RESEARCH ARTICLE

Myelodysplastic syndromes in South America: A multinational study of 1080 patients

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There are previously reported data describing differences between Asian and European patients with Myelodysplastic Syndromes (MDS), few direct comparisons based on cancer registration characteristics or using cohorts to validate scoring systems. This is the first study from South-America, which attempts to describe demographic, clinical features, and outcome of MDS patients. We retrospectively analyzed 1,080 patients with de novo MDS from Argentina (635), Brazil (345), and Chile (100). Chilean patients were younger ($P = 0.001$) with female preponderance ($P = 0.071$). Brazilian series showed a higher predominance of RARS subtype regarding FAB and WHO classifications ($P < 0.001$). Hemoglobin levels were significantly lower in Brazilian and Chilean series ($P < 0.001$), and Chilean series also showed a lower platelet count ($P = 0.028$), with no differences concerning the neutrophil count, % BM blast, and the distribution of cytogenetic risk groups ($P > 0.05$). Chilean series depicted a lower overall survival (OS; 35 months vs. 56 months-Argentine; 55 months-Brazil, $P = 0.030$), which was consistent with a higher predominance of the high-risk group according both to the IPSS and IPSS-R ($P = 0.046$ and $P < 0.001$). The IPSS-R system and its variables showed a good reproducibility to predict clinical outcome for the whole South-American population. Epidemiological and clinical characteristics, distribution among prognostic subgroups, the OS, and the access to disease modifying therapies were more similar between Argentinean and Brazilian compared with Chilean MDS series. This will need further analysis in a larger group of patients. Descriptive and comparative studies are necessary to establish epidemiological features useful for public health attitudes to generate suitable therapeutic schemes.
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Introduction

One of the most challenging problems in hematology is the heterogeneous group of clonal disorders that were formally defined as Myelodysplastic Syndromes (MDS) by the French–American–British (FAB) Cooperative Group in 1982 [1], and subsequently by the World Health Organization (WHO) in 2001 [2]. They are characterized by the presence of cytopenia(s) in combination with a normo/hypercellular bone marrow (BM) exhibiting dysplasia and ineffective hematopoiesis in, at least, one of myeloid cell lines. According to the prevailing dogma, MDS are clonal disorders of hematopoietic stem cells with a substantial risk of transformation to acute myeloid leukemia (AML). Clonal evolution is associated with increasingly ineffective hematopoiesis, progressive impairment of cellular function and worsening peripheral blood cytopenia(s) [1–5].

MDS is highly prevalent in elderly people. Approximately, 75% of MDS patients are older than 60 years of age at diagnosis [6,7] and the incidence rate doubles each decade over 40 years of age. The clinical course of MDS is highly variable, ranging from stable disease over 10 or more years to death within a few months due to cytopenia complications or leukemic transformation. The evaluation of disease risk and outcome of patients with MDS is one of the most critical points due to this impressive clinical heterogeneity [4–7]. Therefore, since the development of the Bournemouth index in 1985 [8], various scoring systems have been designed, based mainly on laboratory characteristics at presentation, to define prognostic subgroups. The International Prognostic Scoring System (IPSS) [6], the gold standard for risk assessment, has been recently revised (IPSS-R) defining five groups of risk based on five cytogenetic groups, new clinical cut-points for relevant cytopenias and for the percentage of BM blasts [7].

Additional Supporting Information may be found in the online version of this article.

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Ethnic differences and regional influences may play a role in the pathogenesis of MDS [9,10]. In the United States (US), Surveillance Epidemiology and End Results (SEER) data suggest that the incidence rates of MDS were highest among whites and non-Hispanics than in blacks; however, with only 4% of MDS cases reported from outpatient clinics to cancer registries [11]. There are previous reported data describing differences between Asian and European patients with MDS. Japanese patients with refractory anemia (RA) according to FAB classification were younger with more severe cytopenias, lower percentage of abnormal karyotypes and a more favorable prognosis than German patients [9,12]. Japanese patients also showed higher frequencies of MDS-unclassified (MDS-U) with pancytopenia and refractory cytopenia with unilineage dysplasia (RCUD) according to the WHO 2008 classification [13]. Another comparative study from New Zealand and Australia described epidemiological characteristic based on cancer registration and found a higher median age at diagnosis and higher male/female (M/F) ratio, which increases with age [14]. Another source of comparative studies might be the use of cohorts to validate scoring systems such us for the development of the WHO based prognostic scoring system [15] or to evaluate the impact of the degree of anemia in the outcome of MDS patients [16]. The leading cohort from Italy showed a lower age at diagnosis, a higher frequency of RA/RCUD/5q- and of low risk-IPSS patients than the validation cohort from Germany [16]. There are few others direct comparisons of MDS patients from other countries and little is known about South-American (SA) patients. There are previous reports that validate prognostic scoring systems in Argentinean population [17–19], and attempts for epidemiological description in Brazilian reduced series [[20], Velloso et al, 2007, personal communication], but epidemiological data in Chile are not available yet. Our aim was to describe clinical characteristics of SA MDS population, to compare our series with diverse ethnicity, and to evaluate prognostic factors and scoring systems.

Methods

Patients. This is a multicenter retrospective analysis of 1080 patients with de novo MDS from Argentina (Ar-635), Brazil (Br-345), and Chile (Ch-100). From the overall Ar population, diagnosed between September 1981 to May 2014, 312 patients belong to the MDS Registry promoted by the Argentinean Society of Hematology where 14 institutions from Buenos Aires, El Palomar, Pilar, Córdoba, and La Plata have been uploading data from patients diagnosed since 2007. The remaining Ar patients belong to a previous registry from the Genetic Department of the National Academy of Medicine, including patients from Buenos Aires, Córdoba, and Paraná, and from the Grupo Hematológico del Sur. Brazilian patients from Fortaleza (100) and Sao Paulo (245) have been diagnosed since November 1987 to April 2012. And, Ch MDS patients were from Santiago, Valparaiso, Talca, Concepción, and Temuco, diagnosed between December 1995 and October 2012 (Fig. 1).

Included patients had a confirmed diagnosis of de novo MDS, based on morphologic abnormalities in the BM, cytopenia(s), and/or the presence of cytogenetic aberrations [21]. Patients were classified following FAB [1] and WHO criteria [3], excluding those with BM blasts >30% and Chronic Myelomonocytic Leukemia (CMML) with white blood cells count $>12 \times 10^9$/L. Treatment-related MDS and those who had a history of toxic substances were excluded from the analysis.

Statistical analysis. To compare differences in baseline presenting characteristic between patients, we used Anova, Kruskall-Wallis or Mann-Whitney tests to analyze continuous data. The chi-square or Fisher exact tests were used to analyze categorical variables. The Kaplan-Meier method was used for the univariate estimation of survival time calculated from the day of diagnosis. Patients undergoing hematopoietic stem cell transplantation (HSCT; 53; 4.9%) or hypomethylating therapy (HMT; 137; 12.7%) were censored up to receiving a disease modifying therapy. Each variable was analyzed using the log–rank test (Mantel-Cox). The level of statistical significance was fixed at 0.05. All analyses were performed using the SPSS software version 17.00 (SPSS, Chicago) and the GraphPad Prism version 5 (GraphPad Software, La Jolla).

Results

Clinical and laboratory features at diagnosis

Epidemiological characteristics, clinical and laboratory features are summarized in Table I. Chilean patients were younger (median age: 64 years old versus 69-Ar, $P < 0.001$ and vs. 68-Br, $P = 0.003$), with a female preponderance (0.8, 1.3-Ar, 1.3-Br, $P = 0.071$). As it is clearly depicted in Fig. 2, Ch series showed a higher predominance of patients younger than 40 years old (19% vs. 7%-Ar, $P < 0.001$; vs. 8%-Br, $P = 0.005$), whereas the distribution among the other ranges of age was similar.

Figure 1. Location of participating institutions from Argentine, Brazil, and Chile. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Gender distribution across most age groups showed a male predominance for the whole series (Fig. 3), and for Ar and Br series when they were analyzed separately (Supporting Information, Fig. 1S). However, a lower M/F gender ratio of 0.8 was observed for patients younger than 45 years old.

The median age at diagnosis was not significantly different between men and women in the overall SA (69 and 68 years old, respectively, $P = 0.374$), in Br ($P = 0.209$) or in Ch ($P = 0.530$) MDS population. However, men from Ar series present with a higher median age at diagnosis (71 vs. 68 years old, $P = 0.040$).

The distribution of patients among FAB and WHO categories was different ($P < 0.001$). According to FAB criteria, Br series showed a higher predominance of RA with Ring Sideroblasts (RARS; 18% vs. 10%-Ar versus 1%-Ch, $P < 0.001$), a lower percentage of RA (50 vs. 57%-Ar vs. 67%-Ch, $P = 0.006$), without statistical differences regarding other subtypes. When low risk MDS patients were classified according to WHO, Br series showed a higher frequency of RARS subtype (10% vs. 3%-Ar vs. 1%-Ch, $P < 0.001$), similar frequency of Refractory Cytopenia with Multilineage Dysplasia (RCMD) with RS than Ar-series (7% vs. 8%-Ar), and a lower frequency of RCMD (35% vs. 44%-Ar vs. 53%-Ch, $P = 0.004$), while the percentage of other subtypes were comparable.

Hemoglobin (Hb) level was significantly higher in Ar series (9.6 g/dL vs. 8.8 g/dL-Br, $P < 0.001$, and vs. 8.7 g/dL-Ch, $P = 0.002$). As it is clearly depicted in Fig. 4, Ar series showed a lower predominance of patients with Hb levels below 7g/dL (10% vs. 26%-Br vs. 24%-Ch, $P < 0.001$). No differences were observed with respect to Hb mean levels of males and females from the whole SA series (9.2 g/dL, $P = 0.695$) and from each series.

Median platelet count was significantly lower in Ch series than in the Ar ($P = 0.014$), showing a higher frequency of patients with

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TABLE I. Laboratory and Clinical Features at the Time of Diagnosis

Variable	Argentine $N = 635$	Brazil $N = 345$	Chile $N = 100$	*P* value	Total 1080
Gender					
Male/Female	356/279	193/152	44/56	=0.071	593/487
Rate	1.3	1.3	0.8		1.2
Age (years)					
Mean ± S.D.	66 ± 15	65 ± 17	59 ± 19	=0.001	65 ± 16
Range	17–93	15–99	15–89		15–99
Median	69	68	64		69
FAB				<0.001	
RA	328 (51.7)	159 (46.1)	67 (67.0)	=0.006	554 (51.3)
RARS	58 (9.1)	59 (17.1)	1 (1.0)	<0.001	118 (10.9)
RAEB	135 (21.3)	78 (22.6)	24 (24.0)	n.s.	237 (21.4)
RAEBt	54 (8.5)	24 (7.0)	8 (8.0)	n.s.	86 (8.0)
CMML-MDS	60 (9.4)[a]	25 (7.2)[a]	–	n.s.[a]	85 (7.9)
WHO	$N = 520$	$N = 299$	$N = 85$	<0.001	$N = 904$
5q-	24 (4.6)	9 (3.0)	4 (4.7)	n.s	37 (4.1)
RCUD	57 (11.0)	40 (13.4)	11 (12.9)	n.s	108 (12.0)
RARS	13 (2.5)	31 (10.4)	1 (1.2)	<0.001	45 (5.0)
RCMD[b]	230 (44.1)	105 (35.1)	45 (52.9)	=0.004	380 (42.0)
RCMD-RS[b]	42 (8.1)	21 (7.2)	0 (0.0)	=0.025	63 (7.0)
RAEB-1	65 (12.5)	44 (14.7)	10 (11.8)	n.s	119 (13.2)
RAEB-2	89 (17.1)	45 (15.1)	14 (16.5)	n.s	148 (16.4)
MDS-U	0 (0.0)	4 (1.3)	0 (0.0)	–	4 (0.4)
BM Blasts (%)					
Mean ± S.D.	4.5 ± 6.3	4.4 ± 5.7	5.5 ± 7.2	=0.161	4.6 ± 6.2
Range	0.0–30.0	0.0–29.0	0.0–29.0		0.0–30.0
Median	2.0	1.6	2.0		2.0
Hemoglobin (g/dL)					
Mean ± S.D.	9.6 ± 2.1	8.8 ± 2.6	8.7 ± 2.6	<0.001	9.2 ± 2.4
Range	4.0–15.3	1.9–16.7	3.6–16.5		1.9–16.7
Median	9.6	8.6	8.5		9.2
Neutrophil count (/μL)					
Mean ± S.D.	2178 ± 1572	2196 ± 1879	2100 ± 1447	=0.569	2176 ± 1703
Range	110–10,200	28–10,300	63–9,680		28–10,300
Median	1,766	1,604	1,447		1,700
Platelets count (/μL)					
Mean ± S.D.	159,632 ± 127,000	157,382 ± 155,741	148,777 ± 165,560	0.028	157,812 ± 146,819
Range	2,000–912,000	1,500–930,000	1,600–800,000		1,500–930,000
Median	127,000	105,000	83,500		117,000

[a] CMML-MDS subtype were excluded for the overall statistical comparison, since Ch did not include CMML-MDS patients.
[b] RCMD without RS and RCMD-RS, merged in the 2008 WHO classification [3], were disclosed for comparison purpose.

platelet count <50,000/μL (35% vs. 25%-Ar, $P = 0.001$, and vs. 25%-Br, $P = 0.040$). No differences were observed with respect to the percentage of BM Blast ($P = 0.161$) and to the absolute neutrophil count ($P = 0.526$). However, Br patients presented a higher frequency of pancytopenic patients than Ar patients (22% vs. 15%-AR, $P = 0.006$), which was not different from Ch series (21%-Ch versus 22%-Br, $P = 0.891$).

Cytogenetic results were available from 632 Ar, 309 Br, and 99 Ch patients. The frequency of abnormal karyotype was similar among the three series ($P = 0.258$). Regarding the most frequent cytogenetic findings, Ch series present with a higher frequency of complex karyotypes (≥ 3 cytogenetic anomalies) than Ar ($P = 0.002$) or Br ($P = 0.004$). However, Ar series showed a borderline higher frequency of chromosome Y loss ($P = 0.073$) and a lower frequency of isolated del(5q) than Br series (12%-Ar vs. 19%-Br, $P = 0.082$, with respect to the total amount of abnormal karyotypes). The subgroups of cytogenetic abnormalities according to IPSS and IPSS-R are summarized in Table II. There were no differences in the distribution of cytogenetic groups of risk according to IPSS ($P = 0.159$) and to the IPSS-R ($P = 0.091$) when the overall data was compared. However, Ar series showed a higher frequency of intermediate risk findings than Ch series according to the IPSS ($P = 0.019$) and to the IPSS-R ($P = 0.016$).

The distribution among IPSS categories tended to be different ($P = 0.046$) with a higher predominance of the high risk group in Ch series (17% versus 9%-Ar, $P = 0.016$, and versus 9%-Br, $P = 0.041$). IPSS-R distribution showed more evident differences ($P < 0.001$), and these differences were predominantly in the distribution of patients into Very Low ($P < 0.001$), Intermediate ($P < 0.001$) and Very High ($P = 0.025$) risk groups. Ch series showed a lower predominance of Very Low risk (7% versus 15%-Br, $P = 0.042$, and versus 22%-Ar, $P < 0.001$), and a higher frequency of Very High risk patients

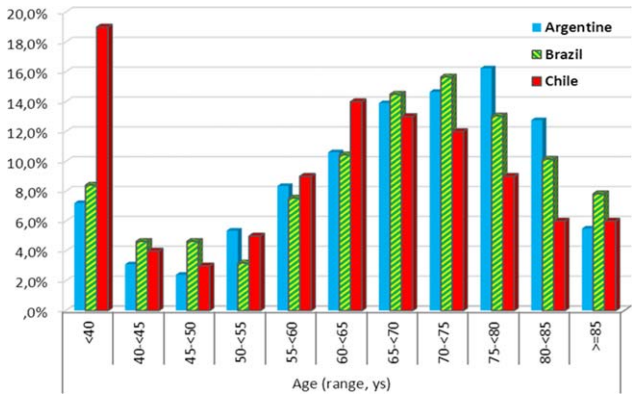

Figure 2. Distribution of Argentinean, Brazilian, and Chilean series according to the range of age. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

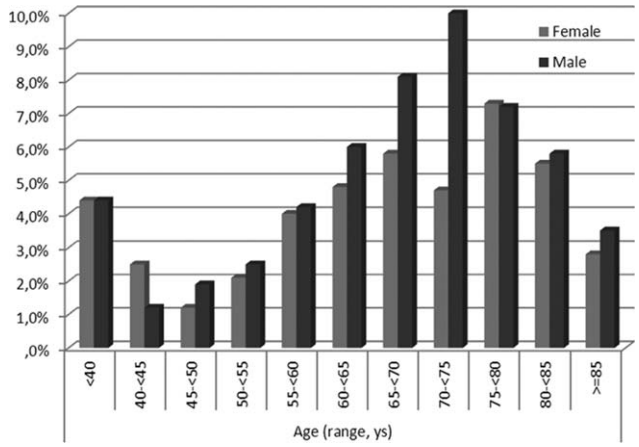

Figure 3. Distribution of MDS patients in the SA series according age and gender. ys: years.

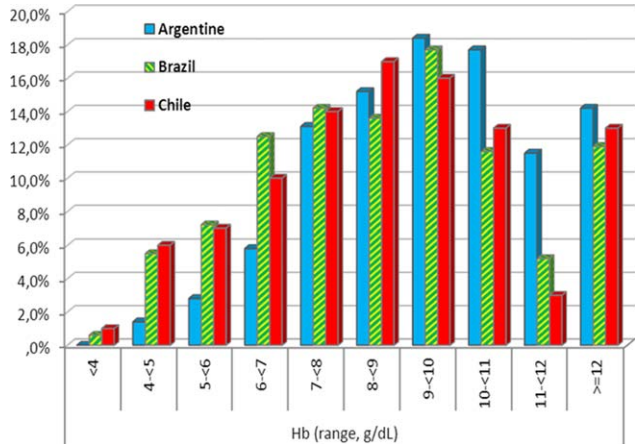

Figure 4. Distribution of Argentinean, Brazilian, and Chilean patients according to hemoglobin levels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that was significantly different from Ar data (20% vs. 10%, $P = 0.015$). However, Ar series showed a lower proportion of patient at the Intermediate risk category (14% versus 23%-Br, $P = 0.002$, and vs. 27%-Ch, $P = 0.002$; Table III). Similar results were obtained when the IPSS-R distribution was analyzed in the WHO- based MDS population. However, no statistical differences were observed with respect to the Very High risk group distribution ($P = 0.107$; Table III).

Prognosis

The follow-up for the whole SA series ranged from 1 to 266 months with a median of 21 months (Ar: range: 1–266 months; median: 21 months; Br: range: 1–171 months; median 24 months; Ch: range 1–204 months, median: 9 months). During the follow up, 497 patients died (Ar: 290, Br: 163, Ch: 44). Concerning causes of death, Ar patients were classified as 119 AML, 52, infection, 9 bleeding, 22 heart failure, 20 comorbidities, 15 post-HSCT, 53 unknown; Br patients: 53, 24, 3, 9, 3, 12, 59; and Ch patients: 15, 8, 4, 13, 1, 0, and 3, respectively. The incidence of death related to AML complications tended to be higher in Ar than Br series (41% vs. 33%-Br, $P = 0.086$).

Different prognostic factors in each MDS population and in the whole SA population were also evaluated (Table IV). Overall survival (OS) was lower in Ch patients, consistent with the higher prevalence

TABLE II. Cytogenetic Findings at the Time of Diagnosis

Variable	Argentine $N = 632$	Brazil $N = 309$	Chile $N = 99$	P value	Total $N = 1040$
Karyotype				=0.258	
Normal	367 (58.1)	186 (60.2)	66 (66.7)		619 (59.5)
Abnormal	265 (41.9)	123 (39.8)	33 (33.3)		421 (40.5)
More frequent Cytogenetic Aberrations[a]					
-Y	18 (6.8)	3 (2.4)	0 (0)	=0.073	21 (5.0)
del(5q)	31 (11.7)	23 (18.7)	6 (18.2)	n.s.	60 (14.3)
del(20q)	16 (6.0)	5 (4.0)	1 (3.0)	n.s.	22 (5.2)
+8	34 (12.8)	11 (8.9)	3 (9.1)	n.s.	48 (11.4)
del(7q)/-7	19 (7.2)	8 (6.5)	1 (3.0)	n.s.	28 (6.7)
Complex (≥3 abnormalities)	47 (17.7)	21 (17.1)	14 (42.4)	=0.002	82 (19.5)
IPSS Cytogenetic Groups of risk				=0.159	
Good	432 (68.4)	217 (70.2)	73(73.7)	n.s.	722 (69.4)
Intermediate	126 (19.9)	53 (17.2)	10 (10.1)	=0.053	189 (18.2)
Poor	74 (11.7)	39 (12.6)	16 (16.2)	n.s.	129 (12.4)
IPSS-R Cytogenetic Groups of risk				=0.091	
Very Good/Good	445 (70.4)	231 (74.8)	73 (73.7)	n.s.	749 (72.0)
Intermediate	120 (19.0)	45 (14.6)	9 (9.1)	=0.024	174 (16.7)
Poor	30 (4.7)	17 (5.5)	9 (9.1)	n.s.	56 (5.4)
Very Poor	37 (5.9)	16 (5.2)	8 (8.1)	n.s.	61 (5.9)

[a] Percentage from abnormal karyotypes.
n.s.: Nonsignificant differences; IPSS: International Prognostic Scoring System [6]; IPSS-R: IPSS revised version [7].

TABLE III. Distribution Among IPSS and IPSS-R Categories

Variable	Argentine	Brazil	Chile	P value	Total
IPSS	$N = 628$	$N = 308$	$N = 99$	=0.046	$N = 1035$
Low	217 (34.6)	90 (29.2)	30 (30.3)	n.s.	337 (32.6)
Int-1	262 (41.7)	143 (46.4)	44 (44.4)	n.s.	449 (43.4)
Int-2	95 (15.1)	47 (15.3)	8 (8.1)	n.s.	150 (14.5)
High	54 (8.6)	28 (9.1)	17 (17.2)	=0.025	99 (9.6)
IPSS-R	$N = 558$	$N = 301$	$N = 97$	<0.001	$N = 956$
Very Low	122 (21.9)	46 (15.3)	7 (7.2)	<0.001	175 (18.3)
Low	225 (40.3)	103 (34.2)	36 (37.1)	n.s.	364 (38.1)
Intermediate	77 (13.8)	68 (22.5)	26 (26.8)	<0.001	171 (17.9)
High	77 (13.8)	44 (14.6)	9 (9.3)	n.s.	130 (13.6)
Very High	57 (10.2)	40 (13.3)	19 (19.6)	=0.025	116 (12.1)
IPSS-R (WHO based)	$N = 470$	$N = 258$	$N = 82$		$N = 810$
Very Low	103 (21.9)	35 (13.6)	6 (7.3)	<0.001	144 (17.8)
Low	194 (41.1)	97 (38.7)	31 (37.8)	n.s.	322 (39.8)
Intermediate	68 (14.5)	59 (22.8)	24 (29.3)	<0.001	151 (18.6)
High	62 (13.1)	34 (13.2)	8 (9.8)	n.s.	104 (12.8)
Very High	43 (9.1)	33 (12.8)	13 (15.9)	n.s.	89 (11.0)

IPSS: International Prognostic Scoring System [6]; IPSS-R: IPSS revised version [7]; WHO: World Health Organization classification [3]; n.s.: nonsignificant differences.

of higher risk group categories (35 months vs. 56 months-Ar vs. 55 months- Br, $P = 0.030$; Fig. 5A). Hb, BM blast, CGR, IPSS, and IPSS-R were useful to predict survival in the three series and in the overall SA MDS population (Fig. 5B–D). Neither ANC nor age was useful for Br patients. Gender, ANC, and platelets count were not useful in Ch series.

Treatment

Concerning disease modifying therapies Ar and Br series showed similar rates of patients that received a HSCT: 31 (4.9%) versus 22 (6.4%; $P = 0.375$) and not different median time to access to the HSCT (11.2 vs. 7.1 months, $P = 0.132$). Ar series showed a higher number of patients that received HMT: 111 (17.5%) versus 26-Br (7.5%), $P < 0.001$, with no differences regarding the time to initiate treatment (4.7 vs. 10.7 months, $P = 0.092$), and in terms of median

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TABLE IV. Univariate Analysis of OS in Argentinean, Brazilian, Chilean, and in the whole South American series

	Argentine			Brazil			Chile			Whole SA		
	Pts (%) 635	Survival 50%, m 56 ± 5	*P* value	Pts (%) 345	Survival 50%, m 55 ± 8	*P* value	Pts (%) 100	Survival 50%, m 35 ± 15	*P* value	Pts (%) 1080	Survival 50%, m 51 ± 4	*P* value =0.030
Gender												
Male	56	41	<0.001	56	40	=0.002	44	17	0.437	55	41	<0.001
Female	44	66		44	85		56	49		45	66	
Age (years)												
≤60	27	77	=0.045	30	43	=0.336	42	74	=0.002	30	63	=0.084
>60	73	50		70	63		58	13		70	49	
Hemoglobin (g/dL)												
≥10	45	98	<0.001	28	135	<0.001	29	NR	=0.021	38	121	<0.001
8-< 10	33	50		31	64		33	32		32	44	
<8	22	33		41	30		38	16		30	30	
ANC (/μL)												
≥800	84	58	=0.006	77	63	=0.084	75	35	0.156	81	57	=0.020
<800	17	29		23	36		25	NR		19	36	
Platelets ($\times 10^3$/μL)												
≥100	63	62	<0.001	53	68	=0.029	45	41	0.612	58	63	<0.001
50 -< 100	18	42		22	47		20	35		20	43	
<50	19	28		24	40		35	17		22	28	
BM Blast (%)												
≤2	58	77	<0.001	58	68	<0.001	53	49	=0.001	57	71	<0.001
>2-<5	11	63		11	70		15	35		11	63	
5-10	16	21		16	36		11	15		16	25	
>10	16	15		15	11		21	7		16	13	
CGR	*N* = 632			*N* = 309			*N* = 99			*N* = 1040		
Very G/Good	70	66	<0.001	75	68	<0.001	74	74	<0.001	72	67	<0.001
Intermediate	19	34		15	20		9	13		17	31	
Poor	5	20		6	9		9	4		6	16	
Very Poor	6	12		5	16		8	7		6	12	
IPSS	*N* = 628			*N* = 308			*N* = 99			*N* = 1035		
Low	35	121	<0.001	29	116	<0.001	30	50	<0.001	33	121	<0.001
Int-1	42	44		46	55		44	49		43	49	
Int-2	15	18		15	16		8	6		14	18	
High	9	13		9	9		17	7		10	9	
IPSS-R	*N* = 558			*N* = 301			*N* = 97			*N* = 956		
Very Low	22	136	<0.001	15	135	<0.001	7	NR	<0.001	18	136	<0.001
Low	40	64		34	70		37	50		38	70	
Intermediate	14	42		23	36		27	74		18	42	
High	14	18		15	16		9	13		14	18	
Very High	10	14		13	11		19	6		12	10	
IPSS-R (WHO)	*N* = 470			*N* = 258			*N* = 82			*N* = 810		
Very Low	22	136	<0.001	14	135	<0.001	7	NR	<0.001	18	136	<0.001
Low	41	67		39	70		38	50		40	68	
Intermediate	15	43		23	37		29	74		19	44	
High	13	18		13	23		10	13		13	18	
Very High	9	15		13	11		16	6		11	11	

IPSS: International Prognostic Scoring System [6]; IPSS-R: IPSS revised version [7]; BM: bone Marrow: ANC: Absolute Neutrophil Count; CGR: Cytogenetic Group of risk according to the IPSS-R [7]; WHO: World Health Organization classification [3]; NR: not reached, Pts: patients, m: months; *N*: number of patients; SA: South American series.

survival after initiating therapy (censored up to receive HSCT; 18.6 months-Ar vs. 16.6 months-Br, $P = 0.987$). However, the use of iron chelation therapy was not statistically different between Ar (17, 2.4%) and Br (15, 4.3%), $P = 0.188$. No Ch patient received HSCT, HMT, or iron chelation therapy.

Discussion

The incidence and clinical characteristics of patients with MDS varies by geographical area, and this has been attributed to genetic or ethnic, occupational, lifestyle, and environmental factors, that have not been fully elucidated [9,22]. Socioeconomic status may also influence the outcome of the disease [23]. Knowledge on epidemiological characteristics of MDS is often based on statistics from selected local populations. On the other hand, there are some growing data from cancer registries [14] or from ongoing programs such us the SEER in US [11]. Because of the lack of large, population-based studies, and Cancer Registries supported by each government, the incidence of MDS in SA has not been well documented yet. This is the first study, which attempts to describe demographic, clinical features and outcome of patients with MDS from SA comparing patients from Argentina, Brazil, and Chile.

Our results indicate that some clinical features of Ar, Br, and Ch patients may be different. The median age at diagnosis was 69 years for the whole SA series, the same as that of the series used for the development of the IPSS [6] and no so far from the 71 years old from the combined databases used for the development of the IPSS-R [7]. However, the median age at diagnosis was lower for Ch series, which might be biased because of the restriction to access to cytogenetic studies for older people in this country. The age at diagnosis

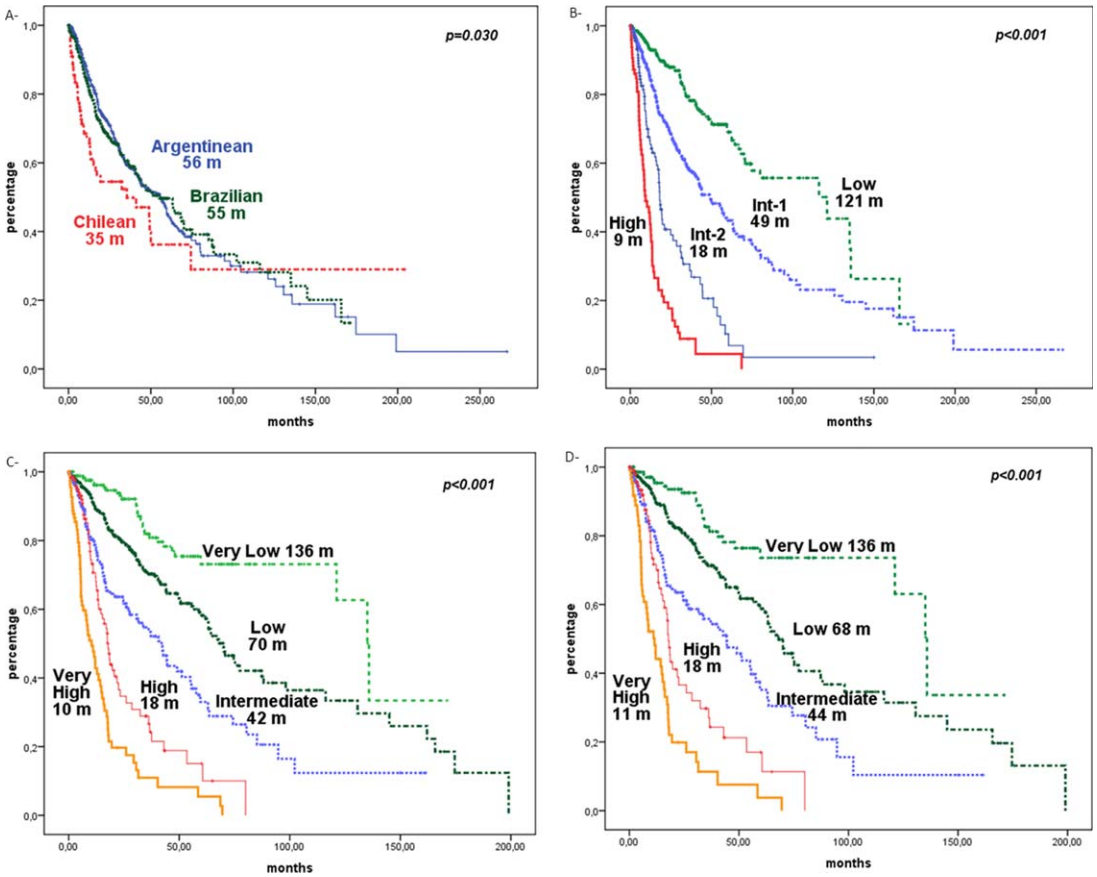

Figure 5. Cumulative OS of South American patients. A: Argentinean, Brazilian, and Chilean series. B: IPSS for the whole SA series of 1035 pts. C: IPSS-R for the FAB classified SA MDS population ($N = 956$ patients). D: IPSS-R for the WHO based SA MDS population ($N = 810$ patients). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was similar between male and females for the whole series; however, it was higher for Ar males (Fig. 3). The median age at diagnosis seems to vary in different countries, being lower in "Eastern" than in "Western" countries: 59 years old in China [22], 60 in Japan [24], 58 in Korea [25], 56 in Thailand [26], and 65 in Taiwan [27], 77 in US [28], 72-73 in Germany [15,16,29], and 65–71 in Italy [15,16,30,31]. However, a new report using a population-based registry data showed a median age of 76 years for Japan [32]. Another comparative study from New Zealand and Australia describing epidemiological characteristic based on cancer registration found a median age at diagnosis of 77–78 years old [14]. Therefore, it seems that the median age is rising as registries are improving.

Brazil series demonstrated a higher frequency of RARS. Although RCMD without RS and RCMD-RS entities were merged in the 2008 WHO classification [3], we differentiated them in Table I to point out that more evident differences were observed in the pure RARS subtype. RARS accounts for 1.5–12% of MDS patients and occurs primarily in older cases with median age of 60-73 years [3,22,33–35] and more frequent in male than females [3,33] or with a similar sex ratio [34,35]. The median age for pure RARS subtype, which accounted for 5.0% of the whole series, was 70 years old (mean age: 67 years) with a M/F ratio of 0.8 and was detected in 2.5, 10.4, and 1.2% of Ar, Br and Ch cases, respectively. One possible explanation to the difference among SA series may be related to the younger mean age of Ch patients with a higher predominance of cases younger than 40 years old (Fig. 2) which reinforces the relation between RARS incidence and older age. It also should be emphasized that non neoplastic causes of ring sideroblasts such as alcohol, zinc administration, copper deficiency, and congenital sideroblastic anemia were all excluded [36].

Series from Brazil and Chile showed higher predominance of hemoglobin level below 7 g/dL (Fig. 4) and a higher percentage of pancytopenic patients according to the IPSS cut-offs [6] when compared with Argentinean series. MDS is more commonly diagnosed and managed in the outpatient setting and referral of an anemic patient to a hematologist occurred more often after complications ensued (e.g., development of other cytopenias, infection, bleeding, or increasing transfusion requirements) [11,37].

Brazil is a country of continental dimensions with widening of social, economic, and ethnic differences and we evaluated two tertiary and university centers of different regions (100 patients from the northeast and 245 from the southeast; Fig. 1). The southeast is the richest and most crowded region of the country. High complexity hospitals receive many immigrants from various parts of Brazil and the median time between the onset of symptoms and the diagnosis of MDS is 6 months. The northeast is poorer and many patients are rural workers who are constantly exposed to pesticides and to other toxic environmental factors. Among northeastern patients, 50% were from rural zones and half of the cases were rural workers (data not shown). Farmers without protection devices, which are common in developing countries, are constantly exposed to these chemicals associated with MDS etiology [22]. A previous work that evaluated clinical characteristic of MDS from Ourense, Spain, where 70% of patients lived in rural environments, showed a frequency of 35% of RARS patients [38], consistent with the higher frequency of this subtype among Brazilian patients. Although not evaluated, we can speculate that these elements may also be associated with a higher predominance of Brazilian patients with lower hemoglobin levels and to the borderline higher frequency of del(5q), as was previously reported [20]. Another hypothesis, these patients from undeveloped

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regions and lower socioeconomic status may have more difficulties to arrive to specialized hematology centers, thus presenting with more pronounced cytopenic states, more red cell allo immunization (data not shown), and, frequently, with pancytopenia (22%), similar to Ch patients (21%), as compared with Ar series (15%). This data is consistent with a previous report of a multicenter observational cross-sectional survey of MDS Brazilian patients showing a median hemoglobin level at presentation of 8 g/dL and iron overload in 21% of cases [Magalhaes et al., 2011, personal communication].

Chilean MDS patients presented with a higher proportion of high risk patients, even though to the original IPSS-R distribution (10 vs. 20%) [7], with a higher proportion of complex karyotypes and, more often, at pancytopenic states. Consequently, those patients showed a shorter median survival than Br and Ar. Chile is a large and narrow country with an organized National Health structure divided into sanitary regions. Chilean MDS patients from the north and south of the country, where the rural population prevails, are derived to the specialized hospitals at the central zone. Bone marrow examination and cytogenetic analysis are only performed at specialized centers and asymptomatic, stable, or very old patients are almost never referred to those centers. Since cases were collected from a reference hospital, their diagnosis may reflect a degree of bias toward younger patients who required aggressive treatment.

Argentina is also a large country, and although our database is based on 20 hematological services including 635 patients, the analysis was restricted to the central geographic area. According to the latest census, this central zone accounts for the highest concentration of population (66.3% of the total Ar population) and economic resources. Health coverage is universal and warranted for all complexity levels under Argentinean law and more than 64% has a medical insurance in addition to free access to public hospitals. Health care factors, such as access to medical services and medical expertise are more accessible in the metropolitan area and in the pampeana zone than in other regions of Argentina [39]. Argentinean series showed a higher proportion of patients belonging to lower-risk categories, being more evident when the IPSS-R was applied. In spite of the observed differences regarding the distribution of patients according to the IPSS-R and its respective cut-off values for hemoglobin and platelet counts when compared to Chile and Brazil, Argentine series showed a similar distribution of patients to the original IPSS-R and to other reports [7,30]. This finding may reflect an accumulative referral of early-MDS cases for evaluation to the specialized Hematological Departments [37]. One could also speculate that Ar-MDS patients may have access to medical care more easily with a prompt diagnosis leading to prolonged survival that may play a role in the differences of outcome with Ch. However, Ar series showed a higher frequency of AML-related deaths, showing a good follow-up of the natural course of the disease. Argentinean MDS Registry started to collect data in 2009 from patients diagnosed since 2007 as an attempt to resolve missing region's data. However, Ar registry is not mandatory and depends on the predisposition of the hematologists to report MDS patients' data without government funding and without any active case finding method.

HMT are available in Argentina since 2007 for the treatment of MDS and included in the obligatory medical plan, in Brazil since 2009, but they are not included among covered medication by the Health Ministry in Chile. We could evidence a higher frequency of patients treated with HMT in Ar series. MDS is commonly managed outside of hospitals, with most patients living for years with their cytopenia(s) looking for different physician's opinions, and usually at private physicians' offices who are not reporting data. However, once a disease modifying therapy is initiated they usually continue at the same medical center. Those patients are more easily reported to population-based registries that may bias the real frequency of patients treated with HMT in Argentina. However, the median time to initiate an HMT and the median OS once initiated the HMT were similar between Ar and Br series, as well as the frequency of HSCT as a suitable therapeutic option or the use of iron chelation therapy.

The value of this study is the inclusion of a large number of patients which reflects a good representativeness because case series were from different clinical institutions from each country, although some bias may be present due to patient referral patterns to the participating institutions, especially in Ch and Br where only 3 institutions participated.

Despite some pointed differences, epidemiological and clinical characteristics, distribution among prognostic subgroups OS, also median time to access to a disease modifying therapy, such us HMT or HSCT, were similar between Ar and Br compared to Ch MDS series. Most likely, different reporting methods and the number of patients might play a role in geographic discrepancies. However, true regional differences might be related to possible different lifestyles, exposure to environmental toxic or infectious agents, genetic background, or access to medical experts' care. Nevertheless, the IPSS-R system and its variables showed a good reproducibility and effectiveness to predict clinical outcome in the overall SA population with similarities regarding the distribution of risk groups and their respectively achieved median survivals [7].

To the best of our knowledge, this is the first study aimed at evaluating clinical characteristics and prognostic factors in the survival of MDS patients from SA. Given the morbidity, mortality, and costs of MDS patients to societies, the need for a greater investment in registries should be a priority of public concern. Descriptive and comparative studies are necessary not only to establish epidemiological features useful for public health strategies but also to define prognostic factors and generate suitable therapeutic schemes.

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Author Contributions

All authors gave significant contributions to draft the article, critically revise the content of the manuscript, and approve the final version.

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