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RESEARCH ARTICLE

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Treatment Patterns and Clinical Outcomes in Patients with Hodgkin Lymphoma from Saudi Arabia, Türkiye, and South Africa: Subgroup Analysis from the International Multicenter Retrospective B-HOLISTIC Study

Suudi Arabistan, Türkiye ve Güney Afrika'daki Hodgkin Lenfoma Hastalarında Tedavi Modelleri ve Klinik Sonuçlar: Uluslararası Çok Merkezli Retrospektif B-HOLISTIC Çalışmasından Alt Grup Analizi

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Abstract

Objective: B-HOLISTIC was a real-world retrospective study of treatment patterns and clinical outcomes in Hodgkin lymphoma (HL) in regions outside Europe and North America. This subgroup analysis reports findings from Saudi Arabia, Türkiye, and South Africa.

Materials and Methods: Patients aged ≥18 years and diagnosed with stage IIB-IV classical HL receiving frontline chemotherapy (frontline cHL) and/or with relapsed/refractory HL (RRHL) from January 2010 to December 2013 were assessed. The primary endpoint was progression-free survival (PFS) in patients with RRHL.

Results: Overall, 694 patients (RRHL: n=178; frontline cHL: n=653) were enrolled. Among patients with RRHL, >80% received first salvage chemotherapy. The most common first salvage regimens were etoposide, methylprednisolone, cytarabine, and cisplatin in Saudi Arabia (78.3%) and dexamethasone, cytarabine, and cisplatin in Türkiye (36.1%) and South Africa (40%). Median PFS (95% confidence interval [CI]) in the RRHL group was 5.1 (3.0-15.9), 19.7 (7.5-not reached), and 5.2 (1.1-10.1) months in Saudi Arabia, Türkiye, and South Africa, respectively. The 5-year PFS and overall survival (95% CI) rates in patients with RRHL were 33.2% (21.6-45.2) and 78.2% (65.9-86.5) in Saudi Arabia, 42.5% (29.5-54.9) and 79.4% (67.2-87.5) in Türkiye, and 13.1% (4.2-27.0) and 53% (35.5-67.8) in South Africa, respectively.

Conclusion: This study showed that the clinical outcomes in Türkiye and Saudi Arabia were generally comparable with those of Western countries during the study period, although Saudi Arabia had lower PFS rates. Conversely, the clinical outcomes in South Africa were suboptimal, emphasizing the need for novel therapies and improved progression to stem cell transplantation. These data may serve as a control group for future studies in these countries and inform clinical decision-making.

Keywords: Developing countries, Hematological neoplasms, Hematopoietic stem cell transplantation, Real-world evidence, Resource limitations, Treatment outcome

Öz

Amaç: B-HOLISTIC, Avrupa ve Kuzey Amerika dışındaki bölgelerde Hodgkin lenfomanın (HL) tedavi modelleri ve klinik sonuçları üzerine gerçek dünyadan retrospektif bir çalışmaydı. Bu alt grup analizinde Suudi Arabistan, Türkiye ve Güney Afrika'dan bulgular bildirilmektedir.

Gereç ve Yöntemler: Ocak 2010'dan Aralık 2013'e kadar öncül kemoterapi (öncül cHL) ve/veya nükseden/dirençli HL (RRHL) alan evre IIB-IV klasik HL tanısı alan ≥18 yaşındaki hastalar dahil edildi. Birincil sonlanım noktası, RRHL'li hastalarda progresyonsuz sağkalım (PFS) idi.

Bulgular: Total olarak 694 hasta (RRHL: n=178; öncül cHL: n=653) verileri kaydedildi. RRHL'li hastaların %80'inden fazlası ilk kurtarma kemoterapisini aldı. En sık kullanılan ilk kurtarma rejimleri Suudi Arabistan'da (%78,3) etoposid, metilprednizolon, sitarabin ve sisplatin iken Türkiye'de (%36,1) ve Güney Afrika'da (%40) deksametazon, sitarabin ve sisplatin idi. RRHL grubunda medyan PFS (%95 güven aralığı [GA]) Suudi Arabistan, Türkiye ve Güney Afrika'da sırasıyla 5,1 (3,0-15,9), 19,7 (7,5-tamamlanmadı) ve 5,2 (1,1-10,1) ay idi. RRHL hastalarında 5 yıllık PFS ve genel sağkalım (%95 GA) oranları Suudi Arabistan'da %33,2 (21,6-45,2) ve %78,2 (65,9-86,5), Türkiye'de %42,5 (29,5-54,9) ve %79,4 (67,2-87,5) ve Güney Afrika'da sırasıyla %13,1 (4,2-27,0) ve %53 (35,5-67,8) idi.

Sonuç: Bu çalışma, Suudi Arabistan'da PFS oranlarının daha düşük olmasına rağmen, çalışma döneminde Türkiye ve Suudi Arabistan'daki klinik sonuçların genel olarak Batı ülkeleriyle karşılaştırılabilir olduğunu gösterdi. Tersine, Güney Afrika'daki klinik sonuçlar optimalin altındaydı; bu da yeni tedavilere olan ihtiyacı ve kök hücre naklinde ilerlemenin gerektiğini vurguluyordu. Bu veriler, bu ülkelerde yapılacak gelecekteki çalışmalar için bir kontrol grubu görevi görebilir ve klinik karar verme sürecine bilgi sağlayabilir.

Anahtar Sözcükler: Gelişmekte olan ülkeler, Hematolojik neoplazmlar, Hematopoietik kök hücre nakli, Gerçek dünyada verileri, Sınırlı kaynaklar, Tedavi sonucu

Introduction

Advances in the management of Hodgkin lymphoma (HL) have improved clinical outcomes, with over 80% of patients with classical HL (cHL) achieving long-term remission with frontline chemotherapy [1]. Despite this, approximately 30% of patients with newly diagnosed advanced-stage cHL experience treatment failure following first-line therapy [2,3,4]. Current international clinical practice guidelines for HL recommend frontline chemotherapy, with or without radiotherapy, for cHL and salvage chemotherapy followed by stem cell transplantation (SCT) for eligible patients with relapsed/refractory HL (RRHL) [1,2,3,4,5].

Most real-world studies on treatment patterns and clinical outcomes in RRHL are confined to Europe and North America [6,7,8,9,10,11]. However, due to differences in the incidence, characteristics, and clinical outcomes of HL based on age, sex, geographical region, and regional health authority regulations and reimbursement rules, these studies may not be relevant to developing countries. For instance, in Saudi Arabia, Türkiye, and South Africa, patients face unique challenges, including differences in cancer burden by race/ethnicity [12,13,14], limited large-scale real-world data availability, disparities in access to cancer treatments, and limited use of value-based care [15,16,17]. Furthermore, South Africa has a high prevalence of human immunodeficiency virus (HIV), which is known to be associated with an increased risk of HL [17]. Improved understanding of treatment patterns and clinical outcomes in these countries may assist healthcare professionals in clinical decision-making, thereby potentially improving outcomes in patients with HL.

The B-CD30+ HOdgkin Lymphoma International Multi-center Retrospective Study of Treatment PractIces and OutComes (B-HOLISTIC) study described the real-world treatment patterns and clinical outcomes in 1703 patients with RRHL and frontline cHL in 12 countries across East Asia, Latin America, the Middle East, South Africa, Russia, and Australia. This large-scale study

reported lower progression-free survival (PFS) rates in RRHL than those reported in real-world studies from Europe and North America [18]. Here, we report subgroup results of the B-HOLISTIC study to provide real-world evidence on treatment practices and clinical outcomes of HL in Saudi Arabia, Türkiye, and South Africa.

Materials and Methods

Study Design and Population

The detailed methodology of the B-HOLISTIC study (ClinicalTrials.gov, NCT03327571) has been published previously [18]. Briefly, retrospective data were obtained from medical records for patients aged ≥18 years with advanced-stage IIB-IV cHL receiving frontline chemotherapy (frontline cHL) and/or with RRHL between January 2010 and December 2013 at highly specialized treatment centers including hospitals, cancer institutes, and medical centers in Saudi Arabia (three centers), Türkiye (eight centers), and South Africa (seven centers). Data were collected from diagnosis until death or last follow-up, whichever occurred first before March 4, 2020. Patients initially diagnosed with frontline cHL that progressed to RRHL during the study were included in both the RRHL and frontline cHL groups.

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. The study was approved by the relevant independent ethics committee/institutional review boards at each center (Koç University Clinical Research Ethics Committee [decision no: 2017.203.IRB1.026, date: 01.11.2018]; King Fasial Specialist Hospital and Research Centre Ethics Committee [reference no: C380/86/40, date: 29.11.2018]; King Abdullah International Medical Research Center [KAIMRC] [reference no: IRBC/1905/18, date: 29.10.2018]; King Abdullah International Medical Research Center [KAIMRC] [reference no: IRBC/0938/18, date: 22.04.2018]; Pharma-Ethics Independent Research Ethics Committee [reference no: 171118730, date: 08.11.2018]). All patients provided written informed consent according to local regulations.

Outcome Measures

The primary endpoint was PFS in patients with RRHL (time from initiation of first salvage treatment for RRHL to first documentation of relapse, disease progression, or death). Secondary endpoints included PFS in the frontline cHL group (time from initiation of frontline treatment for cHL to the first documentation of relapse, disease progression, or death) and treatment patterns, overall survival (OS), best clinical response (complete remission [CR], partial remission [PR], stable disease, or progressive disease) to frontline treatment or first salvage treatment and adverse events (AEs).

Statistical Analysis

All analyses were performed separately for RRHL and frontline cHL groups for all patients with no missing data. Patient demographic and disease characteristics, treatment patterns, and AEs were presented as descriptive statistics (median and range or interquartile range for continuous variables and frequency counts and percentages for categorical variables). PFS and OS were analyzed using the Kaplan-Meier method. All analyses were conducted using SAS Software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Inclusion

Overall, 694 patients (RRHL: n=178; frontline cHL: n=653) were analyzed in this study (Figure 1). Of these, 66, 36, and 35

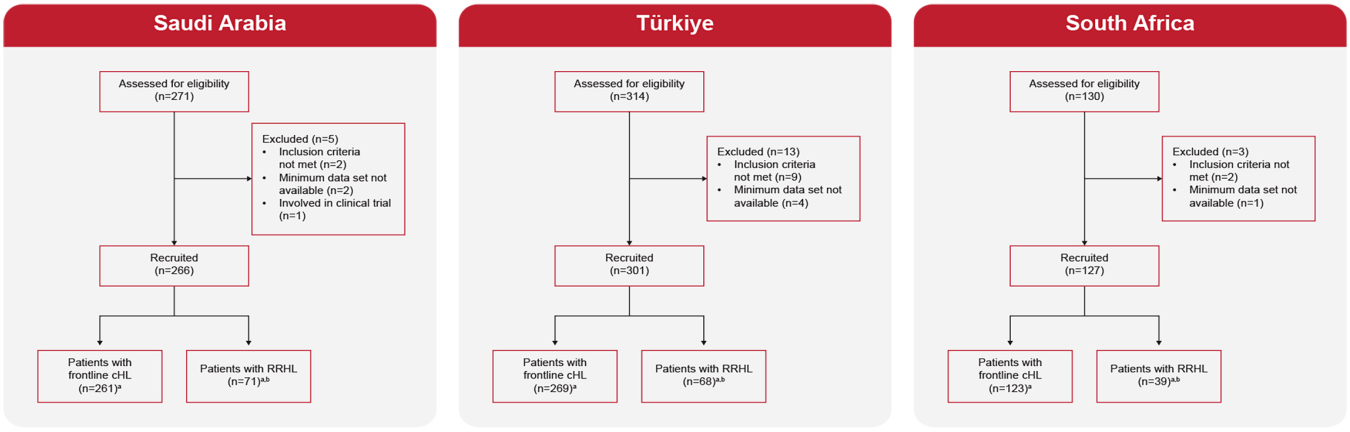


Figure 1. Patient inclusion. [a]: Full analysis set. [b]: Patients in the frontline cHL group who developed relapsed/refractory disease between January 1, 2010, and December 31, 2013: Saudi Arabia (n=66), Türkiye (n=36), and South Africa (n=35). Data collected for these patients were considered for both the frontline cHL and RRHL groups.

cHL: Classical Hodgkin lymphoma; RRHL: relapsed/refractory Hodgkin lymphoma.

patients in the frontline cHL group from Saudi Arabia, Türkiye, and South Africa, respectively, progressed to RRHL and were included in both groups. The reasons for ineligibility included failure to meet the inclusion criteria and non-availability of the minimum data. At the time of the data cut-off date, the median durations of patient follow-up in the RRHL and frontline cHL groups were 5.8 and 6.0 years in Saudi Arabia, 3.6 and 5.4 years in Türkiye, and 1.7 and 5.3 years in South Africa, respectively.

Patient Demographics and Characteristics

In Saudi Arabia, the median (range) age of patients with RRHL and frontline cHL was 26 (18-82) years and 27 (18-81) years, respectively (Table 1). Patients were predominantly Asian and had stage IVB disease. In patients with RRHL and frontline cHL, >70% had B symptoms at diagnosis, >20% had bulky disease of ≥5 cm, and >7% had bone marrow infiltration. At baseline, positron emission tomography/computed tomography (PET/CT) evaluation rates were 41.8% and 64.6% in RRHL and frontline cHL, respectively. Cardiovascular disease was the most common comorbidity (RRHL: 8.5%; frontline cHL: 8.4%).

In Türkiye, the median (range) age of patients with RRHL and frontline cHL was 35 (19-81) years and 36 (18-83) years, respectively (Table 1). Predominantly, patients were Caucasian and had stage IIIB and stage IIB in the RRHL and frontline cHL groups, respectively. At baseline, PET/CT evaluation rates were 31% and 61.3% in RRHL and frontline cHL, respectively. In both groups, >50% had B symptoms at diagnosis, <15% had bulky disease of ≥5 cm, and <15% had bone marrow infiltration. Cardiovascular disease was the most common comorbidity (RRHL: 7.4%; frontline cHL: 4.8%).

In South Africa, the median (range) age of patients with RRHL and frontline cHL was 32 (15-66) years and 35 (18-73) years, respectively (Table 1). Patients were predominantly Caucasian or Black African and presented with high-risk features of advanced disease: >40% had stage IVB disease, >70% had B symptoms at diagnosis, >28% had bulky disease of ≥5 cm, and >20% had bone marrow infiltration. At baseline, PET/CT evaluation rates were <30%. HIV infection was the most common comorbidity (RRHL: 23.1%; frontline cHL: 30.1%).

Treatment Patterns

In the RRHL group, >80% of patients received first salvage chemotherapy, the most common regimens being etoposide, methylprednisolone, cytarabine, and cisplatin in Saudi Arabia (78.3%) and dexamethasone, cytarabine, and cisplatin in Türkiye (36.1%) and South Africa (40%) (Table 2). In Türkiye, one patient received brentuximab vedotin. PET/CT was utilized for response evaluation in 94.4%, 85.3%, and 74.4% of patients in Saudi Arabia, Türkiye, and South Africa, respectively.

Of patients with RRHL eligible for SCT in Saudi Arabia (n=54), Türkiye (n=44), and South Africa (n=30), respectively, 87%, 72.7%, and 66.7% underwent SCT. The most common reasons for not undergoing SCT were loss of response to chemotherapy and patient refusal. Autologous SCT was the preferred consolidation therapy in all three countries. Post-SCT relapse rates were 29.8%, 12.5%, and 50% in Saudi Arabia, Türkiye, and South Africa, respectively.

In the frontline cHL group, all patients received chemotherapy, with doxorubicin, bleomycin, vinblastine, and dacarbazine being the most common regimen (Table 3). One patient from Türkiye received brentuximab vedotin. PET/CT was performed for response evaluation for 86.6%, 90.3%, and 63.4% of patients in Saudi Arabia, Türkiye, and South Africa, respectively.

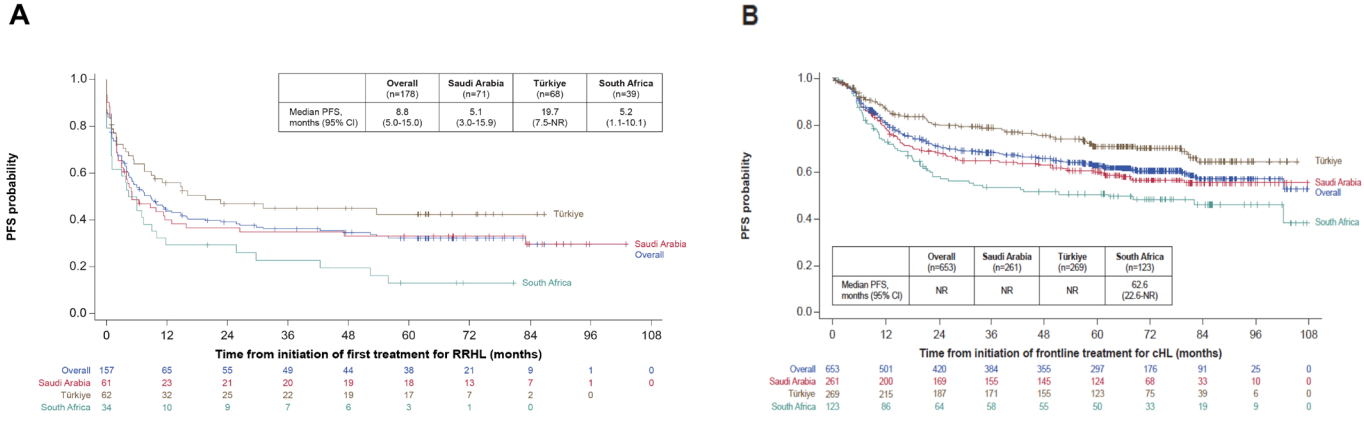


Figure 2. Kaplan-Meier curves for PFS in the MESA region. (A) PFS from initiation of first salvage treatment in the RRHL group[a]. (B) PFS from initiation of frontline regimen in the cHL group. The MESA region includes Saudi Arabia, Türkiye, and South Africa.

[a]: 21 patients with RRHL in the MESA region with missing dates were excluded from the Kaplan-Meier analysis. Median PFS was calculated for all patients.

cHL: Classical Hodgkin lymphoma; CI: confidence interval; NR: not reached; MESA: Middle East and South Africa; PFS: progression-free survival; RRHL: relapsed/refractory Hodgkin lymphoma.

Table 1. Patient demographics and baseline disease characteristics in patients with RRHL and frontline cHL.

	RRHL[a]				Frontline cHL[a]			
Variable	**Overall (n=178)**	**Saudi Arabia (n=71)**	**Türkiye (n=68)**	**South Africa (n=39)**	**Overall (n=653)**	**Saudi Arabia (n=261)**	**Türkiye (n=269)**	**South Africa (n=123)**
Age at diagnosis								
Median age, years (range)	30 (15-82)	26 (18-82)	35 (19-81)	32 (15-66)	32 (18-83)	27 (18-81)	36 (18-83)	35 (18-73)
<60 years, n (%)	161 (90.4)	65 (91.5)	59 (86.8)	37 (94.9)	588 (90.0)	243 (93.1)	230 (85.5)	115 (93.5)
Male, n (%)	107 (60.1)	39 (54.9)	46 (67.6)	22 (56.4)	359 (55.0)	127 (48.7)	167 (62.1)	65 (52.8)
Ethnicity/race, n (%)								
White population/Caucasian	85 (47.8)	0 (0.0)	68 (100.0)	17 (43.6)	300 (45.9)	0 (0.0)	267 (99.3)	33 (26.8)
Asian population	40 (22.5)	37 (52.1)	0 (0.0)	3 (7.7)	163 (25.0)	141 (54.0)	2 (0.7)	20 (16.3)
Black population	15 (8.4)	0 (0.0)	0 (0.0)	15 (38.5)	58 (8.9)	0 (0.0)	0 (0.0)	58 (47.2)
Not reported	13 (7.3)	13 (18.3)	0 (0.0)	0 (0.0)	50 (7.7)	50 (19.2)	0 (0.0)	0 (0.0)
Other	25 (14.0)	21 (29.6)	0 (0.0)	4 (10.3)	82 (12.6)	70 (26.8)	0 (0.0)	12 (9.8)
Ann Arbor stage at first diagnosis, n (%)								
IA-IIA	8 (4.5)	4 (5.6)	3 (4.4)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IIB	20 (11.2)	6 (8.5)	8 (11.8)	6 (15.4)	184 (28.2)	50 (19.2)	96 (35.7)	38 (30.9)
IIIA	25 (14.0)	3 (4.2)	17 (25.0)	5 (12.8)	79 (12.1)	27 (10.3)	44 (16.4)	8 (6.5)
IIIB	33 (18.5)	9 (12.7)	22 (32.4)	2 (5.1)	129 (19.8)	49 (18.8)	59 (21.9)	21 (17.1)
IVA	17 (9.6)	8 (11.3)	5 (7.4)	4 (10.3)	52 (8.0)	17 (6.5)	30 (11.2)	5 (4.1)
IVB	61 (34.3)	35 (49.3)	6 (8.8)	20 (51.3)	209 (32.0)	118 (45.2)	40 (14.9)	51 (41.5)
Stage unknown	14 (7.9)	6 (8.5)	7 (10.3)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PET or PET/CT at baseline[b], n	154	67	58	29	547	226	243	78
n (%)	52 (33.8)	28 (41.8)	18 (31.0)	6 (20.7)	318 (58.1)	146 (64.6)	149 (61.3)	23 (29.5)
Presence of B symptoms at diagnosis, n (%)	115 (64.6)	50 (70.4)	36 (52.9)	29 (74.4)	522 (79.9)	217 (83.1)	195 (72.5)	110 (89.4)
Extranodal involvement at diagnosis, n	177	71	67	39	653	261	269	123
n (%)	83 (46.9)	44 (62.0)	19 (28.4)	20 (51.3)	302 (46.2)	146 (55.9)	84 (31.2)	72 (58.5)
Bone marrow involvement, n (%)								
Negative infiltration	83 (46.6)	36 (50.7)	24 (35.3)	23 (59.0)	347 (53.1)	150 (57.5)	112 (41.6)	85 (69.1)
Positive infiltration	22 (12.4)	5 (7.0)	5 (7.4)	12 (30.8)	82 (12.6)	24 (9.2)	33 (12.3)	25 (20.3)
Not recorded at initial diagnosis	73 (41.0)	30 (42.3)	39 (57.4)	4 (10.3)	224 (34.3)	87 (33.3)	124 (46.1)	13 (10.6)
Bulky disease of ≥5 cm at diagnosis, n (%)	36 (20.2)	16 (22.5)	9 (13.2)	11 (28.2)	210 (32.2)	103 (39.5)	40 (14.9)	67 (54.5)

Table 1. Continued.

Variable	RRHL[a]				Frontline cHL[a]			
	Overall (n=178)	Saudi Arabia (n=71)	Türkiye (n=68)	South Africa (n=39)	Overall (n=653)	Saudi Arabia (n=261)	Türkiye (n=269)	South Africa (n=123)
Most common histological subtype of cHL, n (%)								
Nodular sclerosis cHL	77 (43.3)	37 (52.1)	27 (39.7)	13 (33.3)	410 (62.8)	196 (75.1)	164 (61.0)	50 (40.7)
Mixed cellularity cHL	22 (12.4)	3 (4.2)	14 (20.6)	5 (12.8)	154 (23.6)	29 (11.1)	80 (29.7)	45 (36.6)
Lymphocyte-depleted cHL	3 (1.7)	0 (0.0)	2 (2.9)	1 (2.6)	16 (2.5)	2 (0.8)	7 (2.6)	7 (5.7)
Lymphocyte-rich cHL	4 (2.2)	0 (0.0)	3 (4.4)	1 (2.6)	20 (3.1)	6 (2.3)	11 (4.1)	3 (2.4)
Unknown	3 (1.7)	1 (1.4)	2 (2.9)	0 (0.0)	53 (8.1)	28 (10.7)	7 (2.6)	18 (14.6)
Relapsed or refractory disease, n (%)								
Relapsed only	76 (42.7)	24 (33.8)	41 (60.3)	11 (28.2)	-	-	-	-
Refractory only	69 (38.8)	30 (42.3)	20 (29.4)	19 (48.7)	-	-	-	-
Both relapsed and refractory[c]	33 (18.5)	17 (23.9)	7 (10.3)	9 (23.1)	-	-	-	-
IPS category, n	-	-	-	-	433	193	152	88
Good (0-1), n (%)	-	-	-	-	100 (23.1)	41 (21.2)	46 (30.3)	13 (14.8)
Fair (2-3), n (%)	-	-	-	-	209 (48.3)	93 (48.2)	71 (46.7)	45 (51.1)
Poor (4-7), n (%)	-	-	-	-	124 (28.6)	59 (30.6)	35 (23.0)	30 (34.1)
Unknown, n	-	-	-	-	220	68	117	35
Jousting score[d], n	78	31	32	15	-	-	-	-
0, n (%)	6 (7.7)	1 (3.2)	5 (15.6)	0 (0.0)	-	-	-	-
1, n (%)	32 (41.0)	10 (32.3)	14 (43.8)	8 (53.3)	-	-	-	-
2, n (%)	31 (39.7)	15 (48.4)	11 (34.4)	5 (33.3)	-	-	-	-
3, n (%)	9 (11.5)	5 (16.1)	2 (6.3)	2 (13.3)	-	-	-	-
Unknown, n	31	10	16	5	-	-	-	-

[a]: 66, 36, and 35 patients from Saudi Arabia, Türkiye, and South Africa, respectively, with an initial diagnosis of cHL progressed to RRHL during the study period and were included in both groups. [b]: Only in patients who had at least one PET/CT scan performed during the observational period. [c]: Patients who were both refractory and relapsed are presented as the percentage of patients who were refractory during frontline treatment but relapsed sometime later, after receiving and responding to second-line treatment, or the percentage of patients who responded to frontline treatment but then relapsed and when given second- or third-line treatment were refractory to treatment. [d]: Jousting score parameters are defined as time to relapse of ≤12 months, clinical stage III or IV at relapse, and anemia (hemoglobin of <10.5 g/dL for women and <12 g/dL for men) at relapse. cHL: Classical Hodgkin lymphoma; CT: computed tomography; IPS: International Prognostic Score; PET: positron emission tomography; RRHL: relapsed/refractory Hodgkin lymphoma.

Table 2. Treatment patterns in patients with RRHL.

Variable	Overall[a] (n=178)	Saudi Arabia (n=71)	Türkiye (n=68)	South Africa (n=39)
Patients receiving chemotherapy[b], n (%)	177 (99.4)	71 (100.0)	67 (98.5)	39 (100.0)
Patients receiving first salvage chemotherapy[c], n (%)	155 (87.1)	61 (85.9)	62 (91.2)	32 (82.1)
First salvage chemotherapy[c], n	151	60	61	30
ESHAP, n (%)	55 (36.4)	47 (78.3)	8 (13.1)	0 (0.0)
DHAP, n (%)	35 (23.2)	1 (1.7)	22 (36.1)	12 (40.0)
ICE, n (%)	17 (11.3)	2 (3.3)	12 (19.7)	3 (10.0)
ABVD, n (%)	13 (8.6)	0 (0.0)	9 (14.8)	4 (13.3)
IGEV, n (%)	11 (7.3)	1 (1.7)	1 (1.6)	9 (30.0)
C-MOPP, n (%)	2 (1.3)	0 (0.0)	2 (3.3)	0 (0.0)
Mini-BEAM, n (%)	2 (1.3)	2 (3.3)	0 (0.0)	0 (0.0)
Rituximab, n (%)	2 (1.3)	0 (0.0)	2 (3.3)	0 (0.0)
MINE, n (%)	1 (0.7)	1 (1.7)	0 (0.0)	0 (0.0)
Brentuximab vedotin, n (%)	1 (0.7)	0 (0.0)	1 (1.6)	0 (0.0)
Bendamustine, n (%)	1 (0.7)	0 (0.0)	1 (1.6)	0 (0.0)
BEACOPP, n (%)	1 (0.7)	0 (0.0)	1 (1.6)	0 (0.0)
CHOP, n (%)	1 (0.7)	0 (0.0)	1 (1.6)	0 (0.0)
Other, n (%)	13 (8.6)	7 (11.7)	3 (4.9)	3 (10.0)
Number of chemotherapies, median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
PET or PET/CT scans, n (%)	154 (86.5)	67 (94.4)	58 (85.3)	29 (74.4)
Number of PET or PET/CT scans, median (IQR)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)
CT scans, n	119	42	49	28
n (%)	87 (73.1)	34 (81.0)	41 (83.7)	12 (42.9)
Number of CT scans, median (IQR)	3.0 (1.0-6.0)	2.5 (1.0-7.0)	3.0 (2.0-6.0)	1.0 (1.0-2.5)
RT for first salvage treatment, n (%)	55 (30.9)	26 (36.6)	13 (19.1)	16 (41.0)
Number of RT treatments, median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Patients eligible for SCT, n (%)	128 (71.9)[d]	54 (76.1)	44 (64.7)	30 (76.9)
Patients receiving SCT	99 (77.3)	47 (87.0)	32 (72.7)	20 (66.7)
ASCT	85 (85.9)	40 (85.1)	30 (93.8)	15 (75.0)
Allo-SCT	2 (2.0)	2 (4.3)	0 (0.0)	0 (0.0)
Both	12 (12.1)	5 (10.6)	2 (6.3)	5 (25.0)
Patients who relapsed after SCT	28 (28.3)	14 (29.8)	4 (12.5)	10 (50.0)
Reason for patients eligible for SCT not undergoing SCT, n (%)	29	7	12	10
Loss of response to chemotherapy, n (%)	7 (24.1)	2 (28.6)	1 (8.3)	4 (40.0)
Patient refusal, n (%)	5 (17.2)	4 (57.1)	0 (0.0)	1 (10.0)
Inability to mobilize stem cells, n (%)	2 (6.9)	0 (0.0)	1 (8.3)	1 (10.0)
Cumulative toxicities, n (%)	1 (3.4)	0 (0.0)	0 (0.0)	1 (10.0)
Other, n (%)	1 (3.4)	0 (0.0)	1 (8.3)	0 (0.0)
Unknown, n (%)	13 (44.8)	1 (14.3)	9 (75.0)	3 (30.0)

Table 2. Continued.

Variable	Overall[a] (n=178)	Saudi Arabia (n=71)	Türkiye (n=68)	South Africa (n=39)
Reason for ineligibility for SCT, n	47	17	21	9
Chemo-resistant disease, n (%)	10 (21.3)	7 (41.2)	0 (0.0)	3 (33.3)
Comorbid conditions, n (%)	9 (19.1)	3 (17.6)	2 (9.5)	4 (44.4)
Advanced age, n (%)	3 (6.4)	3 (17.6)	0 (0.0)	0 (0.0)
Patient refusal, n (%)	2 (4.3)	0 (0.0)	2 (9.5)	0 (0.0)
Loss of response to chemotherapy, n (%)	1 (2.1)	0 (0.0)	0 (0.0)	1 (11.1)
Other, n (%)	2 (4.3)	1 (5.9)	1 (4.8)	0 (0.0)
Unknown, n (%)	20 (42.6)	3 (17.6)	16 (76.2)	1 (11.1)

[a]: 66, 36, and 35 patients from Saudi Arabia, Türkiye, and South Africa, respectively, with an initial diagnosis of cHL progressed to RRHL during the study period and were included in both groups. [b]: Following a relapsed/refractory diagnosis. [c]: Following a second relapse/refractory disease. [d]: 123 patients were eligible for SCT and 5 patients initially considered ineligible for SCT subsequently became eligible. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; Allo-SCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; cHL: classical Hodgkin lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; C-MOPP: cyclophosphamide, vincristine, procarbazine, and prednisone; CT: computed tomography; DHAP: dexamethasone, cytarabine, and cisplatin; ESHAP: etoposide, methylprednisolone, cisplatin, and cytarabine; ICE: ifosfamide, carboplatin, and etoposide; IGEV: ifosfamide, gemcitabine, and vinorelbine; IQR: interquartile range; MINE: mesna, ifosfamide, mitoxantrone, and etoposide; Mini-BEAM: carmustine, cytarabine, etoposide, and melphalan; PET: positron emission tomography; RRHL: relapsed/refractory Hodgkin lymphoma; RT: radiotherapy; SCT: stem cell transplantation.

Table 3. Treatment patterns in patients with frontline cHL.

Variable	Overall[a] (n=653)	Saudi Arabia (n=261)	Türkiye (n=269)	South Africa (n=123)
Frontline chemotherapy, n (%)				
ABVD	600 (91.9)	233 (89.3)	251 (93.3)	116 (94.3)
ABVD followed by escalated BEACOPP	19 (2.9)	17 (6.5)	2 (0.7)	0 (0.0)
BEACOPP	7 (1.1)	2 (0.8)	3 (1.1)	2 (1.6)
CHOP	6 (0.9)	0 (0.0)	6 (2.2)	0 (0.0)
DHAP	3 (0.5)	0 (0.0)	3 (1.1)	0 (0.0)
ICE	2 (0.3)	1 (0.4)	0 (0.0)	1 (0.8)
Stanford V	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
C-MOPP	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
IGEV	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Rituximab	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Brentuximab vedotin	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
CVP	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)
Other	38 (5.8)	16 (6.1)	6 (2.2)	16 (13.0)
PET or PET/CT scans, n (%)	547 (83.8)	226 (86.6)	243 (90.3)	78 (63.4)
Number of PET or PET/CT scans, median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	2.0 (2.0-3.0)	2.0 (1.0-4.0)
CT scans, n (%)	429 (65.7)	169 (64.8)	166 (61.7)	94 (76.4)
Number of CT scans, median (IQR)	3.0 (2.0-6.0)	4.0 (2.0-6.0)	3.0 (2.0-5.0)	2.0 (1.0-3.0)
RT for frontline treatment, n (%)	139 (21.3)	69 (26.4)	54 (20.1)	16 (13.0)
Number of RT treatments, median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)

[a]: 66, 36, and 35 patients from Saudi Arabia, Türkiye, and South Africa, respectively, with an initial diagnosis of cHL progressed to RRHL during the study period and were included in both groups. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP: bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride, cyclophosphamide, vincristine sulfate, procarbazine hydrochloride, and prednisone; cHL: classical Hodgkin lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; C-MOPP: cyclophosphamide, vincristine, procarbazine, and prednisone; CT: computed tomography; CVP: cyclophosphamide, doxorubicin, and prednisone; DHAP: dexamethasone, cytarabine, and cisplatin; ICE: ifosfamide, carboplatin, and etoposide; IGEV: ifosfamide, gemcitabine, and vinorelbine; IQR: interquartile range; PET: positron emission tomography; RRHL: relapsed/refractory Hodgkin lymphoma; RT: radiotherapy; Stanford V: doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone.

Table 4. Clinical outcomes in patients with RRHL and patients with frontline cHL.

	RRHL (n=178)[a]				Frontline cHL (n=653)[a]			
Variable	**Overall (n=178)**	**Saudi Arabia (n=71)**	**Türkiye (n=68)**	**South Africa (n=39)**	**Overall (n=653)**	**Saudi Arabia (n=261)**	**Türkiye (n=269)**	**South Africa (n=123)**
PFS, n	157	61	62	34	653	261	269	123
Median, months (95% CI)	8.8 (5.0-15.0)	5.1 (3.0-15.9)	19.7 (7.5-NR)	5.2 (1.1-10.1)	NR	NR	NR	62.6 (22.6-NR)
PFS rate, % (95% CI)								
1-year	43.9 (36.0-51.6)	40.2 (27.8-52.3)	55.9 (42.6-67.3)	29.4 (15.4-45.0)	80.7 (77.5-83.6)	78.4 (72.9-83.0)	86.9 (82.1-90.4)	72.8 (64.0-79.9)
3-year	36.3 (28.7-43.9)	35.0 (23.1-47.0)	45.0 (32.1-57.1)	22.9 (10.5-38.1)	68.3 (64.5-71.8)	64.9 (58.7-70.4)	78.9 (73.3-83.5)	53.4 (44.0-62.0)
5-year	32.3 (24.9-39.9)	33.2 (21.6-45.2)	42.5 (29.5-54.9)	13.1 (4.2-27.0)	62.7 (58.6-66.4)	60.1 (53.7-65.8)	70.9 (64.6-76.3)	50.6 (41.2-59.3)
Median OS, months (95% CI)[b]	NR	NR	NR	64.0 (26.2-NR)	NR	NR	NR	NR
OS rate, % (95% CI)[b]								
1-year	93.8 (89.1-96.5)	94.3 (85.5-97.8)	97.1 (88.8-99.3)	87.2 (71.9-94.5)	94.2 (92.1-95.8)	96.2 (93.0-97.9)	95.4 (92.0-97.4)	87.7 (80.5-92.4)
3-year	78.6 (71.5-84.1)	81.7 (70.0-89.2)	84.6 (73.3-91.4)	62.1 (44.4-75.6)	88.5 (85.7-90.8)	91.7 (87.5-94.5)	91.6 (87.4-94.4)	75.3 (66.4-82.2)
5-year	73.2 (65.7-79.3)	78.2 (65.9-86.5)	79.4 (67.2-87.5)	53.0 (35.5-67.8)	85.3 (82.2-87.9)	89.5 (84.9-92.7)	87.6 (82.6-91.2)	71.5 (62.3-78.9)
Best clinical response[c], n	151	60	61	30	653	261	269	123
Complete remission, n (%)	48 (31.8)	19 (31.7)	24 (39.3)	5 (16.7)	422 (64.6)	188 (72.0)	178 (66.2)	56 (45.5)
Partial remission, n (%)	44 (29.1)	17 (28.3)	15 (24.6)	12 (40.0)	121 (18.5)	27 (10.3)	54 (20.1)	40 (32.5)
Stable disease, n (%)	10 (6.6)	5 (8.3)	3 (4.9)	2 (6.7)	17 (2.6)	6 (2.3)	4 (1.5)	7 (5.7)
Progressive disease, n (%)	37 (24.5)	18 (30.0)	10 (16.4)	9 (30.0)	42 (6.4)	26 (10.0)	10 (3.7)	6 (4.9)
Unknown, n (%)	12 (7.9)	1 (1.7)	9 (14.8)	2 (6.7)	32 (4.9)	5 (1.9)	16 (5.9)	11 (8.9)

[a]: 66, 36, and 35 patients from Saudi Arabia, Türkiye, and South Africa, respectively, with an initial diagnosis of cHL progressed to RRHL during the study period and were included in both groups. [b]: From diagnosis of cHL. [c]: Following first salvage treatment for RRHL and following frontline treatment for cHL. cHL: Classical Hodgkin lymphoma; CI: confidence interval; NR: not reached; OS: overall survival; PFS: progression-free survival; RRHL: relapsed/refractory Hodgkin lymphoma.

Clinical Outcomes

In the RRHL group, the median PFS (95% confidence interval [CI]) was 5.1 months (3.0-15.9) in Saudi Arabia, 19.7 months (7.5-not reached [NR]) in Türkiye, and 5.2 months (1.1-10.1) in South Africa (Table 4; Figure 2A). The PFS rates were low in Saudi Arabia, Türkiye, and South Africa, with 5-year PFS rates of 33.2%, 42.5%, and 13.1%, respectively. Median OS (95% CI) was NR in Saudi Arabia and Türkiye and was 64 months (26.2-NR) in South Africa. The 5-year OS rates were 78.2%, 79.4%, and 53% in Saudi Arabia, Türkiye, and South Africa, respectively. Following first salvage chemotherapy, 31.7%, 39.3%, and 16.7% of patients with RRHL achieved CR in Saudi Arabia, Türkiye, and South Africa, respectively.

In the frontline cHL group, median PFS (95% CI) was NR in Saudi Arabia and Türkiye and was 62.6 months (22.6-NR) in South Africa (Table 4; Figure 2B). The PFS rates in patients with frontline cHL were higher than those in patients with RRHL. Median OS in the frontline cHL group was NR in any of the countries. The 5-year OS rates were 89.5%, 87.6%, and 71.5% in Saudi Arabia, Türkiye, and South Africa, respectively. Following frontline treatment, 72%, 66.2%, and 45.5% of patients achieved CR in Saudi Arabia, Türkiye, and South Africa, respectively.

Safety Outcomes

In both groups, more than 30% of patients experienced AEs: Saudi Arabia (RRHL: 56.3%; frontline cHL: 52.9%), Türkiye (RRHL: 33.8%; frontline cHL: 31.2%), and South Africa (RRHL: 59%; frontline cHL: 70.7%). Neutropenia was the most common treatment-related AE in frontline cHL, affecting 24.5%, 3%, and 29.3% of patients in Saudi Arabia, Türkiye, and South Africa, respectively. Treatment-related serious AEs were reported in both groups: Saudi Arabia (RRHL: 12.7%; frontline cHL: 14.6%), Türkiye (RRHL: 2.9%; frontline cHL: 3.7%), and South Africa (RRHL: 15.4%; frontline cHL: 17.9%).

Discussion

This B-HOLISTIC subgroup analysis reports real-world treatment patterns and clinical outcomes in patients with HL in Saudi Arabia, Türkiye, and South Africa. While treatment patterns generally aligned across the three countries and with the current treatment recommendations [1,5], the clinical outcomes varied among the countries. Although PFS was lower in Saudi Arabia, the OS and response rates were generally comparable to the European and North American data [7,9,10,11]. The clinical outcomes reported in Türkiye were generally comparable to the European and North American data [7,9,10,11]. Conversely, in South Africa, the PFS and response rates were lower and OS rates were comparable to those reported in Europe and North America [7,9,10,11].

The demographic and disease characteristics of patients with RRHL and frontline cHL observed in this subgroup analysis were largely in line with studies from Saudi Arabia [14,19,20], Türkiye [21], and South Africa [13,22] during a similar period. The common frontline and salvage chemotherapy regimens reported in these countries were generally consistent with those reported in real-world studies from other developing and developed countries [6,9,23,24]. Recent studies report improved patient outcomes with novel agents, such as checkpoint inhibitors and brentuximab vedotin, as part of salvage regimens in RRHL [6,7,25,26,27,28,29,30]. However, the use of novel agents was low among the three countries at the time of the current study, possibly due to significant barriers that delayed patient access to treatment, such as drug shortages and costs [16,17]. Furthermore, lack of reimbursement for novel agents in Türkiye may have affected patient access. Although PET/CT scans are recommended for initial staging of HL, evaluating treatment response, and informing treatment decisions [1,31], baseline PET or PET/CT scans were performed for only one-third of patients with RRHL across all three countries in the current study, with the proportion being lowest in South Africa. This may be due to limited PET-guided treatment availability during 2010-2013, with its use still low in many developing countries, including South Africa [32,33,34]. To date, PET/CT-guided HL treatment remains underutilized in South Africa due to limited scanner availability, high costs, shortage of qualified personnel, and non-reimbursement by medical insurance plans [31,35].

In this study, of the three countries assessed, South Africa had the worst clinical outcomes. The limited use of PET-guided treatment may have contributed to treatment outcome uncertainties, resulting in low CR and PR rates. Besides limited use of novel agents and PET-CT, these outcomes were likely influenced by low SCT rates and worse baseline disease burden (comorbid HIV infection in one-third of patients and increased incidence of bone marrow infiltration, bulky disease, and B symptoms). Patients with HIV-associated HL frequently present with Epstein-Barr virus infection and tuberculosis co-infection; these patients often have a higher disease burden and poor prognostic factors [36,37,38]. The National Comprehensive Cancer Network Guidelines encourage HIV testing in at-risk patients [1] and combination antiretroviral therapy for HIV-associated HL has improved outcomes [36]; however, social stigma around HIV can lead to reluctance in seeking medical help [22], resulting in delayed diagnosis and treatment initiation [39]. Besides improvements in HIV treatment uptake [40] and improved availability of a once-a-day antiretroviral drug over the past decade [41], the treatment landscape of HL in South Africa remains relatively unchanged due to inadequate resources, socioeconomic challenges, and lack of national cancer control plans facilitating cancer survivor follow-up care [42,43]. Moreover, large-scale global studies may not accurately represent hematological malignancy cases across Africa due to data quality issues and underdiagnosis [17,43]. Recent reports

from South Africa, although scarce, suggest that treatment outcomes in HL possibly remain poor due to delayed diagnosis, concomitant HIV infection, and poor access to novel treatments [44,45,46]. The South African data from this subgroup analysis can help inform clinical decision-making until a true picture of HL management practices and outcomes in South Africa becomes available. Strategies to improve the uptake of novel treatments in HL and access to SCT in South Africa warrant further research.

Although PFS was lower in Saudi Arabia, the OS and response rates were generally comparable to the European and North American data [7,9,10,11]. Loss of patients to follow-up and inclusion of untreated patients in the final analysis may have influenced the poor median PFS in Saudi Arabia. The favorable OS rates reported in Saudi Arabia in this study align with a retrospective Saudi Arabian study (1997-2012) reporting a 3-year OS rate of 93% in patients with HL [20]. The median PFS reported in Türkiye in this study was generally comparable to the European and North American data [7,9,10]. The favorable clinical outcomes in Türkiye reported in this study may be attributable to increased SCT rates [47], improved social health insurance coverage [48], and a lower proportion of patients with advanced-stage disease, B symptoms, extranodal disease, and bulky disease. Recent reports from Saudi Arabia and Türkiye have reported the use of novel agents as part of salvage regimens or post-SCT consolidation in patients with RRHL, with improved clinical outcomes [26,49,50,51,52,53]. Together, this evidence suggests promising progress in the treatment landscape in Saudi Arabia and Türkiye. Further improvements in clinical outcomes in HL in these countries may be achievable through adequate testing, the continued use of novel agents as part of salvage and/or consolidation therapy along with SCT, and tailored treatment plans to suit patient needs.

Study Limitations

The limitations of the B-HOLISTIC study, as previously described [18], should be considered when interpreting findings from this subgroup analysis. Due to its retrospective nature, this study may not accurately reflect the current treatment landscape of HL. Since patients with an initial diagnosis of cHL who progressed to RRHL during the study period were included in both groups, the findings should be interpreted carefully. When comparing data from real-world studies, it is important to consider differences in definitions of patient demographics, disease burden, treatment patterns, treatment availability, and outcome definitions. Additionally, the AEs reported in this study may have excluded common AEs, such as alopecia or nausea, which are not formally recorded. Furthermore, although beyond the scope of the current study, additional subgroup analyses, including but not limited to those based on HIV status and patient age, may provide valuable insights in the future.

Conclusion

This B-HOLISTIC subgroup analysis showed that, despite similar treatment patterns, the clinical outcomes varied between Saudi Arabia, Türkiye, and South Africa. The clinical outcomes in South Africa were suboptimal, emphasizing the need for evidence-based novel therapies, improved progression to SCT, and better patient access to healthcare facilities. Additionally, these findings may guide future research and inform clinical decision-making in these countries.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. The study was approved by the relevant independent ethics committee/institutional review boards at each center (Koç University Clinical Research Ethics Committee [decision no: 2017.203.IRB1.026, date: 01.11.2018]; King Fasial Specialist Hospital and Research Centre Ethics Committee [reference no: C380/86/40, date: 29.11.2018]; King Abdullah International Medical Research Center [KAIMRC] [reference no: IRBC/1905/18, date: 29.10.2018]; King Abdullah International Medical Research Center [KAIMRC] [reference no: IRBC/0938/18, date: 22.04.2018]; Pharma-Ethics Independent Research Ethics Committee [reference no: 171118730, date: 08.11.2018]).

Informed Consent: All patients provided written informed consent according to local regulations.

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Footnotes

Authorship Contributions

Concept: D.B., M.A-M., Z.H., B.F.; Design: D.B., M.A-M., Z.H., B.F.; Data Collection or Processing: D.B., S.A., S.R., M.P., D.M., J.P.S., L.M.D., Z.M., M.A-M., M.A., M.S.R., I.M., S.K.B., C.B., G.S., B.F.; Analysis or Interpretation: D.B., M.A-M., M.A., Z.H.; Literature Search: D.B., S.A., S.R., M.P., D.M., J.P.S., L.D., Z.M., M.A-.M., M.A., M.S.R., I.M., S.K.B., C.B., G.S., Z.H., Y.P., B.F.; Writing: D.B., S.A., S.R., M.P., D.M., J.P.S., L.D., Z.M., M.A-M., M.A., M.S.R., I.M., S.K.B., C.B., G.S., Z.H., Y.P., B.F.

Conflict of Interest: David Brittain received honoraria from Takeda Pharmaceuticals, Roche, AbbVie, Merck Sharp and Dohme, Amgen, Hetero, AstraZeneca, and Janssen and serves as a member of advisory committees for Takeda Pharmaceuticals, Hetero, and Janssen. Jaimendra Prithipal Singh received consulting fees from Roche, Janssen, and Novartis and serves as a member of the advisory boards of Janssen, Novartis, and Roche. Lydia Dreosti received honoraria from Janssen, Eli Lilly, Novartis, Roche, and Merck Sharp and Dohme as speaker fees and serves as a member of advisory committees for Roche and Eli Lilly. Mubarak Al-Mansour received honoraria from Roche, Janssen, Bristol Myers Squibb, and AstraZeneca and serves as a member of a board of directors or advisory committee for Takeda Pharmaceuticals. Mohsen Alzahrani received honoraria from Takeda Pharmaceuticals, Kite Pharma, Novartis, and Merck Sharp and Dohme and serves as a member of an advisory committee for Takeda Pharmaceuticals. Sevgi Kalayoğlu Beşışık serves as a member of advisory committees for Novartis, Takeda Pharmaceuticals, Amgen, and Janssen. Güray Saydam received honoraria from Novartis, Alexion, Janssen, Bristol Myers Squibb, and Amgen and serves as a member of an advisory committee for Novartis. Zhongwen Huang is an employee of Takeda Pharmaceuticals and holds shares in the company. Yacob Pinchevsky was an employee of Takeda Pharmaceuticals at the time of the study. Burhan Ferhanoğlu serves as a member of the board of directors or advisory committee for Takeda Pharmaceuticals, Janssen, and Pfizer. Saad Akhtar, Sylvia Rodrigues, Moosa Patel, Dhaya Moodley, Zainab Mohamed, M. Shahzad Rauf, Irfan Maghfoor, and Can Boğa have nothing to disclose.

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Data Availability: The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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