastic syndrome with isolated del(5q) and marrow blasts less than 5%; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2.
*Karyotype was as follows: good: normal, –Y, del(5q), del(20q); poor: complex (≥ three abnormalities), chromosome 7 anomalies; and intermediate: other abnormalities.
†RBC transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

PENSAMIENTO ORTODOXO

Dependencia transfusional ≡ Carga transfusional
(Definida según Malcovati) *(Cantidad de CH transfundidos)*

Carga transfusional ≡ Hemosiderosis

Hemosiderosis ≡ Mayor mortalidad

Dependencia transfusional ≡ Quelación del hierro

GUIAS CLINICAS QUE RECOMIENDAN QUELANTES DEL HIERRO

Available online at www.sciencedirect.com
ScienceDirect
Leukemia Research 32 (2008) 1338–1353
Leukemia Research
www.elsevier.com/locate/leukres

Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

Richard A. Wells[a,*], Brian Leber[b], Rena Buckstein[a], Jeffrey H. Lipton[c], Wanda Hasegawa[d], Kuljit Grewal[e], Karen Yee[c], Harold J. Olney[f], Loree Larratt[g], Linda Vickars[h], Alan Tinmouth[i]

Reviews

Iron Chelation Therapy in Patients with Myelodysplastic Syndromes: Consensus Conference Guidelines

Moshe Mittelman MD[1], Gilles Lugassy MD[2], Drorit Merkel MD[3], Hannah Tamary MD[4], Nadav Sarid MD[1], Eliezer Rachmilewitz MD[5] and Chaim Hershko MD[6], for the MDS Israel Group and the Israel Society of Hematology

[1]Department of Medicine, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv
[2]Hematology Institute, Barzilai Medical Center, Ashkelon and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva
[3]Department of Hematology, Sheba Medical Center, Tel Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv
[4]Department of Pediatric Hematology-Oncology, Schneider National Children's Hospital, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv
[5]Hematology Institute, Wolfson Medical Center, Holon, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv

Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology

Emilio Paolo Alessandrino,* Sergio Amadori,° Giovanni Barosi,# Mario Cazzola,* Alberto Grossi,@ Lucio N. Liberato,^ Franco Locatelli,§ Monia Marchetti,# Enrica Morra,** Paolo Rebulla,°° Giuseppe Visani,## Sante Tura@@

Myelodysplastic Syndromes

research paper
haematologica 2002; 87:1286-1306
http://www.haematologica.org/2002_12/1286.htm

*Divisione di Ematologia, #Laboratorio di Informatica Medica, §Dipartimento di Pediatria, IRCCS Policlinico S. Matteo, Pavia; °Cattedra di Ematologia, Università Tor Vergata, Ospedale Sant'Eugenio, Rome; @U.O. di Ematologia, Azienda Ospedaliera Careggi, Florence; ^Divisione di Medicina, Ospedale Civile, Voghera (PV); **Divisione di Ematologia, Ospedale Niguarda Cà Granda, Milan; °°Centro Trasfusionale e di Immunologia dei Trapianti, IRCCS Ospedale Maggiore; ##U.O. Ematologia, Azienda Ospedaliera San Salvatore, Pesaro; @@Istituto Seragnoli, Policlinico Sant'Orsola, Bologna, Italy

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ScienceDirect
Leukemia Research 31 (2007) 727–736
Leukemia Research
www.elsevier.com/locate/leukres

Consensus report

Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference

Peter Valent[a,*], Hans-Peter Horny[b], John M. Bennett[c], Christa Fonatsch[d], Ulrich Germing[e], Peter Greenberg[f], Torsten Haferlach[g], Detlef Haase[h], Hans-Jochen Kolb[i], Otto Krieger[j], Michael Loken[k], Arjan van de Loosdrecht[l], Kiyoyuki Ogata[m], Alberto Orfao[n], Michael Pfeilstöcker[o], Björn Rüter[p], Wolfgang R. Sperr[a], Reinhard Stauder[q], Denise A. Wells[k]

DOI 10.1007/s12185-008-0119-y
PROGRESS IN HEMATOLOGY
Transfusional iron overload and iron chelation therapy

Japanese epidemiological survey with consensus statement on Japanese guidelines for treatment of iron overload in bone marrow failure syndromes

Takahiro Suzuki · Masao Tomonaga · Yasushi Miyazaki · Shinji Nakao · Kazuma Ohyashiki · Itaru Matsumura · Yutaka Kohgo · Yoshiro Niitsu · Seiji Kojima · Keiya Ozawa

PENSAMIENTO HETERODOXO

Dependencia transfusional ≡ **Anemia más grave**
(Definida según Malcovati) *(Transfusión más frecuente)*

Anemia más grave ≡ **Hemopoyesis más afectada**

Hemopoyesis más afectada ≡ **Mayor mortalidad**

Dependencia transfusional ≡ **Enfermedad más grave**

Leukemia Research 33 (2009) 1158–1163

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Open Forum

Myelodysplasia paranoia: Iron as the new radon

David P. Steensma*

Leukemia (2009) 23, 1373

www.nature.com/leu

EDITORIAL

A Tefferi[1] and RM Stone[2]

Iron chelation therapy in myelodysplastic syndrome — Cui bono?

unknown clinical benefit. Controlled clinical trials, and not a litany of consensus statements, are needed to justify such treatment. Primary outcome measures in such trials must portray meaningful health outcome rather than a banal effect on laboratory surrogates of iron overload.

ESTADO DE LA CUESTION

No hay pruebas de que la hemosiderosis post-transfusional afecte a la supervivencia de los pacientes con SMD.

- Supervivencia breve, determinada por la enfermedad.
- En la mayoría, no hay evidencia de hemosiderosis (RMN T2*, necropsia, etc.)
- Ferritina sérica mal marcador de hemosiderosis.

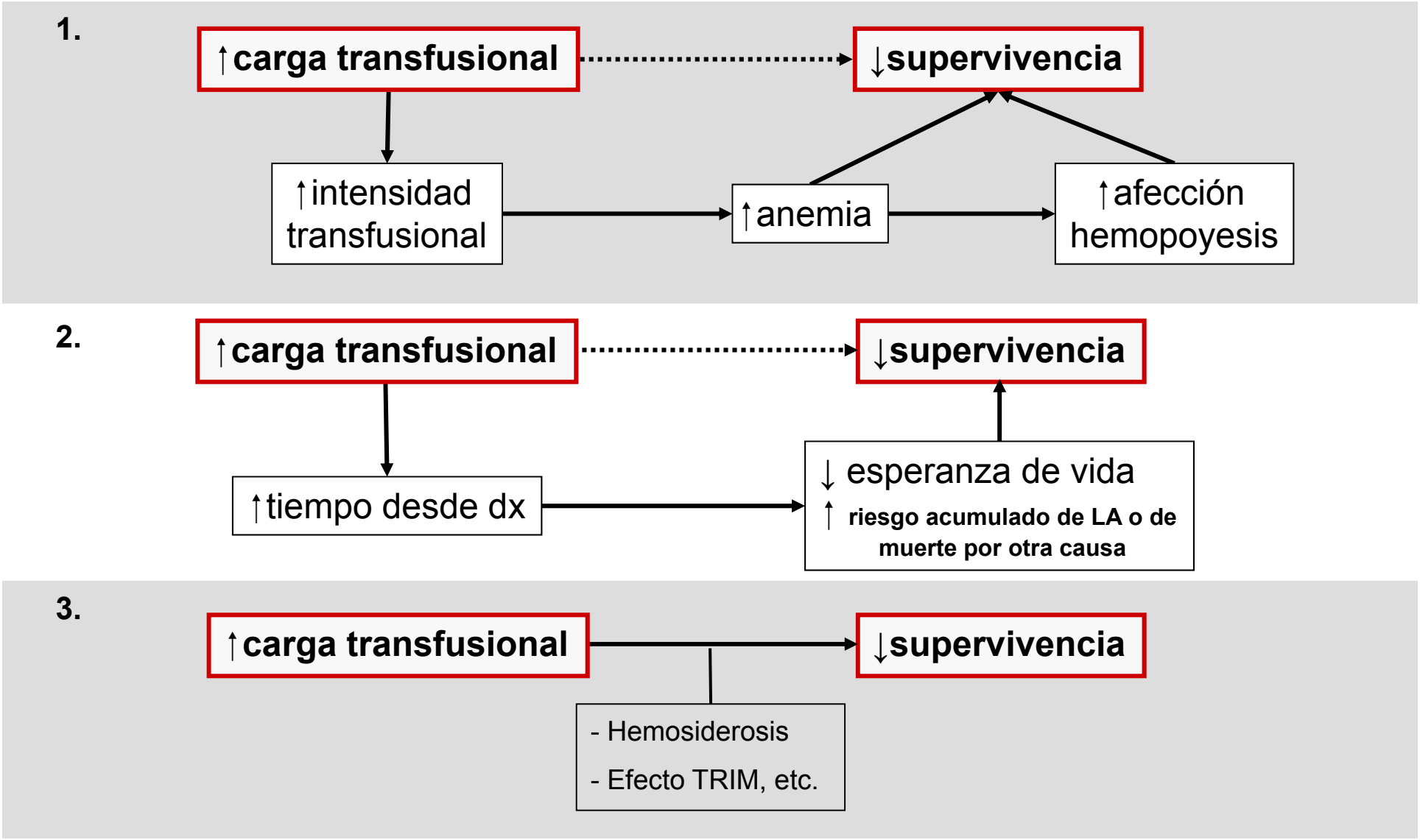
No hay evidencia de que la quelación del hierro influya en la supervivencia de los pacientes con SMD.

- No hay ensayos clínicos controlados.
- Datos observacionales, retrospectivos y de baja calidad.

Evidencia difícil de conseguir

- Ensayo clínico de quelantes del hierro.
- Estudios epidemiológicos prospectivos de calidad.

Objetivo: poner a prueba tres hipótesis sobre la relación causal entre la carga transfusional acumulada y la supervivencia en los pacientes con SMD.



PACIENTES Y METODOS (i)

- Pacientes: SMD/LMMC no proliferativa y dependencia transfusional.
- Efecto: Supervivencia libre de LMA desde la primera transfusión.
- Intensidad transfusional:

$$\frac{\textit{Nº CH en un episodio transfusional x 365}}{\textit{días desde episodio anterior}}$$

- Dintel de carga transfusional acumulada: 25 CH (100 CH).
- Ajuste por las características clínico-hematológicas, edad y tiempo transcurrido cuando se alcanza el dintel de carga transfusional.

PACIENTES Y METODOS (ii)

- **Modelos de Cox anidados**: el impacto pronóstico de la carga transfusional acumulada se ajusta sucesivamente por la intensidad transfusional y el tiempo hasta 25 CH.

- **Hipótesis**: si alguna de esas variables anula el significado pronóstico de la carga transfusional y el modelo resultante presenta mejores parámetros de ajuste y especificación: la asociación pronóstica no implica causalidad (efecto de mediación o confusión).

CARACTERISTICAS DEL ESTUDIO

Seguimiento

- **Periodo:**	**enero 1997 – diciembre 2009**
- Pacientes con SMD:	466
- **Pacientes incluidos**:	**191**
- **Fallecidos:**	**128 (67%)**
- Perdidos de control:	8 (4%)
- Censados:	55 (29%)
- **Transf. leucémica:**	**46 (24%)**

Transfusión

- **Episodios transfus.:**	**5.306**
- Nº CH transfundidos:	10.684 (1.022 en LAM)

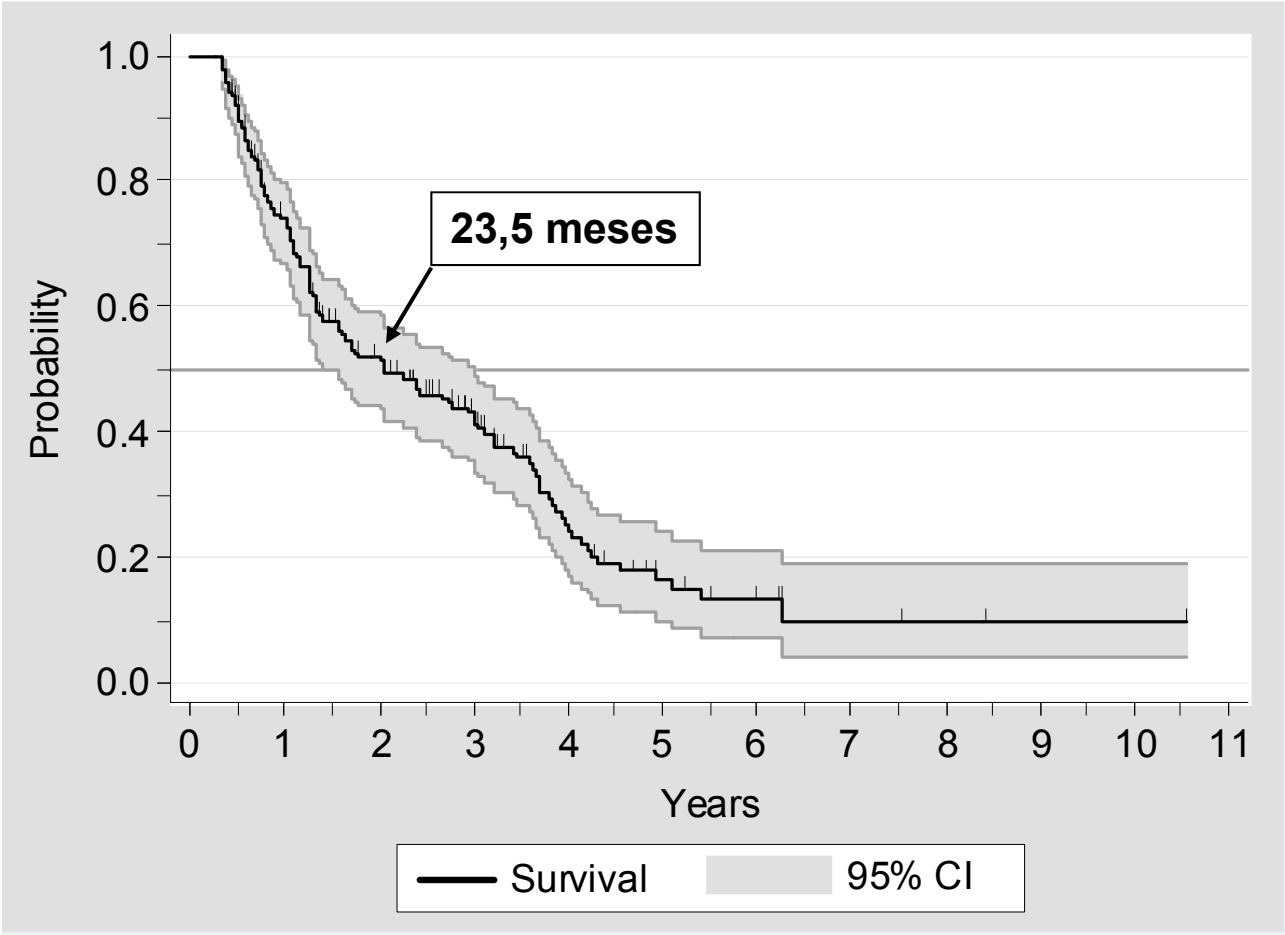
Depend. transfusional

- Desde diagnóstico.	70 (37%)
- Dentro del 1er año:	140 (74%)
- Dentro de 3 años:	171 (90%)

TABLE I. Characteristics of 191 Transfusion-Dependent MDS Patients at Different Time Points During Their Transfusional History

		Cumulative transfusion burden	
	At first transfusion	≥25 RBC units	≥100 RBC units
No. of patients (% of total)	191 (100%)	112 (59%)	29 (15%)
Age at that time in years, median (range)[a]	74 (16–99)	75 (18–99)	73 (28–86)
Sex (male/female)	97 (51%)/94	63 (56%)/49	17 (59%)/12
WHO category			
RA/RARS/del(5q)	24 (13%)	14 (12%)	8 (28%)
RCMD/RCMD-RS	91(48%)	53 (47%)	15 (51%)
RAEB-1/RAEB-2	54 (28%)	32 (29%)	6 (21%)
CMML	22 (11%)	13 (12%)	0
Karyotype-based risk category[b]			
Good/intermediate	141 (85%)	83 (84%)	21 (84%)
Poor	25 (15%)	16 (16%)	4 (16%)
Follow-up from first transfusion, median (range)	–	9.4 (1–69) months	29 (12–62) months

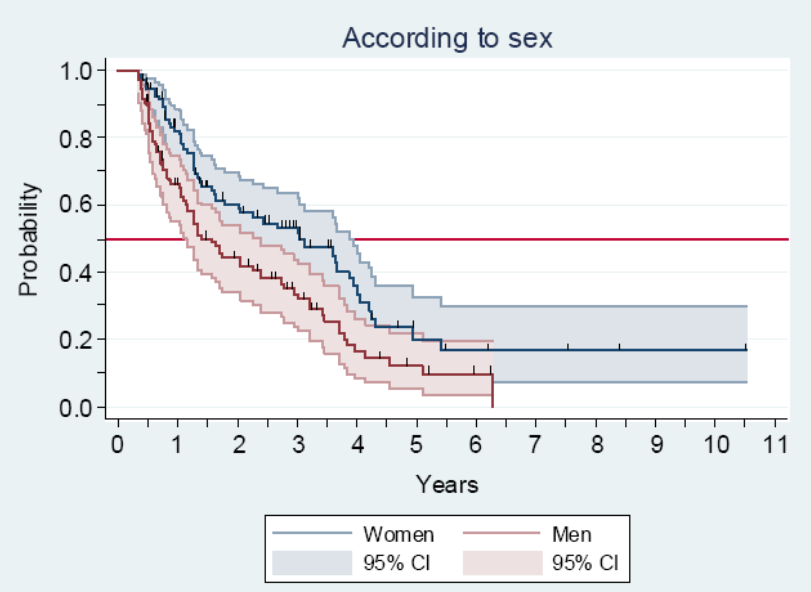
Supervivencia libre de transformación leucémica (desde 1ª transfusión)

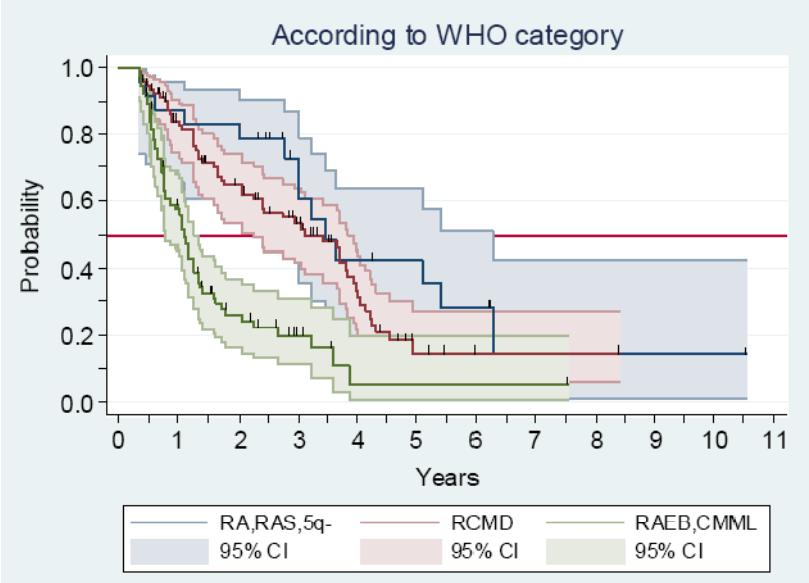


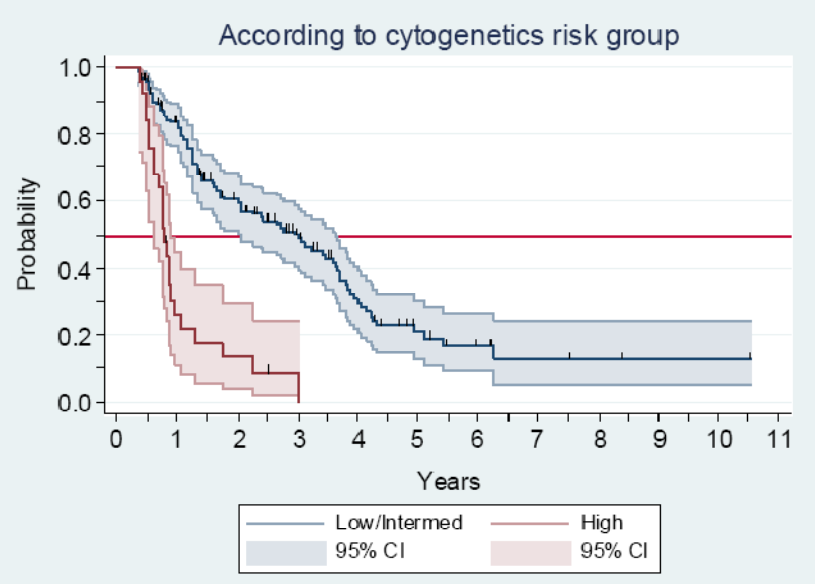
Características de los pacientes con significado pronóstico

	Overall survival		AML-free survival	
Covariate	HR (95% CI)	p	HR (95% CI)	p
Male sex	1.8 (1.2 - 2.7)	0.002	1.7 (1.2-2.6)	0.005
WHO category*	2.7 (1.9 - 3.7)	< 0.001	2.8 (2.0 - 3.9)	< 0.001
Cytogenetics risk group†	4.9 (2.9 - 8.2)	< 0.001	5.2 (3.1 - 8.9)	< 0.001

* Categorization: RA, RAS, isolate del(5q) = 0; RCMD, RCMD-RS=1; RAEB, CMML=2. † Low risk = 0; intermediate or high risk = 1.

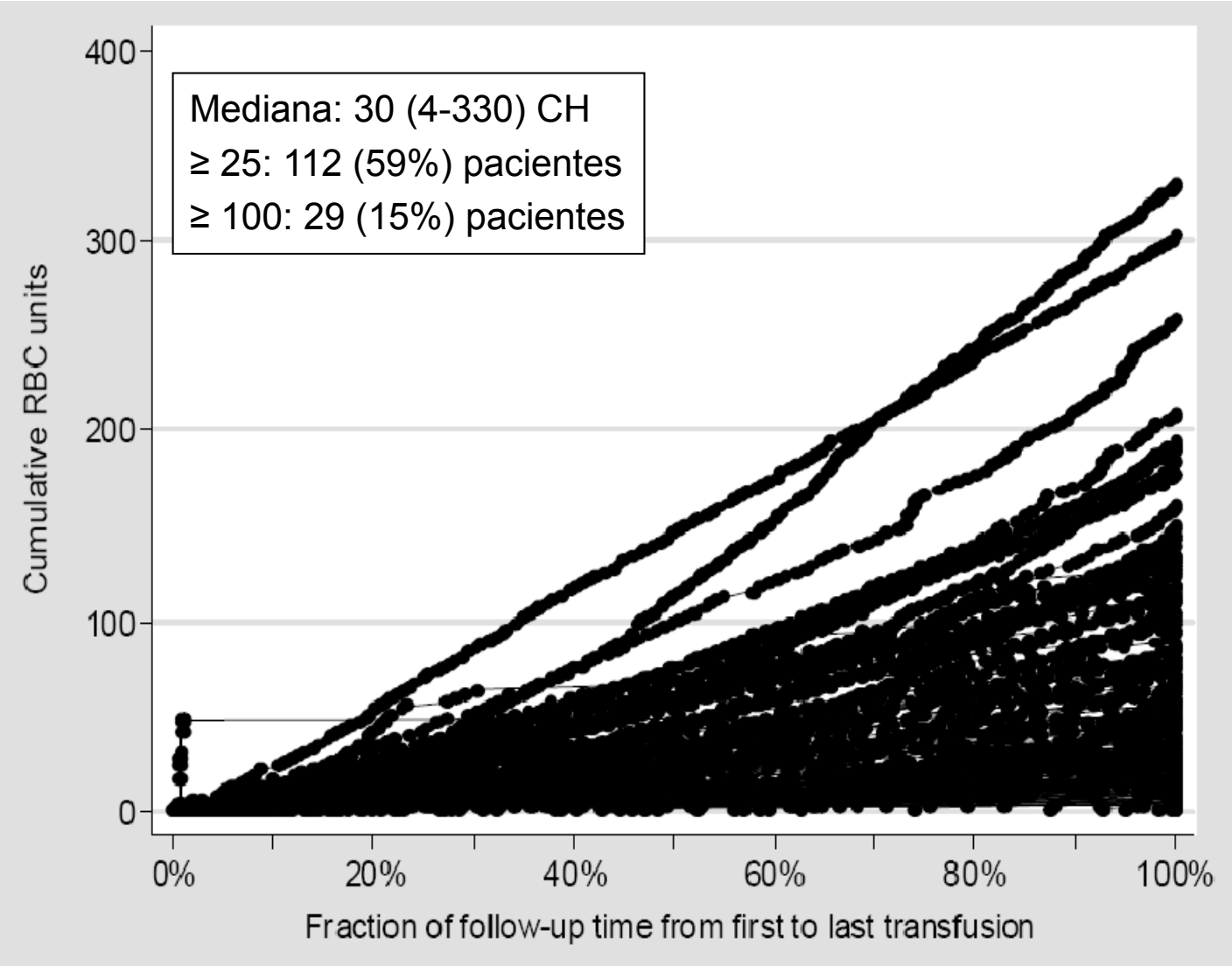






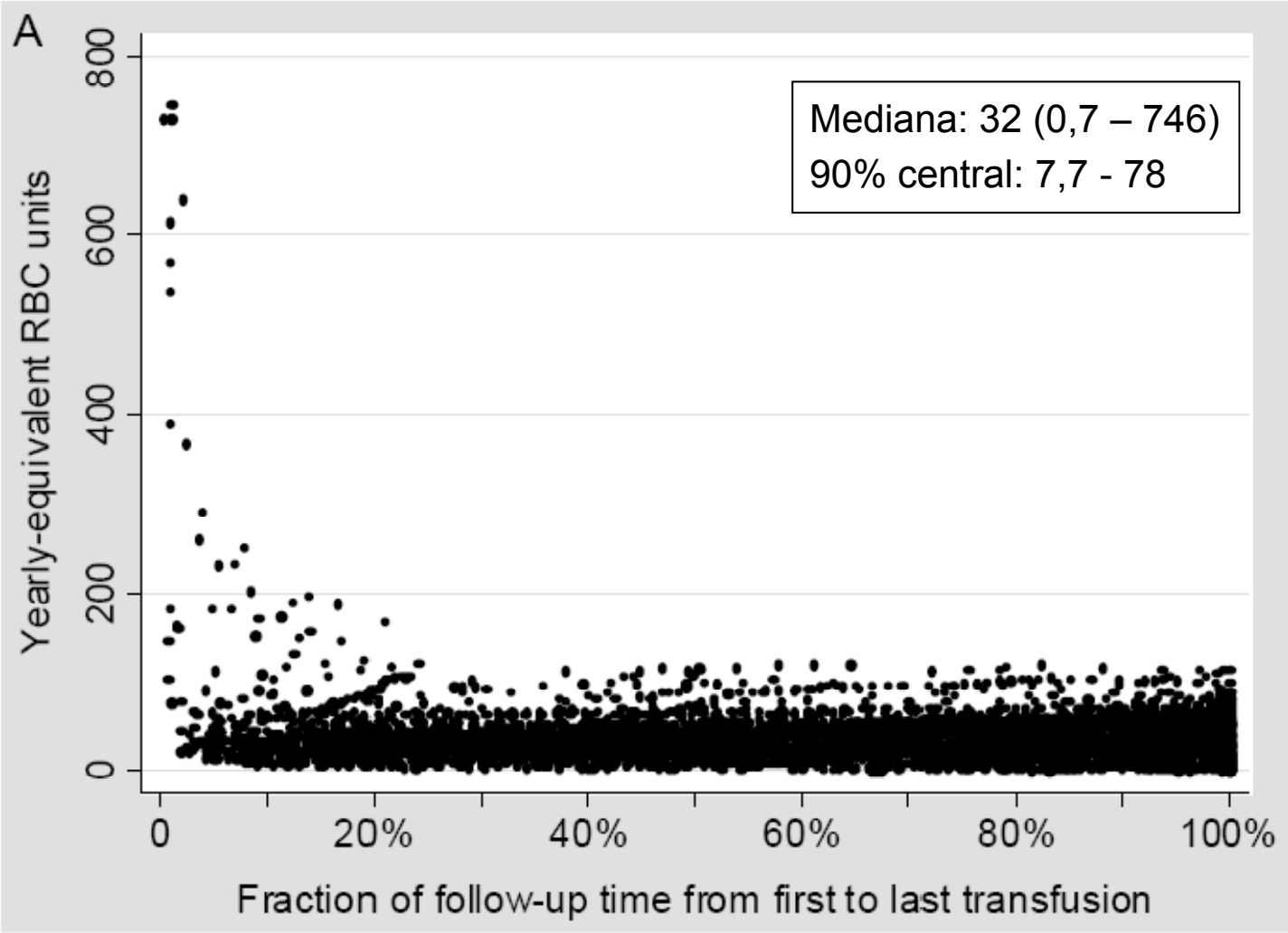
Carga transfusional acumulada (nº CH)

Periodo libre de transformación leucémica



Intensidad transfusional (CH equivalentes-año)

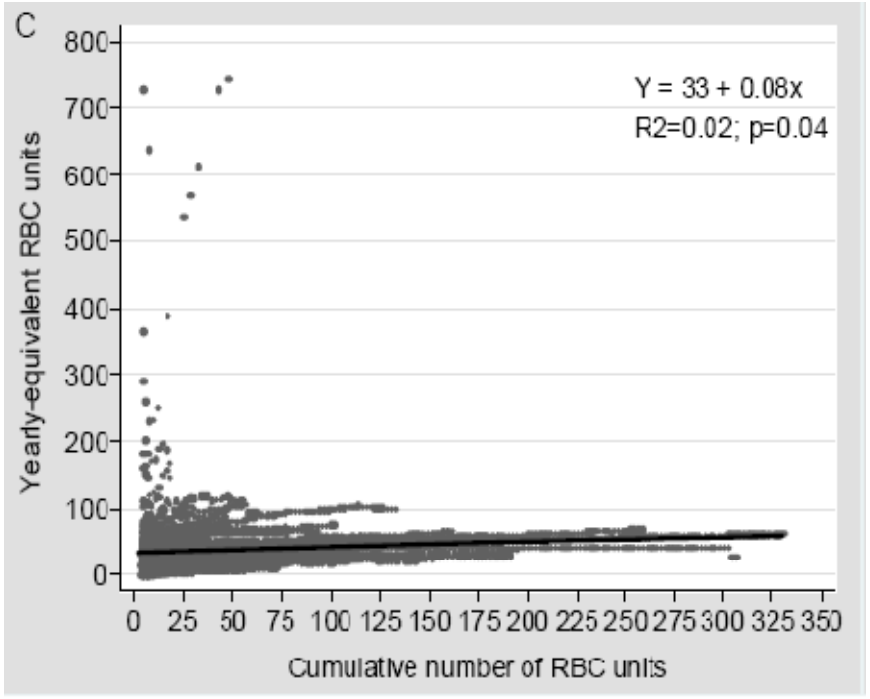
Periodo libre de transformación leucémica



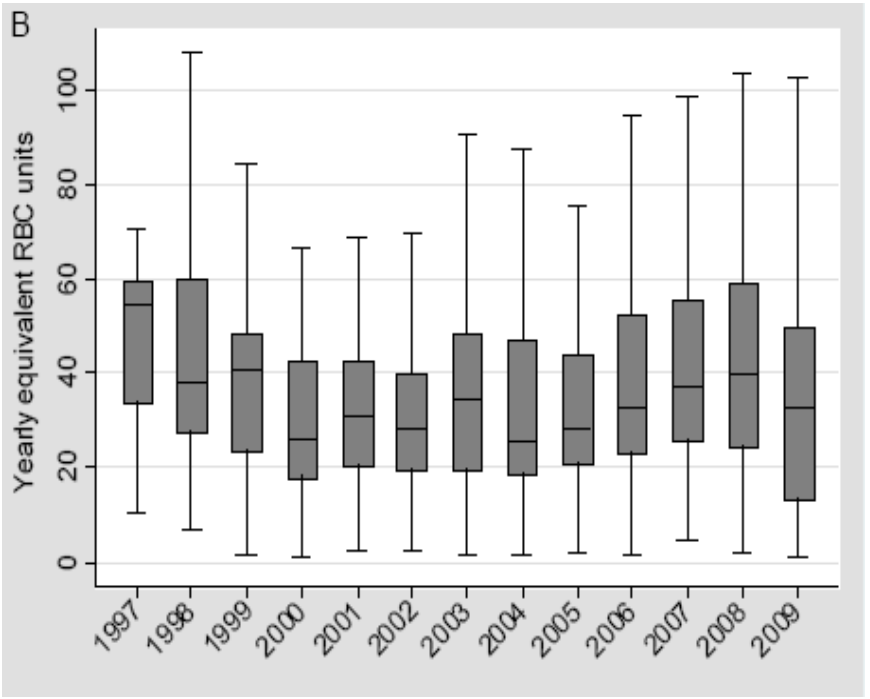
Intensidad transfusional (CH equivalentes-año)

Periodo libre de transformación leucémica

Relación con carga transfusional



Durante el periodo estudiado



Modelos de regresión anidados (i)

Model A AIC: 842 Log-likelihood: -417

Covariate	HR	95% CI	p
Male sex	1.6	1.1 - 2.4	0.011
WHO type	2.5	1.8 - 3.5	< 0.001
Poor prognosis karyotype	3.4	2.0 - 5.9	< 0.001
Transfusion burden ≥ 25 RBC units	2.7	1.7 - 4.3	< 0.001

Model B AIC: 824 Log-likelihood: -407

Covariate	HR	95% CI	p
Male sex	1.6	1.1 - 2.4	0.02
WHO type	3.1	2.2 - 4.4	< 0.001
Poor prognosis karyotype	3.7	2.1 - 6.5	< 0.001
Transfusion burden ≥ 25 RBC units	2.3	1.4 - 3.7	< 0.001
Time from 1st transfusion > 9 months	10.8	2.5 - 46	0.001

LR test: B *vs* A
$X^2 = 20$;
$p < 0{,}0001$

Modelos de regresión anidados (ii)

Model C AIC: 831 Log-likelihood: -410

Covariate	HR	95% CI	p
Male sex	1.4	0.9 - 2.1	0.10
WHO type	2.6	1.8 - 3.6	< 0.001
Poor prognosis karyotype	2.5	1.4 - 4.5	0.001
Transfusion burden ≥ 25 RBC units	1.5	0.8 - 2.6	0.17
Transfusion intensity	1.4	1.2 - 1.7	< 0.001

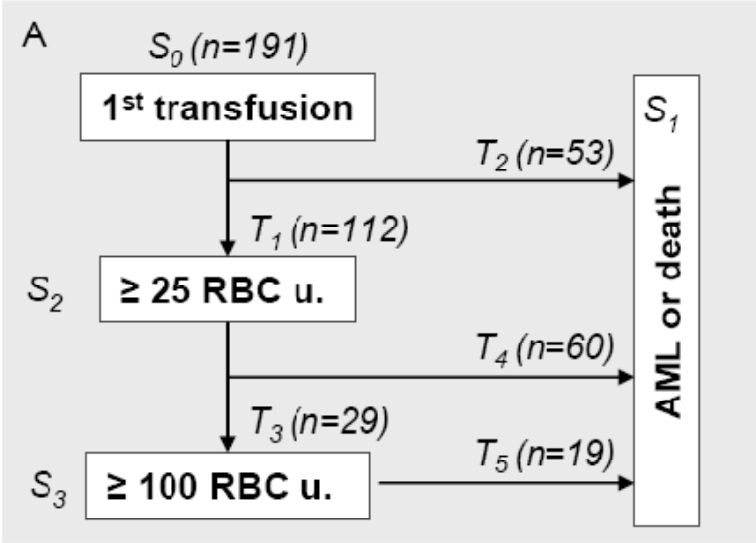
LR test: C *vs* A
$X^2 = 12$;
p = 0,0004

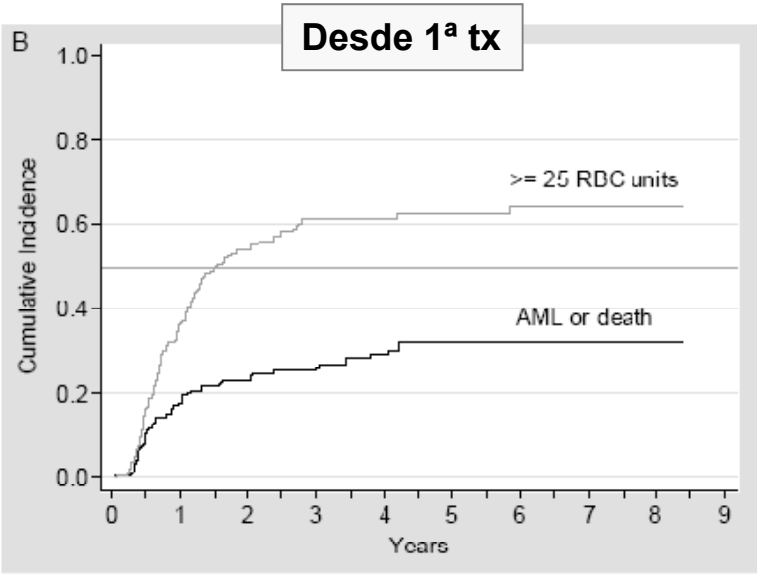
Model D AIC: 819 Log-likelihood: -403

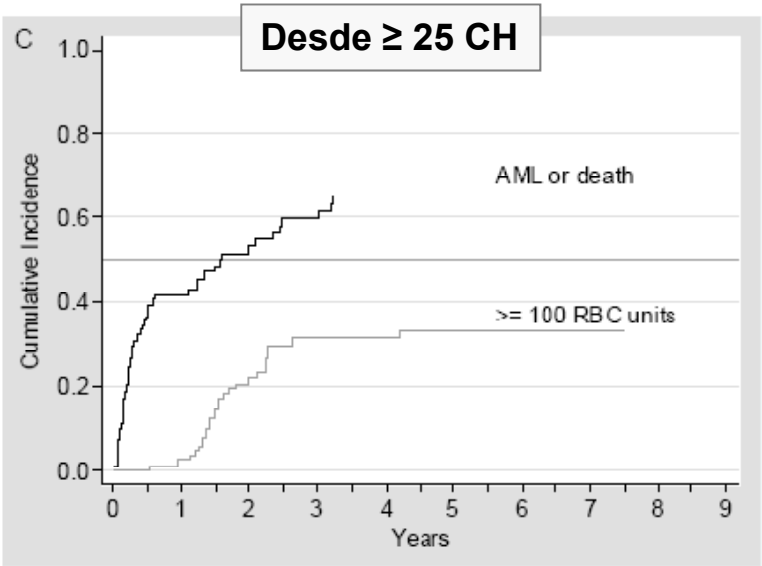
Covariate	HR	95% CI	p
Male sex	1.4	0.9 - 2.1	0.08
WHO type	2.9	2.1 - 4.2	< 0.001
Poor prognosis karyotype	2.9	1.6 - 5.2	< 0.001
Transfusion burden ≥ 25 RBC units	1.5	0.8 - 2.6	0.20
Time from 1st transfusion ≥ 9 months	8.4	1.9 - 36	0.004
Transfusion intensity	1.3	1.1 - 1.5	0.008

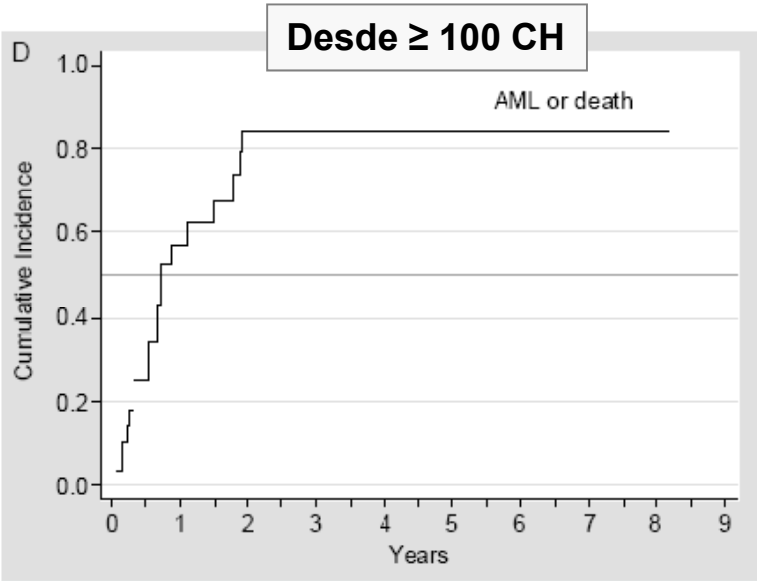
LR test: D *vs* A
$X^2 = 27$;
p < 0,0001

MODELO MULTI-ESTADO (i)









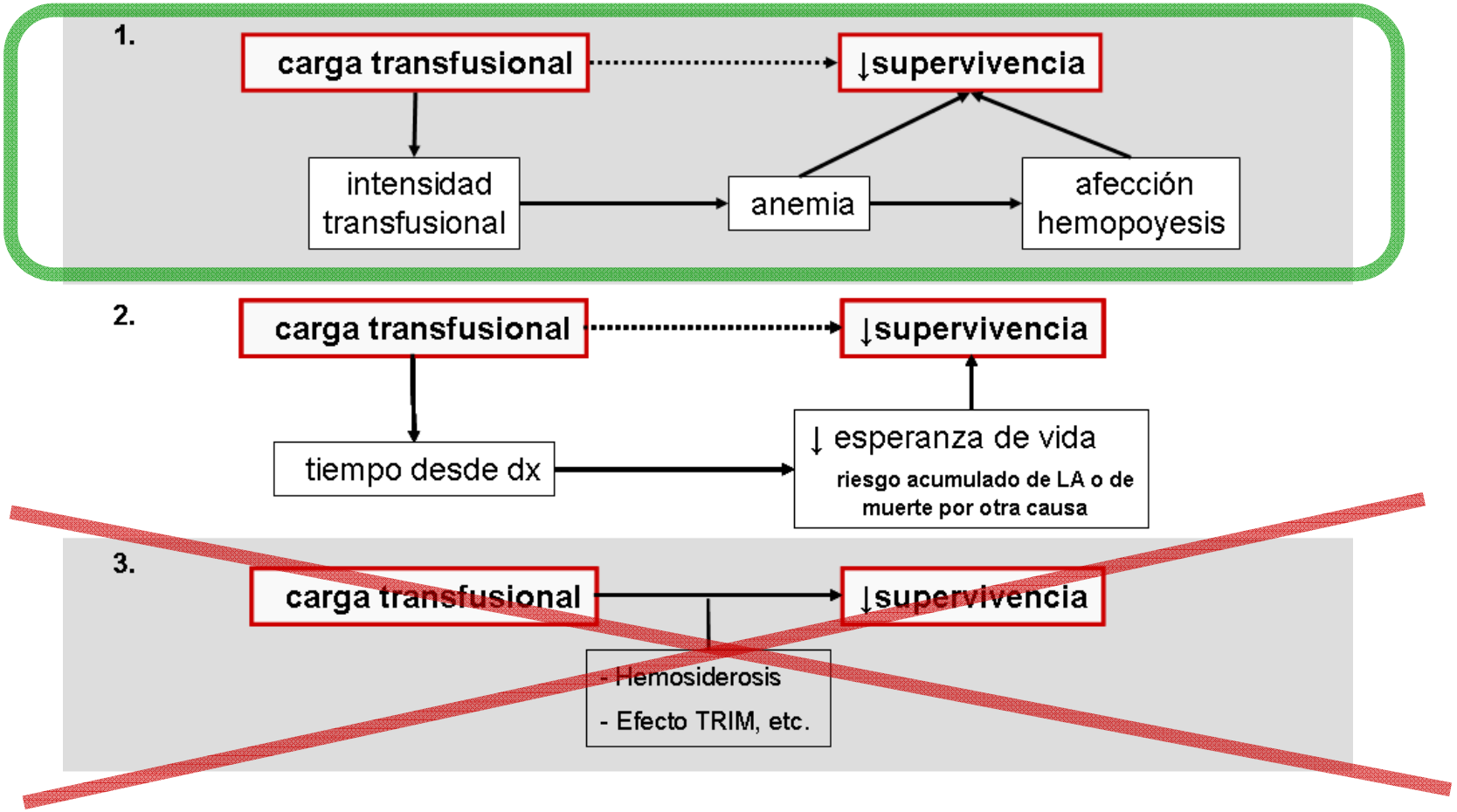
MODELO MULTI-ESTADO (ii)

Variables que “gobiernan” la transición entre estados:

	From 1st transfusion to				From cumulative burden ≥ 25 RBC units to			
	AML or death		≥ 25 RB units		AML or death		≥ 100 RBC units	
Covariate	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Male sex	1.1 (0.6 - 1.9)	0.13	1.0 (0.7 - 1.5)	0.9	1.9 (1.04 - 3.6)	0.04	2.7 (1.01 - 7.3)	0.05
WHO category*	2.8 (1.6 - 5.1)	< 0.001	1.1 (0.8 - 1.5)	0.4	2.1 (1.3 - 3.6)	0.004	0.6 (0.3 - 1.4)	0.23
High risk karyotype †	3.6 (1.5 - 8.7)	0.005	2.4 (1.3 - 4.5)	0.005	2.9 (1.4 - 6.2)	0.005	4.4 (0.9 - 22)	0.07
Transfusion intensity	1.5 (1.1 - 2.1)	0.026						

* Categorization: RA, RAS, isolate del(5q) = 0; RCMD, RCMD-RS=1; RAEB, CMML=2. † High risk=1. low or intermediate = 0.

Objetivo: poner a prueba tres hipótesis sobre la relación causal entre la carga transfusional acumulada y la supervivencia en los pacientes con SMD.



CONCLUSIONES

En los pacientes con SMD:

- La asociación entre carga transfusional y pronóstico NO implica una relación causal; esta mediada/confundida por la intensidad transfusional y el tiempo transcurrido desde el inicio del soporte transfusional crónico.
- La intensidad transfusional es la variable que explica el efecto pronóstico de la dependencia transfusional.
- La transfusión actúa como un mero marcador de gravedad de la enfermedad y carece de valor pronóstico intrínseco.

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