MYELOID NEOPLASIA

Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia

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Key Points

- CMML is a heterogeneous disorder with a highly variable prognosis that clearly requires a specific and widely accepted prognostic scoring system.
- CPSS is a powerful prognostic score that defines 4 risk groups for survival and AML evolution, developed and validated in the largest CMML series to date.

The natural course of chronic myelomonocytic leukemia (CMML) is highly variable but a widely accepted prognostic scoring system for patients with CMML is not available. The main aim of this study was to develop a new CMML-specific prognostic scoring system (CPSS) in a large series of 558 patients with CMML (training cohort, Spanish Group of Myelodysplastic Syndromes) and to validate it in an independent series of 274 patients (validation cohort, Heinrich Heine University Hospital, Düsseldorf, Germany, and San Matteo Hospital, Pavia, Italy). The most relevant variables for overall survival (OS) and evolution to acute myeloblastic leukemia (AML) were FAB and WHO CMML subtypes, CMML-specific cytogenetic risk classification, and red blood cell (RBC) transfusion dependency. CPSS was able to segregate patients into 4 clearly different risk groups for OS ($P < .001$) and risk of AML evolution ($P < .001$) and its predictive capability was confirmed in the validation cohort. An alternative CPSS with hemoglobin instead of RBC transfusion dependency offered almost identical prognostic capability. This study confirms the prognostic impact of FAB and WHO subtypes, recognizes the importance of RBC transfusion dependency and cytogenetics, and offers a simple and powerful CPSS for accurately assessing prognosis and planning therapy in patients with CMML. (*Blood*. 2013;121(15):3005-3015)

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematologic disorder sharing features of myelodysplastic syndromes (MDS) and chronic myeloproliferative disorders. CMML was included in the original FAB (French-American-British) classification for MDS.[1] In 1994, the FAB group distinguished 2 subtypes of CMML, an MDS type (CMML-MD) and a myeloproliferative disorder variant (CMML-MP), depending on the absolute leukocyte count ($<13 \times 10^9$ /L and $\geq 13 \times 10^9$/L).[2] Accordingly, the International Scoring Prognostic System (IPSS) for MDS and its recent revision (IPSS-R) excluded CMML-MP cases.[3,4] More recently, the World Health Organization (WHO) panel of experts included CMML into a new category of mixed myeloproliferative/myelodysplastic neoplasms and differentiated 2 subtypes, CMML-1 and CMML-2, depending on the percentage of blasts in bone marrow (BM) and peripheral blood (PB).[5,6]

CMML has a highly variable clinical course, with wide differences in overall survival (OS) and risk of transformation to acute myeloblastic leukemia (AML). Different studies have identified important prognostic factors[4,6-11] and, in some instances, have built prognostic scoring systems to predict outcome.[4,6-11] However, none of them have gained widespread acceptance, partly because they were raised from small series, included patients without CMML by WHO criteria, and were unable to predict the risk of evolution to AML.

The main aims of this study were to identify independent prognostic factors for OS and risk of AML evolution in a large series of patients with CMML, to develop an easily applicable CMML-specific prognostic scoring system (CPSS) for estimating those outcomes, to validate its predictive capacity in a large and independent cohort, and finally to compare the predictive power of the CPSS with that afforded by other prognostic scoring indexes for CMML patients.

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Table 1. Main clinical and hematologic characteristics at diagnosis in the training and validation cohorts

Characteristic	Training series		Validation series		*P* value*
	Median (range)	N (%)	Median (range)	N (%)	
Overall		558 (100)		274 (100)	
Age, y	73 (19-99)		70 (41-98)		<.001†
≤60		61 (11)		55 (20)	<.001‡
61-70		135 (24)		105 (38)	
>70		362 (65)		114 (42)	
Gender					
Male		377 (68)		191 (70)	.532§
Female		181 (32)		83 (30)	
WHO subtype					
CMML-1		478 (86)		218 (80)	.025‡
CMML-2		80 (14)		56 (20)	
Hemoglobin level, g/dL	11 (1-19)		11 (2-17)		.224†
<10 g/dL		190 (34)		101 (37)	.479§
≥10 g/dL		368 (66)		173 (63)	
Leukocyte count, × 10^9/L	10 (1-156)		13 (1-150)		.143†
<13 × 10^9/L (CMML-MD FAB subtype)		338 (61)		138 (50)	.005§
≥13 × 10^9/L (CMML-MP FAB subtype)		220 (39)		136 (50)	
Platelet count, × 10^9/L	123 (4-928)		105 (1-979)		.091†
<100 × 10^9/L		221 (40)		132 (48)	.019§
≥100 × 10^9/L		337 (60)		142 (52)	
Neutrophil count, × 10^9/L	4.2 (0.1-73.9)		6.3 (0.1-75.0)		.018†
<1.8 × 10^9/L		103 (18)		41 (15)	.218§
≥1.8 × 10^9/L		455 (82)		232 (85)	
Monocyte count, × 10^9/L	2.6 (1.1-40.9)		6.4 (1.1-75.0)		<.001†
<3.0 × 10^9/L		236 (57)		128 (47)	.010§
≥3.0 × 10^9/L		180 (43)		146 (53)	
Blasts in PB					
Absent		367 (79)		193 (70)	.013§
Present		100 (21)		81 (30)	
Blasts in BM, %	3 (0-19)		6 (0-19)		<.001†
<5		347 (62)		116 (42)	<.001‡
5-9		138 (25)		103 (38)	
10-19		73 (13)		55 (20)	
LDH level, U/L	394 (104-2976)		277 (97-7743)		<.001†
≤480 UI/L		242 (68)		94 (46)	<.001§
>480 UI/L		115 (32)		109 (54)	
Ferritin level, mg/dL	170 (6-4000)		318 (58-2010)		.001†
≤500 mg/dL		173 (80)		73 (63)	<.001§
>500 mg/dL		43 (20)		43 (37)	
RBC transfusion dependency‖					
No		441 (79)		205 (75)	.156§
Yes		116 (21)		69 (25)	
CMML-specific cytogenetic risk classification¶					
Low		429 (81)		146 (63)	<.001‡
Intermediate		47 (9)		41 (18)	
High		56 (10)		45 (19)	

*P value is the statistical comparison of the different characteristics in training and validation series.
†Mann-Whitney *U* test.
‡χ^2 test.
§Fisher's exact test.
‖RBC transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months.
¶CMML-specific cytogenetic risk classification: low, normal and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

Patients and methods

Data collection and patient cohorts

We retrospectively collected clinical and hematologic data of patients in whom de novo CMML was diagnosed according to WHO 2008 criteria at the participating institutions in the Spanish MDS cooperative group (GESMD, supplemental Appendix 1) at the Department of Hematology, San Matteo Hospital, Pavia, Italy, and at the Düsseldorf MDS registry, Heinrich Heine University Hospital, Düsseldorf, Germany. Accordingly, those patients with a percentage of blasts in PB or BM ⩾20% and those with known *PDGFR* rearrangements were excluded from the analysis. Most cases were diagnosed at centers with recognized expertise in the diagnosis of MDS and all cases were carefully reviewed locally before inclusion. However, in an attempt to cope as much as possible with the real world, no central morphologic review was carried out. The local ethics committees approved the studies, which followed the 2000 revision of the Declaration of Helsinki.

The patients comprised a training cohort, aimed at defining the variables to be included in the CPSS, and a validation cohort, aimed at confirming the

Table 2. Survival and risk of AML evolution according to the main clinical and hematologic characteristics at diagnosis in the training cohort

	OS				AML evolution			
						Cumulative probability of AML evolution (%)		
Characteristic	No. of patients (%)	Median (mo)	Proportion alive at 5 y (%)	Log-rank (*P* value)	Time to 25% probability (mo)	2 y	5 y	Log-rank (*P* value)
Overall	558 (100)	31	31		38	17	29	
Age, y				.008				.071
<70	190 (34)	37	37		28	22	34	
≥70	207 (66)	28	27		39	15	25	
Gender				.021				.074
Male	377 (68)	29	28		30	17	34	
Female	181 (32)	42	36		66	17	22	
WHO subtype				<.001				<.001
CMML-1	478 (86)	37	34		59	13	25	
CMML-2	80 (14)	12	12		10	47	54	
Hemoglobin level, g/dL				<.001				<.001
<10	190 (34)	18	16		19	29	40	
≥10	368 (66)	43	38		60	13	25	
Hemoglobin level, g/dL				<.001				.015
<8 in females and <9 in males	91 (16)	13	12		20	30	40	
≥8 in females and ≥9 in males	467 (84)	38	35		40	16	28	
Leukocyte count, × 10^9/L				<.001				<.001
<13 (CMML-MD FAB subtype)	338 (61)	44	42		73	14	20	
≥13 (CMML-MP FAB subtype)	220 (39)	21	16		25	23	49	
Platelet count, × 10^9/L				.054				.850
<100	221 (40)	30	29		35	21	30	
≥100	337 (60)	36	32		57	15	28	
Neutrophil count, × 10^9/L				.021				.470
<1.8	101 (18)	53	42		60	20	24	
≥1.8	457 (82)	29	29		38	17	31	
Monocyte count, × 10^9/L				.001				.068
<3	234 (57)	42	40		83	14	20	
≥3	182 (43)	26	21		35	17	34	
Blasts in PB				<.001				<.001
Absent	367 (77)	39	34		60	12	25	
Present	100 (21)	15	11		12	39	48	
Blasts in BM, %				<.001				<.001
<5	347 (62)	36	34		59	12	26	
5-9	138 (25)	43	35		60	16	24	
10-19	73 (13)	11	10		9	49	58	
LDH level, U/L				<.001				.456
≤480	242 (68)	43	43		65	14	25	
>480	115 (32)	20	11		26	14	25	
Ferritin level, mg/dL				<.001				<.001
≤500	173 (80)	42	35		83	10	15	
>500	43 (20)	20	16		13	30	48	
RBC transfusion dependency*				<.001				<.001
No	441 (79)	40	38		59	14	25	
Yes	116 (21)	14	9		14	32	47	
CMML-specific cytogenetic risk classification†				<.001				<.001
Low	429 (81)	39	36		60	12	24	
Intermediate	47 (9)	18	20		12	31	45	
High	56 (10)	12	7		11	56	67	

*RBC transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months.

†CMML-specific cytogenetic risk classification: low, normal and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

prognostic value of the CPSS in an independent population. The training cohort consisted of 558 patients with de novo CMML identified in the database of the GESMD and diagnosed between 1980 and 2010. The validation cohort consisted of 274 patients in whom de novo CMML was diagnosed at the Heinrich-Heine-University Hospital between 1982 and 2009 (n = 153) and at the San Matteo Hospital between 1992 and 2009 (n = 121). The median follow-up time for surviving patients was 16 months (range, 1-170 months) in the training cohort and 12 months (1-196 months) in the validation cohort.

Prognostic factors

Different patient and disease characteristics, recorded at the time of diagnosis, were examined to establish their possible relationship with OS

Table 3. CPSS: Variables and scores used for predicting likelihood of survival and leukemic evolution in the individual patient with CMML

	Variable scores		
Variable	**0**	**1**	**2**
WHO subtype	CMML-1 blasts (including promonocytes) <5% in the PB and <10% in the BM	CMML-2 blasts (including promonocytes) from 5% to 19% in the PB and from 10% to 19% in the BM, or when Auer rods are present irrespective of blast count	—
FAB subtype	CMML-MD (WBC count $<13 \times 10^9$/L)	CMML-MP (WBC count $\geq 13 \times 10^9$/L)	—
CMML-specific cytogenetic risk classification*	Low	Intermediate	High
RBC transfusion dependency†	No	Yes	—

WBC, white blood cell.

*CMML-specific cytogenetic risk classification: low, normal and isolated –Y; intermediate, other abnormalities; and high, trisomy 8, complex karyotype (≥3 abnormalities), and abnormalities of chromosome 7.

†RBC transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months.

and evolution to AML. These include basic demographic data (age and sex), hematologic parameters (hemoglobin level, absolute leukocyte count, absolute neutrophil count, absolute platelet count, absolute monocyte count, and presence of blasts in PB), percentage of blasts in BM, serum lactate dehydrogenase (LDH) and ferritin levels, red blood cell (RBC) transfusion dependency, and cytogenetic findings. All characteristics were analyzed as dichotomous variables and the cutoff points selected for each one were those presented in Tables 1 and 2. Hemoglobin level was dichotomized in 2 ways to assess the different cutoff points used respectively by the IPSS[3] and the Pavia group in a recent report.[12] March 2002 was the date that divided the training cohort in 2 groups with the same number of patients and was selected as cutoff point to evaluate a potential influence in the results of changes in the practical management of CMML patients over time and to exclude its possible association with other relevant prognostic variables. No differences in any outcome by date of diagnosis were evident (data not shown). Karyotypes were classified using the International System for Cytogenetic Nomenclature Criteria 2009[13] and stratified according to the recently published CMML-specific cytogenetic risk classification: low risk, normal karyotype and isolated loss of Y chromosome; poor risk, trisomy 8, abnormalities of chromosome 7, and complex karyotype (⩾3 chromosomal abnormalities); and intermediate risk, all other chromosomal abnormalities.[7] RBC transfusion therapy was not administered according to predefined criteria and was based on physician's criteria that took into account hemoglobin level, presence of symptoms of anemia, and comorbidities. As in the WHO-based prognostic scoring system (WPSS),[12] RBC transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months.

Statistical analysis

Comparisons of proportions and ranks of variables between different groups were performed by χ^2, Fisher's exact, Student *t*, or Mann-Whitney *U* test, as appropriate. Unadjusted time-to-event analyses were performed using the Kaplan-Meier estimate and log-rank tests were used for comparisons. Multivariate analysis was performed using Cox's proportional hazards regression model. Characteristics selected for possible inclusion in the multivariate model were those for which there was some indication of association with OS or AML evolution in univariate analysis ($P < .20$). The forward stepwise procedure was stopped when the *P* value for entering an additional variable was above .05. OS was measured from the time of diagnosis to the time of last follow up or death from any cause. Evolution to AML was measured from the time of diagnosis to the date of AML (presence of more than 19% of blasts in BM or PB). Most patients received only supportive care (RBC and platelet transfusions and antibiotics as required). None of the patients had received azacitidine or decitabine. Patients undergoing hematopoietic allogeneic stem cell transplantation or intensive AML-type chemotherapy were considered as censored data at the date of transplant or the date of starting chemotherapy, whichever came first. Therefore, our cohorts, as in the IPSS project, consisted of essentially untreated patients, excluding any potential source of bias as a result of treatment. Patient follow up was updated on May 15, 2010, and all follow-up data were censored at that point. Two-sided *P* values $< .05$ were considered statistically significant. In line with the essentially exploratory nature of the study, no adjustment for multiple testing was applied. The strength of the new CPSS and other previously published prognostic scoring indexes for CMML was assessed using the concordance probability estimates (CPE)[14] for the Cox proportional hazards model with ties. CPE is a probability that ranges between 0 and 1. A CPE of 0.5 is what you would achieve by pure chance, whereas 1.0 signifies perfect discrimination between the 2 tests. The statistical package SPSS version 17.0 (SPSS Inc., Chicago, IL) was used for all survival analyses. CPE were computed with the R v2.9.0 statistical programming language (R Development Core 2008).

Table 4. CPSS: Variables and scores used for predicting likelihood of survival and leukemic evolution in the individual patient with CMML

Risk group	Overall score
Low	0
Intermediate-1	1
Intermediate-2	2-3
High	4-5

Results

Characteristics of the training cohort

The training cohort included a total of 558 CMML patients. Their main characteristics at diagnosis are shown in Table 1. The median age was 73 years (range, 19-99 years), median OS was 31 months, and the cumulative probability of AML transformation was 29% at 5 years. According to FAB criteria, 338 of the patients (61%) had CMML-MD and 220 (39%) had CMML-MP. By WHO classification, 478 patients (86%) were CMML-1 and 80 patients (14%) were CMML-2. Karyotype was available in 532 patients (abnormal in 131 [24%]), and according to the CMML-specific cytogenetic risk classification,[7] 429 (81%) belonged to the good-risk category, 47 (9%) to the intermediate-risk category, and 56 (10%) to the poor-risk category. A total of 116 of 557 patients (21%) were RBC transfusion dependent at diagnosis.

Univariate and multivariate analysis of outcomes in the training cohort

Table 2 shows in detail the results of univariate analysis for OS and risk of AML evolution in the training cohort. Variables significantly associated with OS were age ($P = .008$), gender ($P = .021$), CMML WHO subtype ($P < .001$), hemoglobin level ($P < .001$), CMML FAB subtype ($P < .001$), neutrophil count ($P = .021$),

Table 5. OS and risk of AML evolution according to the CPSS-defined risk categories in the training and validation cohorts

	OS				Risk of AML evolution			
						Cumulative probability of AML evolution (%)		
Risk category	No. of patients (%)	Median (mo)	Proportion alive at 5 y (%)	Log-rank (*P* value)	Time to 25% probability (mo)	At 2 y	At 5 y	Log-rank (*P* value)
Training cohort				<.001				<.001
Low	217 (41)	72	55		95	7	13	
Intermediate-1	155 (29)	31	25		40	14	29	
Intermediate-2	141 (26)	13	10		11	37	60	
High	19 (4)	5	0		4	73	73	
Pairwise comparisons	Low vs intermediate-1, $P < .001$; Low vs intermediate-2, $P < .001$; Low vs high, $P < .001$; Intermediate-1 vs intermediate-2, $P < .001$; Intermediate-1 vs high, $P < .001$; Intermediate-2 vs high, $P < .001$				Low vs intermediate-1, $P = .023$; Low vs intermediate-2, $P < .001$; Low vs high, $P < .001$; Intermediate-1 vs intermediate-2, $P < .001$; Intermediate-1 vs high, $P < .001$; Intermediate-2 vs high, $P = .015$			
Validation cohort				<.001				<.001
Low	60 (26)	61	51		59	8	24	
Intermediate-1	71 (31)	31	29		24	25	41	
Intermediate-2	90 (39)	15	11		13	49	52	
High	10 (4)	9	0		4	100	100	
Pairwise comparisons	Low vs intermediate-1, $P = .028$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P < .001$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .007$				Low vs intermediate-1, $P = .034$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .041$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .021$			

monocyte count ($P = .001$), presence of blasts in PB ($P < .001$), percentage of blasts in BM ($P < .001$), serum LDH level ($P < .001$), ferritin level ($P < .001$), RBC transfusion dependence ($P < .001$), and CMML-specific cytogenetic risk classification ($P < .001$). Characteristics significantly associated with risk of AML evolution were CMML WHO subtype ($P < .001$), hemoglobin level ($P < .001$), CMML FAB subtype ($P < .001$), presence of blasts in PB ($P < .001$), percentage of blasts in BM ($P < .001$), ferritin level ($P < .001$), RBC transfusion dependence ($P < .001$), and CMML-specific cytogenetic risk classification ($P < .001$).

Five variables maintained their independent prognostic significance for OS after multivariate analysis: CMML FAB subtype (hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.27-2.36; $P < .001$), CMML WHO subtype (HR, 2.05; 95% CI, 1.40-3.01; $P < .001$), CMML-specific cytogenetic risk classification (HR, 1.60; 95% CI 1.26-2.05; $P < .001$), RBC transfusion dependence (HR, 1.90 95% CI, 1.37-2.65; $P < .001$), and LDH level (HR, 2.20; 95% CI, 1.58-3.05; $P < .001$).

The same variables, with the exception of LDH level, were also strong predictors of AML evolution risk in multivariate analysis: CMML FAB subtype (HR, 2.48; 95% CI, 1.41-4.36; $P = .001$), CMML WHO subtype (HR, 2.52; 95% CI, 1.24-5.11; $P < .001$); CMML cytogenetic risk categories (HR, 2.16; 95% CI, 1.46-3.19; $P < .001$), and transfusion dependence (HR, 2.05; 95% CI, 1.10-3.84, $P = .025$).

Development of a CPSS

We defined a CPSS including those 4 variables showing independent prognostic impact for both OS and AML evolution: CMML FAB and WHO subtypes, CMML-specific cytogenetic risk classification, and transfusion dependence (Tables 3 and 4). We assigned the same weight to each variable based on their similar hazard ratios in the proportional hazards regression models (see above). A score was calculated for each patient by adding together the points corresponding to their risk factors. According to this score, patients were divided into the following 4 risk groups: low (score = 0), intermediate-1 (score = 1), intermediate-2 (score = 2-3), and high (score = 4-5; Tables 3 and 4). The risk groups defined by the CPSS in the training cohort had significantly different probabilities of death (median OS, 72, 31, 13, and 5 months, respectively; $P < .001$; Table 5 and Figure 1A) and risk of AML evolution (cumulative probability of AML evolution at 5 years, 13%, 29%, 60%, and 73%, respectively; $P < .001$; Table 5 and Figure 1B). All pairwise comparisons among the 4 risk groups were statistically significant for OS and risk of AML evolution (Table 5).

Validation of CPSS

The prognostic impact of the CPSS was evaluated in an independent validation cohort of 274 patients. The main characteristics of patients included in the validation series are shown in Table 1. There were statistically significant differences in several clinical and hematologic features between the training and validation cohorts. A significant difference between both cohorts was also noted in the risk of AML transformation (29% in the training vs 45% in the validation cohort at 5 years; $P < .001$). Median OS in both series was comparable (31 months in the training vs 25 months in the validation cohort; $P = .231$).

The risk groups defined by the CPSS in the validation cohort had significantly different OS length (median OS, 61, 31, 15, and 9 months, respectively; $P < .001$; Table 5 and Figure 2A) and risk of AML evolution (cumulative probability of AML evolution at 5 years, 24%, 41%, 55%, and 100%, respectively; $P < .001$; Table 5 and Figure 2B). Again, all pairwise comparisons among the 4 risk groups in the validation cohort were statistically significant for both OS and risk of AML evolution (Table 5). Additionally, there were no significant differences in OS and risk of AML evolution between the learning and validation cohort within each of the 4 CPSS risk groups, further substantiating the validation of the score (Table 6).

Comparison of CPSS with other prognostic scoring systems for CMML

Finally, we compared the strength of the CPSS and other previously published prognostic indexes for CMML for which there were available data in both the training and validation cohorts.[3,8,10,11]

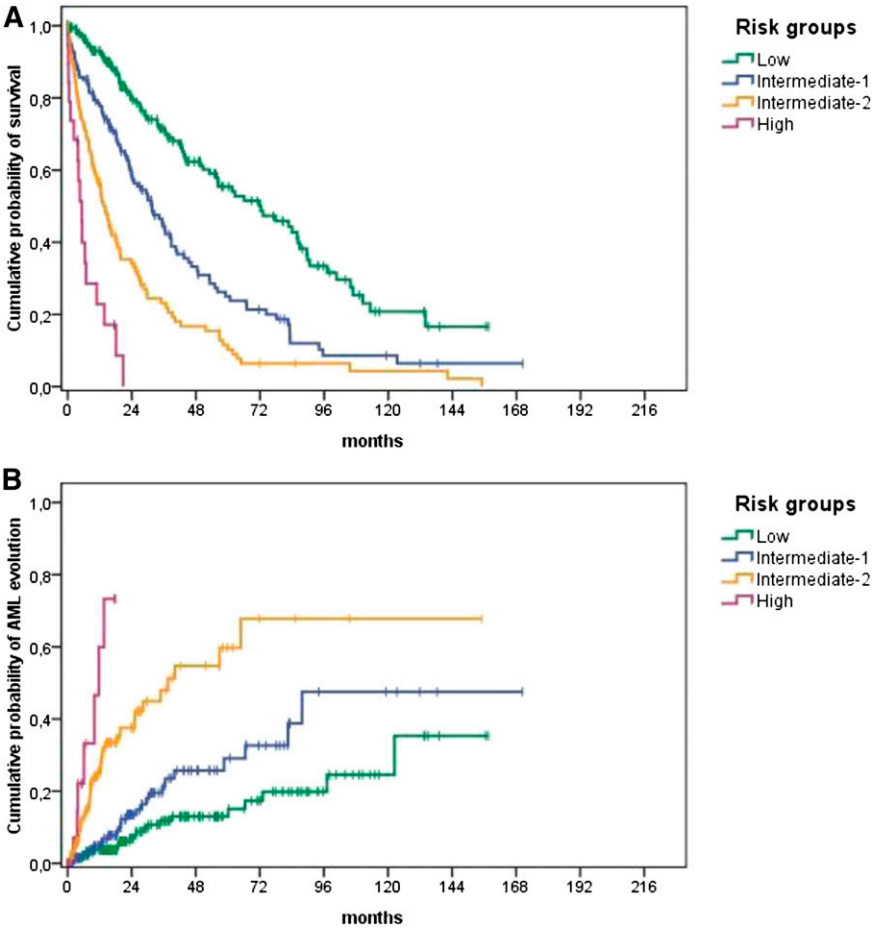

Figure 1. Outcomes according to the CPSS in the training cohort. Unadjusted actuarial probability of (A) OS ($P < .001$) and (B) risk of AML transformation ($P < .001$).

All the prognostic scoring systems were capable to separate at least 2 risk groups with statistically significant differences in OS and all showed a CPE >0.5 (Tables 7 and 8). CPSS, IPSS, and IPSS-R had the greater CPE of all scoring systems for OS and risk of evolution to AML both in the training and validation cohorts. However, only CPSS was able to segregate 4 risk groups with significant differences in pairwise comparisons for both outcomes in both series (Tables 7 and 8).

An alternative CPSS with hemoglobin level instead of RBC transfusion dependency

The inclusion of RBC transfusion dependency in a scoring system has been criticized because it is not does not allow to apply the model until the value for that variable is known. A recent paper in patients with MDS (CMML was excluded) has shown that the prognostic capacity of model including hemoglobin level (cut-points, 9 g/dL for males and 8 g/dL for females) instead of RBC transfusion dependency is equivalent to the original model (WPSS) that included RBC transfusion dependency.[15] Thus, we evaluated whether a similar model would be valuable in CMML.

In the training cohort of this report there was a close negative correlation between RBC transfusion dependency and hemoglobin level (Spearman's $R = -0.478$, P value $< .001$). In all instances, when hemoglobin level with different cutoff points, including the ones used by Malcovati et al,[15] and RBC transfusion dependency) were included into the multivariate regression procedures, RBC transfusion dependency was always selected and hemoglobin level left out. The hemoglobin cutoff point level that offered the best performance was 10 g/dL (both for males and females). All the multivariate analyses performed for building the CPSS in the training cohort were repeated using this cutoff point for hemoglobin level and excluding RBC transfusion dependency from the analyses.

The variables independently associated with OS were CMML FAB subtype (HR, 1.75; $P = .001$), CMML WHO subtype (HR, 2.03; $P < .001$), CMML-specific cytogenetic risk classification (HR, 1.49; $P = .001$), hemoglobin level (HR, 1.74; $P < .001$), and LDH level (HR, 2.15; $P < .001$). Characteristics with independent impact in the risk of AML evolution were CMML FAB subtype (HR, 2.01; $P = .001$), CMML WHO subtype (HR, 3.32; $P < .001$), CMML-specific cytogenetic risk classification (HR, 1.96; $P = .001$), and hemoglobin level (HR, 1.75; $P = .01$). Because the variables selected were the same present in the CPSS, with the exception of hemoglobin instead of RBC transfusion dependency, and their hazard ratios were very close to the ones obtained for the CPSS, we built an alternative CPSS, where a hemoglobin level <10 g/dL was scored 1 point, hemoglobin level ≥10 g/dL was scored 0, and the remaining 3 variables (CMML FAB subtype, CMML WHO subtype, and CMML-specific cytogenetic risk classification) were scored as in Tables 3 and 4 for the CPSS. As shown in Tables 7 and 8, the CPE of this alternative CPSS and CPSS were almost identical for all outcomes in both cohorts and this alternative CPSS was able to stratify the patients in 4 statistically different risk groups for OS in the training and validation cohorts and for AML in the training sample. However, in contrast to CPSS, this

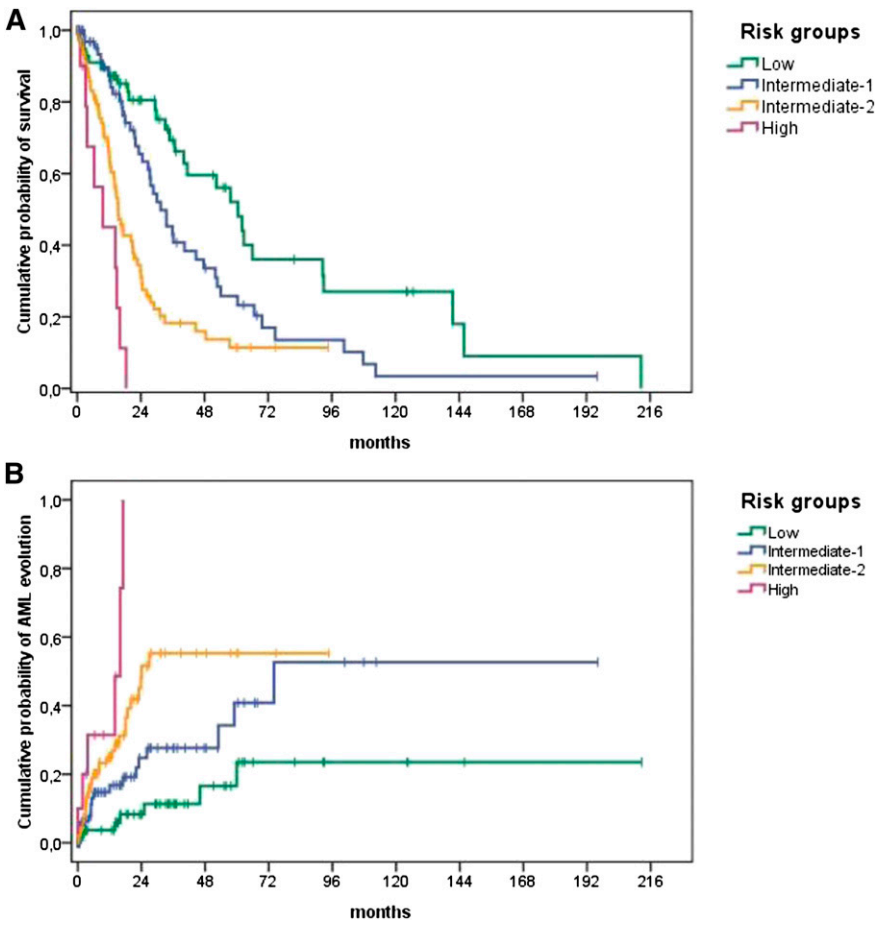

Figure 2. Outcomes according to the CPSS in the validation cohort. Unadjusted actuarial probability of (A) OS ($P < .001$) and (B) risk of AML transformation ($P < .001$).

alternative CPSS did not clearly segregate 4 risk groups for AML evolution in the validation cohort (P value for pairwise comparison of low versus intermediate-1 risk groups = .074).

Discussion

This study, based on the largest CMML data set collected until now, confirms the previously known prognostic impact of WHO and FAB-defined CMML subtypes and specific chromosomal abnormalities and shows, for the first time, the relevance of RBC transfusion dependency at diagnosis in patients with CMML. By combining these 4 variables, we developed an easily applicable prognostic index (CPSS) that defines 4 different prognostic risk categories for estimating both OS and AML transformation. CPSS was validated in an independent cohort of patients from 2 centers with expertise in MDS and performed better than other previously published prognostic indexes for CMML, including the IPSS.

In 1994, the FAB group distinguished 2 subtypes of CMML based on absolute leukocyte count,[2] but the prognostic significance of this distinction is still controversial.[16-19] Our study confirms that it provides independent prognostic information: patients with CMML-MP had a shorter survival and higher risk of AML than patients with CMML-MD. Years later, the WHO classification moved CMML to a new category of myeloproliferative/myelodysplastic neoplasms and defined CMML-1 and CMML-2 subtypes according to the percentage of blasts in PB and BM. This categorization has consistently shown a clear impact in most studies.[4,7-11] The results of multivariate analysis of our series clearly demonstrate that blasts percentage in PB and BM is one of the most important independent prognostic parameters in patients with CMML, a finding that highlights the usefulness of accounting for the proportion of these cells in PB and BM and the validity of the WHO classification for CMML.

Table 6. Comparison of OS and risk of AML evolution within each of the 4 risk groups defined by the CPSS in the training and validation cohort

	OS*			Risk of AML evolution†		
Risk category	Training cohort	Validation cohort	Log-rank (P value)	Training cohort	Validation cohort	Log-rank (P value)
Low	72	61	.724	7	8	.775
Intermediate-1	31	31	.756	14	25	.116
Intermediate-2	13	15	.445	37	49	.684
High	5	9	.578	73	100	.850

*Median (months).
Cumulative probability of AML evolution at 2 years (%).

Table 7. Comparative analysis of the predictive capacity of scoring systems for CMML patients by their concordance probability estimate and ability to segregate different risk groups for OS and evolution to AML in the training cohort

Scoring system and risk groups	Median OS (mo)	Predictive capacity for OS	AML evolution at 2 y (%)	Predictive capacity for AML evolution
CPSS		**CPE = 0.658**		**CPE = 0.694**
Low	72	Low vs intermediate-1, $P < .001$; low vs	7	Low vs intermediate-1, $P = .023$; low vs
Intermediate-1	31	intermediate-2, $P < .001$; low vs high,	14	intermediate-2, $P < .001$; low vs high,
Intermediate-2	13	$P < .001$; intermediate-1 vs intermediate-2,	37	$P < .001$; intermediate-1 vs intermediate-2, $P <$
High	5	$P < .001$; intermediate-1 vs high, $P < .001$;	73	.001; intermediate-1 vs high, $P < .001$;
		intermediate-2 vs high, $P < .001$		intermediate-2 vs high, $P = .015$
Worsley et al[10]		**CPE = 0.573**		**CPE = 0.593**
Low	42	Low vs high, $P < .001$	10	Low vs high, $P < .001$
High	22		27	
Germing et at[8]		**CPE = 0.563**		**CPE = 0.595**
Low	83	Low vs intermediate, $P = .162$; low vs high,	17	Low vs intermediate, $P = .386$; low vs high,
Intermediate	38	$P = .028$; intermediate-1 vs high, $P < .001$	10	$P = .077$; intermediate-1 vs high, $P = .001$
High	15		35	
Gonzalez-Medina et al[11]		**CPE = 0.574**		**CPE = 0.594**
Low	43	Low vs high, $P < .001$	11	Low vs high, $P < .001$
High	18		28	
Greenberg et al (IPSS)[3]		**CPE = 0.597**		**CPE = 0.636**
Low	41	Low vs intermediate-1, $P = .002$; low vs	9	Low *vs.* intermediate-1, $P = .090$; low *vs.*
Intermediate-1	31	intermediate-2, $P < .001$; low vs high,	18	intermediate-2, $P < .001$; low *vs.* high,
Intermediate-2	12	$P < .001$; intermediate-1 vs intermediate-2,	50	$P < .001$; intermediate-1 *vs.* intermediate-2,
High	1	$P = .001$; intermediate-1 vs high, $P < .001$;	73	$P = .001$; intermediate-1 *vs.* high, $P < .001$;
		intermediate-2 vs high, $P = .018$		intermediate-2 *vs.* high, $P = .142$
Greenberg et al (IPSS-R)[4]		**CPE = 0.618**		**CPE = 0.672**
Very low	59	Very low vs low, $P = .026$; very low vs	5	Very low vs low, $P = .480$; very low vs
Low	39	intermediate, $P < .001$; very low vs high,	10	intermediate, $P = .006$; very low vs high,
Intermediate	26	$P < .001$; very low vs very high, $P < .001$; low	23	$P < .001$; very low vs very high, $P < .001$;
High	9	vs intermediate, $P < .001$; low vs high, $P <$	57	low vs intermediate, $P < .012$; low vs high,
Very high	6	.001; low vs very high, $P < .001$; intermediate	86	$P < .001$; low vs very high, $P < .001$;
		vs high, $P = .038$; intermediate vs very high,		intermediate vs high, $< .001$; intermediate vs
		$P < .001$; high vs very high, $P = .273$		very high, $P < .001$; high vs very high,
				$P = .115$
Alternative CPSS		**CPE = 0.658**		**CPE = 0.695**
Low	72	Low vs intermediate-1, $P < .001$; low vs	7	Low vs intermediate-1, $P = .045$; low vs
Intermediate-1	36	intermediate-2, $P < .001$; low vs high,	13	intermediate-2, $P < .001$; low vs high,
Intermediate-2	15	$P < .001$; intermediate-1 vs intermediate-2,	33	$P < .001$; intermediate-1 vs intermediate-2,
High	5	$P < .001$; intermediate-1 vs high, $P < .001$;	76	$P < .001$; intermediate-1 vs high, $P < .001$;
		intermediate-2 vs high, $P < .001$		intermediate-2 vs high, $P < .001$.

CPE, concordance probability estimate.

None of the previously developed prognostic scoring systems for CMML have included cytogenetic findings and RBC transfusion dependency at diagnosis. In a previous study from our group, we developed a cytogenetic risk classification for CMML with 3 significantly different risk groups in terms of OS and AML evolution (low risk, including normal karyotype and isolated loss of Y; poor risk, including trisomy 8, abnormalities of chromosome 7, and complex karyotype [$\geq$3 abnormalities]; and intermediate risk, with all other chromosomal abnormalities).[7] The current study has confirmed the independent prognostic capacity of this cytogenetic risk stratification both in the training and validation cohorts. RBC transfusion dependency has demonstrated a major prognostic impact in patients with MDS classified according to WHO criteria and was 1 of the 3 variables used to generate the WPSS.[12,20] However, the potential prognostic relevance of RBC transfusion dependency in patients with CMML had never been evaluated. Our results clearly demonstrate the strong and independent impact of RBC transfusion dependency on both OS and AML evolution risk, supporting that its inclusion in the prognostic scoring system adds clinically relevant information. RBC transfusion dependency was preferred to hemoglobin level in all multivariate models, likely because the former reflects not only the degree of anemia but also the weight of other variables such as age and comorbidity. However, we were able to show that an alternative CPSS including hemoglobin level instead of RBC transfusion dependency was almost as efficient as CPSS for prognostication. This alternative model could be useful, especially in those patients deserving urgent therapy and in whom RBC transfusion dependence is still not established.

A previous study had shown that patients with an elevated serum LDH level had a clear poorer survival.[8] In the training cohort of the current study there was an independent relationship between LDH serum level and OS. However, LDH serum level did not significantly influence OS in the validation series nor was it able to predict the risk of progression to AML in any of the samples. Serum LDH level showed a statistically significant correlation with FAB morphologic subtype but not with WHO classification subtype (data not shown). Because our aim was to develop a prognostic scoring system that was able to predict the clinical outcome both in terms of OS and risk of AML evolution, serum LDH level was not included in the CPSS.

The CPSS is a simple and powerful prognostic index that is able to predict not only OS but also the risk of progression to AML and to

Table 8. Comparative analysis of the predictive capacity of scoring systems for CMML patients by their concordance probability estimate and ability to segregate different risk groups for OS and evolution to AML in the validation cohort

Scoring system and risk groups	Median OS (mo)	Predictive capacity for OS	AML evolution at 2 y (%)	Predictive capacity for AML evolution
CPSS		**CPE = 0.653**		**CPE = 0.668**
Low	61	Low vs intermediate-1, $P = .013$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .001$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .009$	8	Low vs intermediate-1, $P = .034$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .041$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .021$
Intermediate-1	31		25	
Intermediate-2	15		49	
High	9		100	
Worsley et al[10]		**CPE = 0.554**		**CPE = 0. 587**
Low	35	Low vs high, $P = .008$	33	Low vs high, $P = .003$
High	20		44	
Germing et at[8]		**CPE = 0.558**		**CPE = 0.588**
Low	12	Low vs intermediate, $P = .239$; low vs high, $P = .583$; intermediate-1 vs high, $P < .001$	26	Low vs intermediate, $P = .731$; low vs high, $P = .351$; intermediate-1 vs high, $P = .002$
Intermediate	31		27	
High	15		50	
Gonzalez-Medina et al[11]		**CPE = 0.559**		**CPE = 0.533**
Low	31	Low vs high, $P = .006$.	29	Low vs high, $P = .310$.
High	16		41	
Greenberg et al (IPSS)[3]		**CPE = 0.636**		**CPE = 0.700**
Low	40	Low vs intermediate-1, $P = .063$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 *vs.* intermediate-2, $P = .001$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .052$	9	Low vs intermediate-1, $P = .071$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .001$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .318$
Intermediate-1	29		21	
Intermediate-2	15		68	
High	4		67	
Greenberg et al (IPPS-R)[4]		**CPE = 0.643**		**CPE = 0.698**
Very low	52	Very low vs low, $P = .075$; very low vs intermediate, $P = .046$; very low vs high, $P < .001$; very low vs very high, $P < .001$; low vs intermediate, $P < .989$; low vs high, $P = .001$; low vs very high, $P < .001$; intermediate vs high, $< .001$; intermediate vs very high, $P < .001$; high vs very high, $P = .022$	5	Very low vs low, $P = .262$; very low vs intermediate, $P = .027$; very low vs high, $P < .001$; very low vs very high, $P < .001$; low vs intermediate, $P < .040$; low vs high, $P < .001$; low vs very high, $P < .001$; intermediate vs high, $= .001$; intermediate vs very high, $P = .001$; high vs very high, $P = .475$
Low	40		16	
Intermediate	30		30	
High	15		58	
Very high	8		80	
Alternative CPSS		**CPE = 0.664**		**CPE = 0.669**
Low	62	Low vs intermediate-1, $P = .023$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .001$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .043$	7	Low vs intermediate-1, $P = .074$; low vs intermediate-2, $P < .001$; low vs high, $P < .001$; intermediate-1 vs intermediate-2, $P = .010$; intermediate-1 vs high, $P < .001$; intermediate-2 vs high, $P = .081$
Intermediate-1	36		23	
Intermediate-2	15		52	
High	10		82	

CPE, concordance probability estimate.

segregate 4 risk groups with clearly distinct outcomes for both end points. The predictive capability of the CPSS was reproduced in an external validation cohort and its strength was superior to that offered by other previously published scoring systems.[3,8,10,11] Further, none of the other scoring systems tested were able to discriminate 4 risk categories with statistically significant differences among them. The confirmatory prognostic value of the CPSS is particularly relevant given the fact that, as would be expected in a retrospective study, there were statistically significant differences in several patient and disease characteristics and outcomes between the training and validation cohorts.

Unfortunately (and this a potential weakness of this study), we were unable to compare the new CPSS with 2 relevant prognostic scoring systems reported by investigators from the MD Anderson Cancer Center,[9,21,22] one specific for patients with CMML[9,21] and the other for patients with MDS and CMML (global MD Anderson prognostic score [MDAPS]), because some parameters used in them were not available for analysis in most patients of our series. Nonetheless, a previously published study of a series of 212 patients with CMML—the majority of them included in the validation cohort of the current report—showed that CMML-specific MDAPS was unable to demonstrate the capacity of segregating 4 risk groups with statistically significant differences in survival among them, suggesting that it does not represent a major improvement in predicting the survival of CMML patients.[8] The MDAPS has never been specifically validated in CMML. Given that the 4 variables composing the CPSS are present, although with somewhat different cutoff points, among the 8 characteristics required to build the global MDAPS, we anticipate this score will efficiently predict outcomes in CMML. However, whether it is able to significantly discriminate 4 risk groups for both survival and risk of AML evolution remains to be proven.

Recent molecular findings in gene mutations are being detected with increasing frequency that show the enormous underlying molecular heterogeneity of CMML.[23] Comprehensive analyses reported an overall mutation frequency higher than 90%.[24] Recurrent mutations involve splicing factors (*SRSF2*), epigenetic regulators (*ASLX1, TET2, DNMT3A, IDH1/2, EZH2*, and *UTX*), tyrosine kinases (*JAK2, KRAS, NRAS,* and *CBL*), and transcription factors (*RUNX1*).[24-29] Recent series in patients with MDS suggest that mutations in specific genes help explain the clinical heterogeneity of the disease and that the identification of these abnormalities would

improve their prognostic stratification.[27-31] In CMML, however, the results reported so far on the prognostic impact of these new molecular markers are conflicting. Thus, further studies on the field are critical to clarify their influence on outcomes and to prove the need to incorporate them into daily clinical practice.

In the meantime, the CPSS developed herein is an easily applicable and validated prognostic index that may prove most valuable for assessing prognosis, planning therapy, and designing future clinical trials in patients with CMML.

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Authorship

Contribution: E.S., U.G., M.C., and G.S. designed the study. E.S., L.M., A.K., B.N., L.A., E.L., B.X., M.L.A., D.V., M.G.D.P., K.N., B.H., and I.A. collected and assembled data from study patients. E.S., U.G., M.C., J.C., L.M., I.L., and G.S. analyzed and interpreted the data. All authors wrote and approved of the manuscript.

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Appendix: Study Group

The following institutions and investigators from the GESMD participated in the study: Hospital Universitario La Fe, Valencia (G. Sanz, E. Such, J. Cervera, L. Senent, A. Avaria); Hospital Clinic, Barcelona (X. Calvo, M. Belkaid, M. Nomdedeu, D. Costa); Hospital del Mar, Barcelona (L. Arenillas, L. Florensa, F. Solé, C. Pedro); Hospital Central de Asturias, Oviedo (E. Luño, T. Bernal); Hospital Germans Trias i Pujol, Badalona (B. Xicoy, J. Jiménez, J. Grau); Hospital Morales Meseguer, Murcia (M.L. Amigo, F. Ortuño); Hospital Universitario Vall D'Hebron, Barcelona (D. Valcarcel, T. Vallespí); Hospital General Universitario, Valencia (F. Carbonell, R. Collado); Hospital Univeristario 12 de Octubre, Madrid (J. Martínez, M.T. Cedeña); Hospital Universitario, Salamanca (C. del Cañizo, M. Diez-Campelo); Hospital Txagorritxu, Vitoria (M.T. Ardanaz); Hospital Clínico Universitario, Valencia (M. Tormo); Hospital Virgen Blanca, León (F. Ramos); Hospital de la Ribera, Alcira (S. Bonanad); Hospital Arnau de Vilanova, Lleida (V. Marco); Hospital de La Princesa, Madrid (V. Gómez); Hospital Carlos Haya, Málaga (A. Bailén); Hospital. Clínico San Carlos, Madrid (A. Villegas); Hospital U. Virgen del Rocio, Sevilla (J. Falantes); Hospital de Sagunto, Sagunto (M.J. Arilla); Hospital de Cabueñes, Gijón (A. Fernández-González); Hospital Puerta de Hierro, Madrid (G. Bautista); Hospital Dr Peset, Valencia (R. Andreu); Hospital Severo Ochoa, Madrid (M.J. Requena); Hospital Valle de los Pedroches, Pozoblanco (R. Ríos); Hospital Nuestra Senora de Aránzazu, San Sebastian: (M.A. Etxebeste); Hospital Son Llatzer, Palma de Mallorca (J. Bargay); Fundación Hospital de Alcorcón, Madrid (L. Villalón); Hospital Universitario de Canarias, Santa Cruz de Tenerife (B. González); Hospital de Mataró, Barcelona (A. Soley); Hospital Marques de Valdecilla, Santander (A. Insunza); Hospital de Jerez, Jerez de la Frontera (L. Hermosín); Hospital Duran i Reynals, L'Hospitalet (R. Duarte); Hospital General de Castellón (G. Cañigral); Hospital Universitario Virgen de la Victoria, Málaga (R. García); Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria (M. Caballero); Complexo Hospitalario de Pontevedra, Pontevedra (M.J. Allegue); Hospital Sant Pau, Barcelona (S. Brunet); Universidad de Navarra, Pamplona (M.J. Calasanz); and Centro Nacional de Investigaciones Oncológicas, Madrid (J. Cruz, S. Alvarez).

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