Original article

Real-World Evidence of Epidemiology and Clinical Outcomes in Multiple Myeloma, Findings from the Registry of Hemato-Oncologic Malignancies in Colombia, Observational Study

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ABTRACT

Multiple myeloma represents 1% of all newly diagnosed neoplasms; the data available on its treatment and outcomes in Latin American countries is scarce. The results of this multicenter observational study in Colombia provide an overview of clinical characteristics and outcomes in 890 real-world patients, highlighting the impact of access barriers on diagnosis and treatment outcomes.

Introduction/Background: Multiple Myeloma (MM) is a plasma cell derived clonal disorder that represents around 1% of all newly diagnosed neoplasms. Limited data regarding MM treatment in Latin America is available, and access to novel agents for a substantial portion of the population is limited by their high costs. **Materials (or Patients) and Methods:** RENEHOC is a bidirectional (retrospective and prospective) multicenter observational registry of hematological malignancies in Colombia. MM patients included up to July 2020 were analyzed on this report. **Results:** 890 are reported with a median follow-up of 18 months (IQR: 7-42 months). Patients were classified by age group ($\leq$ or $>$ 65 years). Median age at diagnosis was 67 years (IQR: 59-75 years) and 47.1% of patients were women. 709 patients (79.6%) received Bortezomib-based schemes as part of the first line. Two hundred and fifty-two patients (28.3%) were consolidated with Autologous Stem Cell Transplantation (ASCT) in first-line. ASCT consolidation and age were the main independent factors influencing outcomes; in the non-ASCT cohort, 5-year overall survival was 48.7% (CI 41.8-55.2) compared to 80.7% (CI 73-86.4) in ASCT patients. **Conclusion:** This data depicts the reality of MM in Colombia, which likely reflects other Latin American countries, where access barriers to diagnosis and treatment are echoed in advanced stage diagnosis and a low rate of transplants. These seem to negatively impact survival despite the availability of most novel drugs approved for this disease. Thus, emphasizing the paradox that prevails in most of the region: availability without equitable access.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 000, No.xxx, 1–9

Keywords: Autologous transplantation, Diagnosis, Disease registry, Therapy, Latin America

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Submitted: Aug 28, 2021; Revised: Nov 1, 2021; Accepted: Dec 8, 2021; Epub: xxx

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2152-2650/$ - see front matter

https://doi.org/10.1016/j.clml.2021.12.009

Please cite this article as: Virginia Abello et al, Real-World Evidence of Epidemiology and Clinical Outcomes in Multiple Myeloma, Findings from the Registry of Hemato-Oncologic Malignancies in Colombia, Observational Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2021.12.009

INTRODUCTION

Cancer is currently the second leading cause of morbidity and mortality worldwide, second only to cardiovascular disease, with over 19 million new cases reported in 2020 and nearly 10 million cancer-related deaths.[2] For the same year, the Global Cancer Observatory (Globocan) reported more than 100,000 new cancer cases and more than 54,000 cancer-related deaths in Colombia.[3] It is estimated that by 2040, the number of new cancer cases will increase by 86% and associated deaths will almost double.[4]

In line with global trends, cancer is also the second leading cause of death after cardiovascular disease in Colombia. Of 236,932 deaths reported by the National Administrative Department of Statistics (DANE) in 2018, cancer is responsible for 16,489. Of these, 4,461 are hematological neoplasms.[5]

The Cuenta de Alto Costo (CAC) or high-cost account, an organization created to trace high expenditure diseases, has been recording data on patients with cancer in the country since 2014. It reported that between January 2, 2018 and January 1, 2019, there were 279,155 prevalent cases and 29,151 new cases of cancer, for a prevalence of 587.70 cases of 100,000 inhabitants (95% CI: 58544-589.97). During this period, the CAC recorded 18,108 deaths in this population. However, despite the burden of disease associated with cancer, data on epidemiology and clinical outcomes in the Colombia is scarce.

Multiple myeloma (MM) is a clonal proliferative disorder derived from plasma cells associated with non-specific clinical manifestations including anemia, bone lesions, renal failure, and hypercalcemia.[6] There are currently four population-based cancer registries in Colombia that cover four cities (Cali, Bucaramanga, Manizales and Pasto) and only 10% of the population.[7] Based on these registries, Globocan estimated an incidence of 1,375 new cases of MM in 2020 in Colombia with a mortality of 1,035 death per year.[3] In contrast, the DANE reported 771 deaths from MM in the country,[5] while the CAC recorded 2,746 prevalent cases, 305 incident cases and 342 deaths from MM in 2018.[9] The significant discrepancies between these three main sources of data are a matter of concern, and a testament to the difficulty in reliably capturing the country's situation.

MM related mortality has decreased in developed countries since 2006, due to the introduction of proteosome inhibitors, immunomodulators, and other new therapeutic strategies.[10] However, there are no comprehensive mortality data in Colombia. Based on the Cali Population-based Cancer Registry (RPCC), shows MM-related mortality seems to be increasing, despite most novel treatment agents being available in the country.

These data limitations are commonplace in most countries in the region.[11] Although some regional registries exist, they do not provide data on treatment regimens and most of them do not conduct long-term follow-up, limiting their utility in observing progression-free survival (PFS) and overall survival (OS).

In an effort to bridge the existing knowledge gaps, the Colombian Association of Hematology and Oncology (ACHO) decided to develop the Colombian Registry of Hematologic Neoplasms (RENEHOC). This is an observational initiative that seeks to collect real-world evidence, including demographic and clinical characteristics, therapeutic patterns of different Colombian institutions, and will allow clinical outcomes in MM to be identified. Thus, strategies to improve the prognosis of Colombian patients with MM may be proposed and developed based on the findings.

This report describes RENEHOC findings regarding treatment patterns, access, and clinical outcomes of patients with MM registered by the researchers through July 2020.

MATERIALS AND METHODS

Study design

RENEHOC is a bidirectional (retrospective and prospective) multicenter observational registry of hematological malignancies –acute and chronic leukemias, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, and MM– established and sponsored by ACHO since 2018 to describe the epidemiology of these diseases. Participating researchers and institutions were selected and invited by ACHO. The registry was activated on May 1, 2018 and allowed the inclusion of newly diagnosed patients for a prospective follow-up (incident cases), and of patients diagnosed in the last decade through retrospective data collection.

Data up to July 2020 was included in this analysis, at which time 14 institutions and 24 researchers were actively participating in the registry. (Table 1). The participating institutions searched their institutional databases, provided their registry with an electronic capture tool designed for this purpose that was parameterized to reduce the risk of error in data collection. This process made it possible to capture demographic, clinical, and treatment pattern variables in a standardized manner.

The data audit was carried out by a specialized team, which asked the institutions that included patients to check for non-concordant and extreme data. In case of missing data, the participating institutions were asked to confirm if the absence was due to unavailability. Statistical analysis was performed using the STATA program, version 12.0.

Statistical analysis

Qualitative variables were analyzed using absolute and relative frequencies. Quantitative variables were analyzed for normality using the Shapiro-Wilks test. Normally distributed quantitative variables were summarized using averages and standard deviation, and non-normally distributed quantitative variables were summarized using medians and interquartile ranges.

The variables were also categorized by analyzing the data of the total population and by subgroups classified by age, $\leq$ or $>$ 65 years. A categorization of creatinine, hemoglobin, calcium, albumin, and B2-microglobulin (ß2M) variables was also developed to reflect the definitions of symptomatic MM, as established by the International Myeloma Working Group (IMWG)[12] and the International Staging System (ISS) classification.[13]

In addition to the above, a time-to-event analysis was performed using the Kaplan-Meier method to describe disease-free survival (DFS) and OS. DFS was defined at the discretion of the treating physician. Finally, an exploratory univariate analysis was performed using the log-rank statistical test with OS as the outcome to reduce data bias derived from the retrospective nature of the study, considering OS is an incontrovertible outcome.

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Table 1 RENEHOC's MM Population Covered by Participating Centers

City	Patients(n = 890)	Participating Centers(n = 14)
Bogotá	305 (34.3%)	6
Bucaramanga	216 (24.3%)	1
Cali	199 (22.3%)	3
Medellin	170 (19.1%)	4

Funding

ACHO funded the research through resources obtained from unrestricted research grants from Takeda Pharmaceutical Co, AbbVie Inc, Dr. Reddy's, and Amgen Inc. The sponsors were not involved in the study design, data analysis, and had no access to the data collected.

Ethical aspects

ACHO developed the research protocol, and each researcher was responsible for submitting the study for approval by the participating institution's Research Ethics Committee (REC). A central ethics committee was established at the beginning of the study for researchers without access to one. The protocol recommended that all patients sign an informed consent form. However, considering the retrospective non-interventional characteristics of the study, a waiver of consent was allowed, provided that the ethics committee of each center was informed.

RESULTS

Baseline clinical and demographic characteristics

Between May 2018 and July 2020, 243 hematologist oncologists, practicing in 14 institutions in four main Colombian cities (Bogota, Medellin, Cali, and Bucaramanga), agreed to participate and include their patients in the registry. At the date of the last follow-up, 890 patients with MM had been included, and the median follow-up was 18 months (IQR: 7-42 months). Although RENEHOC allowed the inclusion of patients treated in the last 10 years, patients diagnosed since 2008 were also included. Most of the patients were included since 2015 (503 patients; 56.5%), which explains the short follow-up time.

The baseline characteristics of the patients are shown in Table 2. The median age at diagnosis was 67 years (IQR: 59-75 years), and 47.1% of patients were women. A total of 14.4% were classified as ISS I; 20.2% as ISS II, and 35.1% as ISS III. Most patients had a Durie-Salmon III classification at diagnosis (58.8%). The most frequent defining symptom of MM was pathologic fracture, observed in 42.6% of cases, followed by anemia (37.4%), renal failure (16.4%) and hypercalcemia (11.7%). The most frequent subtype was IgG heavy chain MM, found in 36.9% of the cases.

For this analysis, patients were characterized according to their age (≤ or > 65 years), considering that data on other eligibility criteria for autologous stem cell transplantation (ASCT) was not collected, and that patients under 65 years are, for the most part, candidates for consolidation with high-dose Melphalan.[14] A total of 44.7% of the patients were ≤ 65 years and 55.3% were > 65 years. A higher frequency of pathological fractures (47.5% vs. 38.6%, $P <$ .000) and plasmacytomas (25.4% vs. 18.9%, P : .02) were found in patients aged ≤ 65 years compared to those > 65 years, respectively.

Data on cytogenetic alterations was only available in 17.9% (n = 160) of the population, rendering the sample too small for analysis.

Treatment characteristics and clinical outcomes

A total of 359 transplant-eligible (TE) patients (90%) and 350 transplant non-eligible patients (TNE) (71%) received Bortezomib-based schemes as part of the first-line therapy; 190 TE patients (47.7%) and 111 TNE patients (22.6%) received Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD); 103 TE patients (25.9%) and 90 TNE patients (18.3%) received Bortezomib-Thalidomide-Dexamethasone (VTD); and 32 TE patients (8.0%) and 84 TNE patients (17.1%) received Bortezomib and Dexamethasone (VD). A total of 328 TE patients (82.4%) and 311 TNE patients (63.2%) received triplet combinations, which included Bortezomib or an immunomodulator. When the 2 groups are combined, the overall response rate was considerably higher for VTD at 79.2% (P : .001), followed by 65.4%, and 59.2% for CyBorD, and VD. Figure 1 describes the response rates of the three main treatment regimens in detail.

The analysis of the subgroups according to age showed significant differences in the frequency of treatment use. The use of triple combinations, such as CyBorD and VTD was significantly lower in the group of patients > 65 years of age compared to the group ≤ 65 years of age, respectively 22.6% vs. 47.7% for CyBorD; and 18.3% vs. 25.9% for VTD. VD was the most frequently used regimen in the group of patients > 65 years, compared with the younger group (17.1% vs. 8%;). Other melphalan-based regimens, such as MPT (9.1% vs. 0.2%;) and VMP (10% vs. 0.5%;), were also frequently used in the > 65 aged population.

Two hundred and fifty-two patients (28.3%) were consolidated with PHT in first-line therapy. The majority of patients, 159 (63%), were concentrated in the group of patients aged ≤ 65 years; while 93 patients > 65 years received an intensification with ASCT (37%). Age was the most important factor related to consolidation with ASCT. Of the ≤ 65-year-old patients that were transplant eligible, 39.9% ($P <$ .001) indeed received an ASCT. Of the > 65 group, 18.9% ($P <$ .001) were consolidated by ASCT. The median age was 62 years old (IQR: 56-67).

The majority of patients who received intensification with ASCT (70.2%) continued with maintenance therapy. The most frequently used drug was Lenalidomide (61.6%), followed by Thalidomide (18.1%), and Bortezomib (10.7%). The characteristics of the therapeutic trends and clinical outcomes are summarized in Table 3.

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Table 2 RENEHOC's MM Patients Demographics and Clinical Characteristics at Diagnosis

Variable	Total (n = 890)	≤ 65 years(n = 398; 44.7 %)	>65 years(n = 492; 55.3 %)
Age at diagnosis m (IQR)	67 (59 - 75)	59 (54 - 62)	74 (69 - 79)
Gender			
Female, n (%)	419 (47.1)	186 (46.7)	233 (47.3)
Male, n (%)	471 (52.9)	212 (53.3)	259 (52.7)
Durie-Salmon (%)			
I	43 (4.8)	17 (4.3)	26 (5.3)
II	109 (12.2)	57 (14.3)	52 (10.6)
III	523 (58.8)	233 (58.5)	290 (58.9)
Unknown	215 (24.2)	91 (22.9)	124 (25.2)
ISS (%)			
I	128 (14.4)	61 (15.3)	67 (13.6)
II	180 (20.2)	78 (19.6)	102 (20.7)
III	312 (35.1)	137 (34.4)	175 (35.6)
Not reported	270 (30.3)	122 (30.7)	148 (30.1)
Immunofixation (%)			
IgG	328 (36.9)	144 (36.2)	184 (37.4)
IgA	131 (14.7)	63 (15.8)	68 (13.8)
Negative	24 (2.7)	13 (3.3)	11 (2.2)
Other	95 (10.7)	36 (9.0)	59[12]
Not reported	312[35]	142 (35.7)	170 (34.6)
Signs/symptoms at diagnosis (%)			
Hypercalcemia	104 (11.7)	58 (14.6)	46 (9.4)
Renal failure	146 (16.4)	61 (15.3)	85 (17.3)
Anemia	333 (37.4)	139 (34.9)	194 (39.4)
Pathological fracture	379 (42.6)	189 (47.5)	190 (38.6)
Calcium mg/dL median (IQR)	9.3 (8.6 – 10.2)	9.4 (8.6 - 10.6)	9.2 (8.6 - 10)
≤ 11	465 (52.3)	189 (47.5)	276 (56.1)
> 11	104 (11.7)	58 (14.6)	46 (9.4)
Not reported	321[36]	151 (37.9)	170 (34.5)
Creatinine mg/dL (IQR)	1.01 (0.8 - 1.84)	0.99 (0.78 - 1.8)	1.07 (0.8 - 1.92)
≤ 2	517 (58.1)	226 (56.8)	291 (59.1)
> 2	146 (16.4)	61 (15.3)	85 (17.3)
Not reported (%)	227 (25.5)	111 (27.9)	116 (23.6)
Hemoglobin mg/dL median (IQR)	10.1 (8.3 - 12)	10.2 (8.2 - 12)	10 (8.3 - 11.9)
< 10 (%)	333 (37.4)	139 (34.9)	194 (39.4)
≥ 10 (%)	368 (41.4)	166 (41.7)	202 (41.1)
Not reported (%)	189 (21.2)	93 (23.4)	96 (19.5)
Albumin g/dL (IQR)	3.4 (2.8 - 3.9)	3.4 (2.8 - 4)	3.4 (2.8 - 3.9)
< 3.5 (%)	308 (34.6)	125 (31.4)	183 (37.2)
≥ 3.5 (%)	256 (28.8)	116 (29.2)	140 (28.5)
Not reported (%)	326 (36.6)	157 (39.4)	169 (34.3)
B2-microglobulin mg/L (IQR)	4.2 (2.8 - 7.7)	3.7 (2.5 - 7.8)	4.4 (2.9 - 7.7)
B2-microglobin < 3.5 (%)	216 (24.3)	104 (26.1)	112 (22.8)
B2-microglobulin 3.5 - 5.5 (%)	124 (13.9)	51 (12.8)	73 (14.8)
B2-microglobulin > 5.5 (%)	253 (28.4)	106 (26.6)	147 (29.9)
Not reported (%)	297 (33.4)	137 (34.5)	160 (32.5)

Time-to-event analysis

For time-to-event analyses, the median follow-up was 18 months, and right censoring was performed at the time of the patient's last known follow-up.

Median DFS was 62 months (95% CI: 53-75); the estimated 5 year DFS was 52% (CI 46-56.3). The median OS was 88 months (95% CI: 75-106); the estimated 5 year OS was 62% (CI 56.9-66.8). Figure 2 shows DFS and OS for the entire observed group.

In the exploratory univariate analysis (posthoc), age and intensification with ASCT were variables that were independently associated with better OS. Patients aged ≤ 65 years had a significantly better OS than older patients –median unreached (95% CI:56-99) vs. 75 months (95% CI:42-65) (HR: 0.48. [95% CI: 0.35-0.65 $P < .0001$]), and 5 year overall survival of 70.2% (CI 61.2-77.5) vs. 55.7% (CI 49.3-61.6), respectively. In turn, patients who received consolidation with ASCT had a better OS than those who did not –median 149 months (95% CI: 82-160) vs. 57 months, respectively

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Figure 1 Response rates* to first-line treatment in MM patients according to most common treatment protocols. *Defined by treating physician. CyBORD = Cyclophosphamide, Bortezomib, Dexamethasone; MRD = Complete response with negative minimal residual disease; PD = Progressive disease; PR = Partial Response; sCR = Stringent complete response; SD = Stable disease; VGPR = Very good partial response; VTD = Bortezomib, Thalidomide, Dexamethasone; VD = Bortezomib, Dexamethasone.

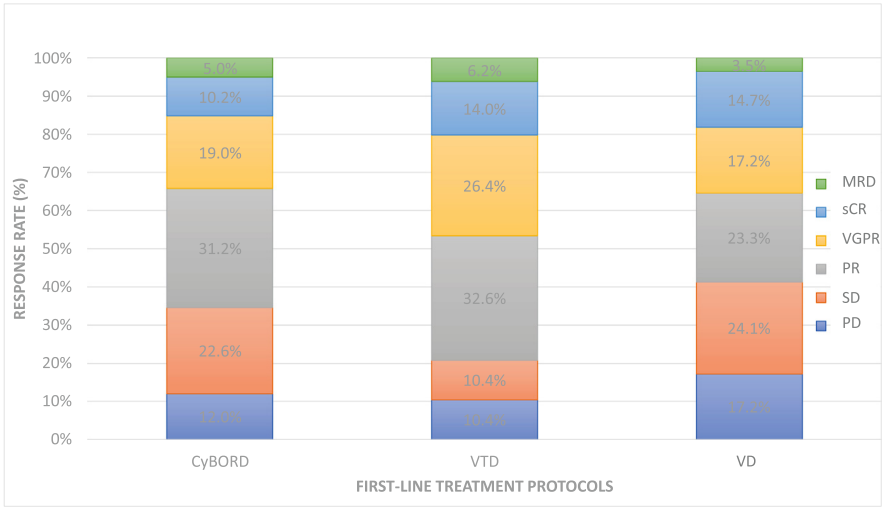

Figure 2 Survival outcomes among RENEHOC's MM patients. (A) Overall survival (OS) among all patients. (B) Disease free survival (DFS) among all patients.

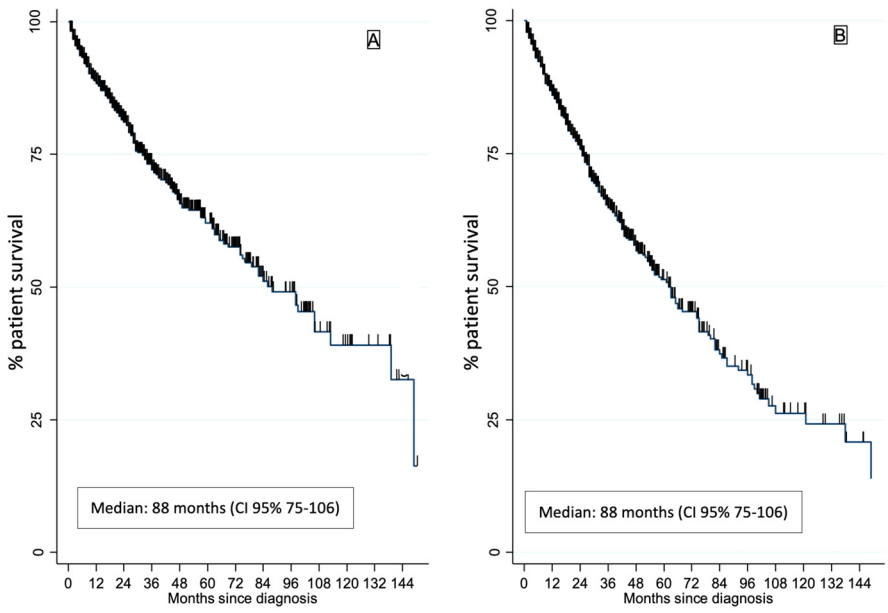

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Table 3 Summary of Therapeutic Trends and Clinical Outcomes

Variable	Total (n = 890)	≤ 65 years(n = 398; 44.7 %)	> 65 years(n = 492; 55.3 %)
First-line treatment, n (%)			
CyBorD	301 (33.8)	190 (47.7)	111 (22.6)
VTD	193 (21.7)	103 (25.9)	90 (18.3)
VD	116[13]	32[8]	84 (17.1)
MVP	51 (5.7)	2 (0.5)	49[10]
MPT	46 (5.2)	1 (0.2)	45 (9.1)
PAD	27[3]	19 (4.8)	8 (1.6)
VAD	23 (2.6)	7 (1.8)	16 (3.3)
VRD	21 (2.4)	13 (3.3)	8 (1.6)
LD	14 (1.6)	2 (0.5)	12 (2.4)
Other	62[7]	17 (4.3)	45 (9.1)
Not reported	36[4]	12[3]	24 (4.9)
CyBorD response, n (%)			
≥ VGPR	103 (34.2)	72 (37.8)	31[28]
PR	94 (31.2)	54 (28.4)	40[36]
SD	68 (22.6)	44 (23.1)	24 (21.6)
PD	36 (12.6)	20 (10.5)	16 (14.4)
VTD response, n (%)			
≥ VGPR	90 (46.6)	46 (44.7)	44 (48.9)
PR	63 (32.6)	34[33]	29 (32.2)
SD	20 (10.4)	12 (11.7)	8 (8.9)
PD	20 (10.4)	11 (10.7)	9[10]
Response to BD, n (%)			
≥ VGPR	41 (35.7)	14 (43.7)	27 (32.2)
PR	27 (23.5)	10 (31.3)	17 (20.2)
SD	28 (24.3)	5 (15.6)	23 (27.4)
PD	20 (17.4)	3 (9.4)	17 (20.2)
Autologous hematopoietic stem cell transplantation, n (%)	252 (28.3)	159 (39.9)	93 (18.9)
Yes	620 (69.7)	232 (58.3)	388 (78.9)
No	18[2]	7 (1.8)	11 (2.2)
Not reported			
Rate by induction treatment, n (%)			
CyBorD	101 (33.6)	74[39]	27 (24.3)
VTD	74 (38.3)	49 (47.5)	25 (27.8)
VD	31[27]	11 (34.2)	20 (23.8)

Abbreviations: CyBorD = cyclophosphamide-bortezomib-dexamethasone; LD = lenalidomide-dexamethasone; MVP = melphalam- bortezomib-dexamethasone MPT = melphalan- prednisonone-thalidomide; PAD = bortezomib- doxorubicin-dexamethasone; PD = progressive disease; PR = progressive response; VTD = bortezomib-thalidomide-dexamethasone; VD = bortezomib- dexamethasone; VAD = vincristine- doxorrubicine- dexamethasone; VRD = bortezomib-lenalidomide- dexamethasone; VGPR = very good partial response; ; SD = stable disease.

(95% CI: 29-43), (HR: 0.26 [95% CI: 0.18-0.36 $P < .0001$]). The estimated 5-year OS was 80.7% (CI 73-86.4) vs. 48.7% (CI 41.8-55.2), for patients who did or did not receive ASCT, respectively. Figure 3 depicts the OS according to age and ASCT status.

DISCUSSION

To our knowledge, this is the largest series of MM patients analyzed in Colombia. Until now, little data was available on the demographics, clinical characteristics, treatment patterns, and outcomes of Colombian patients with this disease. This real-world data is crucial and makes it possible to reveal the country's treatment trends.

The data sources available in Colombia offer fragmented data and it is possible that there is significant underreporting in some cases. Globocan collected data from four population-based registries (Cali, Bucaramanga, Manizales, and Pasto, representing 10% of the population)it w through which it estimated that Colombia would have a MM incidence of 2.8 cases of 100,000 inhabitants in 2018.[3] In the same year, Cuenta de Alto Costo recorded 2,746 prevalent cases, 305 incident cases and 342 deaths due to MM.[9] The MiMENTe (National and Territorial Epidemiology of Multiple Myeloma) study, based on a comparison between RIPS (Individual Health Services Delivery Registry), CAC, and Globocan, reported that between 2009 and 2018, 26,356 patients were diagnosed with MM in Colombia, for a standardized incidence rate of 1.79 cases of 100,000 inhabitants.[15] According to Globocan, the worldwide incidence ranges between < 0.62 and 4.9 of 100,000 inhabitants. One of the limitations of this registry is that, given that RENEHOC does not keep a population registry, and that there is a high population mobility within the Colombian health system, it is not possible compare the incidence with that reported by other data sources.

In this study, the characteristics of 890 Colombian patients with MM treated in 14 centers in 5 cities of the country were reported. One of the most striking findings is that most patients

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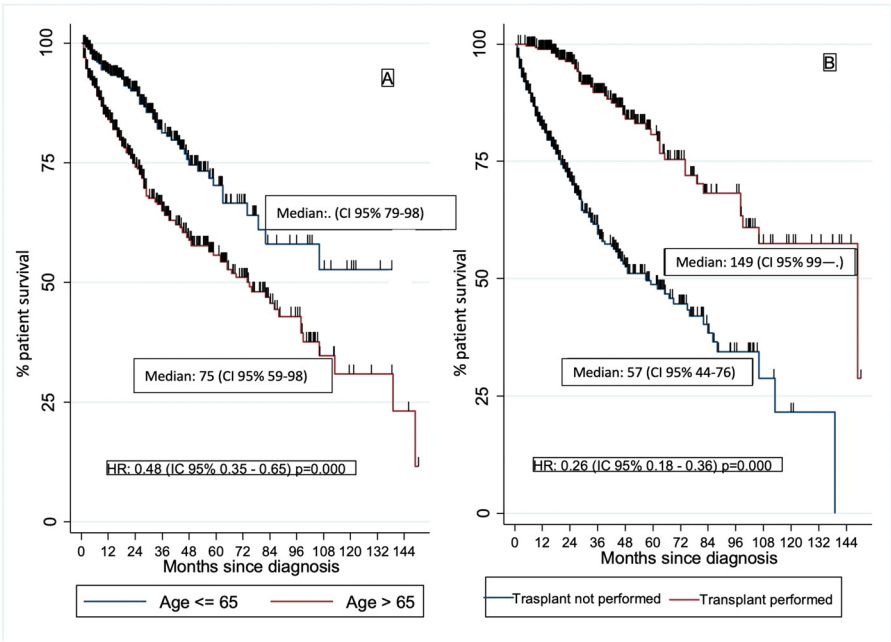
Figure 3 Overall survival by subgroups of interest: age and transplantation, and non-transplantation. (A) Overall survival among patients aged ≤ 65 vs. > 65 years. (B) Overall survival for patients who were consolidated al first line with ASCT vs. No ASCT.



were diagnosed at advanced disease stages (Durie-Salmon, DS IIIA, or IIIB: n = 523; 77.4%), and had a high ISS (ISS III: n = 312; 50.3%), whereas in international descriptions, patients with ISS III represent around 19-28%.[16-18] This finding reflects the magnitude of late diagnosis in the country. According to this data, the median time from symptom onset to diagnosis was 3 months. This highlights the need to overcome the access barriers to healthcare for patients with MM in Colombia, as well as to improve the level of physician training and awareness on plasma cell neoplasms at the primary care level. Further, specialized training is required to order interpret protein electrophoresis in patients with anemia, renal failure, or bone alterations for existing specialists.

Diagnostic delays have been widely linked to a negative impact on the clinical course of MM and represent a global issue.[19] Delays at several points of the patient journey, which lead to more advance stages at the time of diagnosis were also reported by several Latin American countries, such as Mexico, Peru, and Brazil.[20,21] Prolonged delays of >3 months from symptom onset have also been reported in high-income countries such as the United Kingdom[19] and the United States.[22,23]

MM has great heterogeneity in terms of outcomes and there are several relevant prognostic factors to predict disease behavior. Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) have proved to have such a substantial impact[24] that the IMWG recommended their incorporation into the Revised Multiple Myeloma International Staging System (R-ISS).[25] Cytogenetic characterization allows making therapeutic decisions that can change the course of the disease in high-risk patients.[26] For this series, cytogenetic risk characterization was performed only in 17.9% (n = 160), so its influence on patient outcomes could not be established and a treatment strategy adapted to the risk of the disease was not performed. Cytogenic studies are available in Colombia, hematologists are trained to use and order them, and they are technically covered by the public health system. Despite this, many insurers continue to not authorize them due to their high costs. The insurers' responsibility to do so is not always enforced due the limited oversight of the health system.

Although the study design allowed for the inclusion of patients treated within the last decade, 65% of the patients in the series were diagnosed between 2014 to 2018. Therefore, most of the patients in this cohort were usually treated with triplet protocols based on Bortezomib (79%) along with Cyclophosphamide or Thalidomide, even for patients > 65 years. Although better response rates were obtained with the VTD combination (Figure 1), no significant differences in survival were found between the different treatment groups. Compared to multiple clinical studies, overall response rates (PR or higher) appear to be slightly lower in this cohort of patients; 65% for CyBorD, compared to 78.1-83.4%, reported previously,[16,17] and 79.2% for VTD, compared to 85-94%.[16,18,27] This difference could be explained by the observational and retrospective nature of this study, with no selection of the patients compared with the clinical trials that require inclusion and exclusion criteria.

This study has also confirmed the role of first line consolidation with ASCT in improving the outcomes of MM patients, which has

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been demonstrated in multiple prospective clinical trials, even in the context of novel agent-based combinations.[28-33] Although this is not a prospective randomized study and it is not designed to conclude causality in the difference in outcomes, this does represent a relevant finding considering the low access to ASCT observed in this study, even among those who are eligible based on age. In Colombia, factors such us low density of transplant teams,[36] centralization of specialized centers in large cities, lack of funding, and oversaturated programs play an important role in the low ASTC access rate. This low rate of access to ASCT is not only frequent in Colombia. Other real-world experiences report similar data.[1,34,35] However, Colombia's access rate continues to be inferior compared to countries such as Argentina, where almost 70% of patients undergo transplantation.[37]

The median OS in this registry was 88 months, which contrasts with that described in the Pharos registry (The Dutch population based hematological registry for observational studies),[38] where the median for first-line treatment patients was only 37 months. The differences observed in OS were repeated for the analysis of patients $\leq$ 65 years old, with a survival not reached in RENEHOC, compared to 31 months of survival in the Pharos registry. Patients $>$ 65 years of age achieved a survival of 31.9 months in the Pharos registry, compared to 75 months in RENEHOC. These differences could be explained by the short follow-up of this registry, which reflects the fact that most of the patients are concentrated in the last 5 years. Thus, periodic follow-up analyses must be conducted.

This study has other important limitations that should be pointed out. First, it is not a representative sample of the country since it is not a population-based study. The reporting centers are located in four of the country's main cities, and most of them are academic centers where 92% of the patients reported their type of insurance corresponds to the contributory regimen. Although this is an initial effort, it is important to include more centers to fully capture the reality of the more remote areas and patients affiliated to the subsidized regimen. It is widely known that treatment patterns and access to care can differ widely in these contexts, which greatly impacts disease outcomes.[39, 40] A second limitation is the retrospective nature of most of the data obtained from medical records, which is reflected in the lack of important data in some cases. Thus, there may be some confusion in the exact dates of relapses in the retrospective patient cohort. For this reason, we have focused primarily on OS for this analysis, which is an important limitation of the study of a disease characterized by relapses and remissions.

CONCLUSIONS

This is the largest multicenter series reported so far in Colombia, despite the limitations mentioned above. This initiate denotes the reality of MM in Colombia and highlights the access barriers to diagnosis and treatment that patients with MM face, which are reflected in advance stage diagnosis and a low rate of transplants. Despite the fact that most of the novel drugs approved around the world are available in Colombia, a large portion of the population continues to have limited access to these. Consequently, delays in diagnosis and treatment seem to have a negative impact on outcomes. Understanding Colombia's reality is essential to develop strategies and evoke actions to improve the prognosis of these patients. The design of this project, led by ACHO, will allow for continuous data generation, not only in MM, but also in other hematological diseases. Eventually, this project could become a reference for other countries in the region that have similar challenges related to the generation of local data that impacts clinical behaviors in daily practice.

Acknowledgments

ACHO's RENEHOC has received research funding from unrestricted research grants from Takeda Pharmaceutical Co, AbbVie Inc, Dr. Reddy's, and Amgen Inc. The sponsors were not involved in the study design, data analysis, and had no access to the data collected.

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