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Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: A population-based registry study

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Abstract

Cervical cancer is the leading cause of cancer death in African women. We sought to estimate population-based survival and evaluate excess hazards for mortality in African women with cervical cancer, examining the effects of country-level Human

Abbreviations: AFCRN, African Cancer Registry Network; ASRS, age-standardised relative survival; CI, confidence interval; DCO, death-certificate-only; FIGO, International Federation for Gynaecology and Obstetrics; HDI, Human Development Index; IARC, International Agency for Research on Cancer; ICD-10, International Classification of Disease 10th revision; ICSS, International Cancer Survival Standard; KM, Kaplan-Meier; LFU, loss to follow-up; MV, morphologically verified; PBCR, population-based cancer registry; RS, relative survival; SSA, sub-Saharan Africa; TNM, Tumour Node Metastasis; WHO, World Health Organisation.

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Development Index (HDI), age and stage at diagnosis. We selected a random sample of 2760 incident cervical cancer cases, diagnosed in 2005 to 2015 from 13 population-based cancer registries in 11 countries (Benin, Cote d'Ivoire, Ethiopia, Kenya, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Uganda and Zimbabwe) through the African Cancer Registry Network. Of these, 2735 were included for survival analyses. The 1-, 3- and 5-year observed and relative survival were estimated by registry, stage and country-level HDI. We used flexible Poisson regression models to estimate the excess hazards for death adjusting for age, stage and HDI. Among patients with known stage, 65.8% were diagnosed with Stage III-IV disease. The 5-year relative survival for Stage I-II cervical cancer in high HDI registry areas was 67.5% (42.1-83.6) while it was much lower (42.2% [30.6-53.2]) for low HDI registry areas. Independent predictors of mortality were Stage III-IV disease, medium to low country-level HDI and age >65 years at cervical cancer diagnosis. The average relative survival from cervix cancer in the 11 countries was 69.8%, 44.5% and 33.1% at 1, 3 and 5 years, respectively. Factors contributing to the HDI (such as education and a country's financial resources) are critical for cervical cancer control in SSA and there is need to strengthen health systems with timely and appropriate prevention and treatment programmes.

KEYWORDS
cervical cancer, stage, Human Development Index, survival, Africa

1 | INTRODUCTION

Cervical cancer is the most common cause of cancer death in African women.[1] Women with cervical cancer in sub-Saharan Africa (SSA) are frequently diagnosed at advanced stages[2-4], have poor access to appropriate diagnosis and treatment[5] and have prolonged treatment waiting times[6] leading to poor survival outcomes.[5] Several observational cohort and case-series studies have described the poor survival in women with cervical cancer in SSA,[3,4,6] however, these estimates are not always generalizable to the population at large. Survival is the complex result of several factors such as the availability of screening programmes, socioeconomic factors, stage at diagnosis, availability of treatment infrastructure and health personnel to give timely and appropriate care[4-6] and co-morbidities such as HIV.[7] Data from population-based cancer registries (PBCRs) provide an opportunity to calculate generalizable survival estimates, which approximate real-life scenarios in the context of their respective registry areas. The role of the PBCR has evolved beyond basic reporting of incident cancers to include epidemiological research[8] and monitoring population-based indicators of cancer control such as incidence, survival and mortality[9] to inform evidence-based cancer policies.[8]

The African Cancer Registry Network (AFCRN) is the regional cancer registration hub comprising a network of PBCRs in Africa, in collaboration with the International Agency for Research on Cancer (IARC).[10] In addition to strengthening and establishing population-based cancer registration in the region, the AFCRN provided a harmonised platform to study cervical cancer survival across 13 PBCRs from 11 SSA countries. In the current study, we sought to estimate observed and relative population-based survival and evaluate excess hazards for mortality in African women with cervical cancer, examining the effects of age and stage at diagnosis on survival at 1, 3 and 5 years after diagnosis.

What's new?

Cervical cancer is the leading cause of cancer deaths among women in Africa. Some parts of Africa are more highly developed than others, where "development" is measured by life expectancy, *per capita* income, and education levels. Here, the authors compare cervical cancer survival rates across 13 population-based cancer registries in 11 African countries, taking development into account. Overall, 3 year survival rates were 44.5%, compared to 73.7% in the United States. In countries with a medium or low development index, patients were 4 times more likely to die than those in countries with a high development index.

2 | METHODS

2.1 | Study population

Cervical cancer data were obtained from 13 population-based AFCRN member registries: Cotonou (Benin), Abidjan (Cote d'Ivoire), Addis Ababa (Ethiopia), Eldoret (Kenya), Nairobi (Kenya), Mauritius, Maputo (Mozambique), Namibia, Eastern Cape (South Africa), Seychelles, Kampala (Uganda), Bulawayo (Zimbabwe) and Harare (Zimbabwe). We selected a random sample of invasive cervical cancer cases (ICD-10: C53) diagnosed in black African women between 2005 and 2015 from each registry. A random sample was taken from each individual registry. Some registries had greater capacity to follow-up patients than others. The number of cases sampled per registry was determined by the ease of obtaining follow-up information. With passive follow-up, a larger number of cases could be included, when active methods were used fewer cases could be included. All patients had to be aged 15 years or older at time of diagnosis. We included primary cervical cancer diagnoses only, thus we excluded cervical cancer recurrences but included patients with another cancer at a different site. Cases registered based on information from a death certificate only (DCO) were excluded. We measured survival time from date of cancer diagnosis to the earliest of (a) date of last contact and (b) date of death or date of database closure (December 31, 2017).

2.2 | Covariates

2.2.1 | Vital status

Vital status was ascertained through a combination of active and passive follow-up methods. All registries used active follow-up methods except Mauritius where vital status was ascertained only through record linkage to the death registry. The completeness of death registration with cause-of-death information in Mauritius was estimated to be 100% in 2012.[11] Patients who were not linked to the death registry in Mauritius, were assumed to be still alive. In Mauritius, we conducted a 10% random check on the supposedly alive cases (with no matching death certificate) and verified on the individual case notes at the radiotherapy department to check whether they were still attending outpatients department there as of December 31, 2013, and found that all 10% were still alive. In all other registries, clinical records were reviewed to determine vital status and date of last contact. Where this information was not available from record review, any documented telephone number was used to contact the patient or their next of kin. Registry staff conducted home visits to trace patients who could not be contacted by telephone. Patients whose vital status was still unknown after these procedures were deemed "lost-to follow-up".

2.2.2 | Stage at diagnosis

Information on clinical stage of cervical cancer cases was abstracted from patient records by registrars at the time of registration. Many registries had recorded stage according to the four categories (I-IV) of the International Federation of Gynaecology and Obstetrics (FIGO) staging system.[12] Others had used the T, N and M system of the Union for International Cancer Control[13]: this was converted to the equivalent FIGO stage. Occasionally only "summary stage"[14] was available in the registry record. Stage at diagnosis was classified as Stage I-II and Stage III-IV. We created a separate "Missing Stage" category for records without staging information. Information on stage at diagnosis was not available for Mauritius and Kampala registries.

2.2.3 | Histological subtypes

Among patients with histologically verified cancers, we classified them according to the following IARC groupings[15] using ICD-O-3 morphological codes: squamous cell carcinoma (morphological codes 8050-8078 and 8083-8084), adenocarcinoma (8140-8141, 8190-8211, 8230-8231, 8260-8265, 8310, 8380, 8382-8,384, 8440-8490, 8570-8574 and 8576), unspecified carcinoma (8010-8035), other specified carcinoma (such as 8560, 8430 and 8950), sarcoma (8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9120-9133, 9150 and 9540-9581) and unspecified malignant neoplasm (8000-8005).

2.2.4 | HDI classification

The HDI is a combined score of life expectancy, education and *per capita* income indicators used for ranking the level of development of countries.[16] Using the 2015 Human Development Report,[16] we assigned HDI to the included countries and categorised them into high, medium and low HDI. The cut-off points were HDI of less than 0.550 for low human development, 0.550 to 0.699 for medium human development, 0.700 to 0.799 for high human development and 0.800 or greater for very high human development.[16] We used these HDI categories to compare survival across the different registry areas.

2.2.5 | Country-level screening coverage

Country-level screening coverage for each country was extracted from the Human Papillomavirus and Related Diseases Report.[17] The Women's Health Survey 2003 (WHS 2003) country-level screening coverage estimates for women in urban areas aged 18 to 69 years were used for registries in Cote d'Ivoire, Ethiopia, Kenya, Mauritius, Namibia and Zimbabwe.[17] For South Africa, the WHS 2003 screening coverage for rural women aged 18 to 69 years was used for the rural Eastern Cape Cancer Registry. For Seychelles, the National Health Survey of Noncommunicable Diseases (2013 and 2014) was used and for Mozambique, screening coverage estimates were from the Strategic Health Plan (PESS) 2014 to 2019.[17] There was no available screening information for Uganda and Benin.

Screening coverage was categorised into the following categories; <5%, 5 < 15%, 15% or more and "No screening data available".

2.3 | Statistical analyses

2.3.1 | Survival

For each registry, we present the total number of cervical cancer cases reported in the respective study periods, the size of the random sample, the sampling fraction and the proportion of included and excluded cases in the survival analysis. DCO and cases with no follow-up information or with inconsistent follow-up dates were excluded. We also reported data quality indicators such proportions of DCO and morphologically verified cancers.

We applied the semicomplete approach[18] and estimated observed survival probabilities at 1, 3 and 5 years of follow-up. We plotted Kaplan-Meier (KM) curves of overall observed survival and also stratified by the country-level Human Development Index (HDI) for 2015,[16] age-group, morphological subtype and FIGO[12] stage at diagnosis.

To adjust for mortality due to other causes, we calculated Ederer II relative survival estimates at 1, 3 and 5 years after diagnosis using the "strs" command in STATA 15. Relative survival is the ratio of the observed (all-cause) survival to the expected survival.[19] Country-specific expected survival probabilities were calculated from age-specific life tables of women in the general population for each registry area[18] for the period under study.

Direct age-standardisation was done using International Cancer Survival Standard-2 weights for cancer sites with broadly constant incidence by age.[20]

2.3.2 | Lifetables

Five-year age-specific death rates by sex and country were obtained from the WHO Mortality database[21] and expanded using a Poisson regression model to create a complete lifetable by 1 year age-group and year of diagnosis. More details on the life table modelling are included in Supporting Information.

2.3.3 | Assessing loss to follow-up

We reported the proportion of loss to follow-up (LFU) at 1, 3 and 5 years after diagnosis. Whenever LFU exceeds 10% in a survival study, it is desirable to investigate whether such censoring is random or informative.[18] We used a Cox model to test the randomness of LFU and to investigate whether LFU was associated with age or stage at diagnosis.

2.3.4 | Modelling excess hazards

We used flexible Poisson regression models with restricted cubic splines[22] to model excess mortality in cervical cancer patients. We split follow-up time into monthly intervals assuming the baseline hazard to be constant within each monthly interval. We then generated restricted cubic splines using the "rcsgen" Stata command,[22] and fitted univariable and multivariable Poisson models by stage, country HDI and country-level cervical screening coverage and age at diagnosis. We also explored the interaction between country HDI and stage at diagnosis (Tables S4 and S5).

2.3.5 | Estimation of average survival

The estimate of the average survival for the 11 countries was calculated as the mean of the survival in each, weighted by the number of cervix cancer patients included in the dataset for that country, as a proportion of the total number of cases, from Globocan 2018.[1] This simply reflects the different size of the datasets from each country. It does not assume that regional survival figures can be extrapolated nationally.

3 | RESULTS

The 2760 cases were randomly selected from those recorded in black African women in 13 PBCRs in 11 countries of SSA, representing 52.6% of all cervical cancer cases registered during the study period in these registries. Of the 13 registries, Mauritius, Seychelles and Namibia had national coverage, Eastern Cape covered a rural area and the rest were urban registry areas. We excluded 25 women (0.9%) with no follow-up information or with inconsistent follow-up dates, for a final dataset of 2735 (Table 1). The 2735 women included in the survival analysis contributed a total of 5317.8 person-years, with a median (IQR) follow-up of 0.7 years (0.05-3.5). There were a total of 1158 deaths during the study period. Our sampling fraction ranged from 14.1% in Bulawayo to 100% in Eastern Cape, Maputo, Mauritius and Seychelles. All registries had morphological verification (MV %) for at least 74% of cancers, except for Bulawayo, Kampala and Abidjan (Table 1).

The average age at cervical cancer diagnosis in the study cohort was 53.4 years (standard deviation ±14.5), ranging from 44.9 years in Kampala, Uganda to 56.1 years in the Eastern Cape, South Africa (Table 2). The age distribution at diagnosis varied by registry and is presented in Figure S1. The median duration of follow-up ranged from 1.2 months in Bulawayo, Kampala, Maputo and Eldoret to 5.7 years in Mauritius. Staging information was only available for 45% of all patients, with all registries having some staging information except for Mauritius and Kampala. Seychelles and Nairobi (of high and medium HDI respectively), had the highest proportions of early stage disease diagnosis (Figure S2). Nearly two-thirds (65.8%) of patients with known stage were diagnosed at FIGO Stages III and IV.

The majority (89.4%, 2444) of patients had histological confirmation of cervical cancer. Of these, 71.9% (1758) were squamous cell carcinomas, 4.6% (112) were adenocarcinomas, 0.2% (4) were sarcomas, 1.7% (42) were unspecified malignant neoplasms, 20.5% (502) were unspecified carcinomas and 1.1% (26) were other specified carcinomas. There were no differences in cervical cancer survival by morphological subtype (Figure S6).

TABLE 1 Total number of cervical cancer diagnoses, included and excluded cases, and data quality indicators by population-based cancer registry

Country	HDI 2015[a]	Cervical Screening Coverage in women aged 18 -69[b]	Registry	Period of diagnosis	Total number of cervical cancer cases during study period	Histologically verified (%)	No. (%) of DCO during study period excluded	Number of randomly sampled cases for survival study	Sampling fraction (%)	Included for survival analyses n (%)	No. excluded (%)
Benin	Low	—	Cotonou	2013-2014	53	84.2	0 (0.0)	38	71.7	38 (100)	0 (0)
Cote d'Ivoire	Low	6.9	Abidjan	2012-2013	329	68.5	11 (3.3)	200	62.9	200 (100)	0 (0)
Ethiopia	Low	1.6	Addis	2012	216	94.4	0 (0.0)	214	99.1	214 (100)	0 (0)
Kenya	Medium	4	Eldoret	2009-2013	411	93.1	12 (2.9)	145	36.3	145 (100)	0 (0)
Kenya	Medium	4	Nairobi	2009-2013	939	76.4	29 (3.1)	149	16.4	144 (96.6)	5 (3.4)
Mauritius	High	10.6	Mauritius	2005-2009	428	98.4	0 (0.0)	428	100	428 (100)	0 (0)
Mozambique	Low	1.0	Maputo	2015	145	96.4	21 (14.5)	124	100	112 (90.3)	12 (9.7)
Namibia	Medium	17.8	Namibia	2012-2013	210	74.0	0 (0.0)	76	36.2	74 (97.4)	2 (2.6)
Seychelles	High	74.6	Seychelles	2008-2013	44	97.7	0 (0.0)	44	100	43 (97.7)	1 (2.3)
South Africa	Medium	9.6	Eastern Cape	2008-2013	931	94.3	0 (0.0)	931	100	931 (100)	0 (0)
Uganda	Low	—	Kampala	2009-2013	479	58.3	6 (1.2)	151	31.9	151 (100)	0 (0)
Zimbabwe	Low	10.8	Bulawayo	2012-2013	443	69.0	18 (4.1)	60	14.1	58 (96.7)	1 (3.3)
	Low	10.8	Harare	2009-2013	621	89.8	33 (5.3)	200	34.0	197 (98.5)	3 (1.5)
Total cases					5249	89.4	130 (2.5)	2760	53.9	2735 (99.1)	25 (0.9)

Abbreviation: DCO, death certificate only.

[a]HDI: Human Development Index (source: United Nations Development Program. Human Development Report 2015)

[b]Country-level screening coverage (source: Human Papilloma Virus and Related Diseases Report 2017. https://hpvcentre.net/datastatistics.php) The Women's Health Survey 2003 data was used for Cote d'Ivoire, Ethiopia, Kenya, Mauritius, Namibia, South Africa and Zimbabwe. For Seychelles, the National Health Survey of Noncommunicable Diseases (2013-2014) was used and for Mozambique, screening coverage estimates were from the Strategic Health Plan (PESS) 2014-2019.

TABLE 2 Patient characteristics: mean age at diagnosis, median years of follow-up and observed (all-cause) survival

			Year 1				Years 2 and 3				Years 4 and 5		
Country, Registry	Number of cases included	Mean (SD) age at diagnosis	No. of deaths (%)	LFU	% LFU	1-year observed survival (%)	No. of deaths (%)	LFU	% LFU	3-year observed survival (%)	No. of deaths (%)	5-year observed survival (%)	Median (IQR) follow-up (years)
Benin, Cotonou	38	55.8 (15.4)	8 (21.1)	22	57.9	70.4 (49.4-83.9)	2 (5.3)	4	10.5	46.9 (18.1-71.5)	0	46.9 (18.1-71.5)	0.2 (0.09-0.8)
Cote d'Ivoire, Abidjan	200	52.7 (13.0)	31 (15.5)	84	42.0	80.4 (73.3-85.8)	47 (23.5)	7	3.5	34.0 (25.2-43.0)	6 (3.0)	23.0 (14.3-32.9)	0.5 (0.02-2.0)
Ethiopia, Addis	214	51.7 (12.7)	77 (36.0)	38	17.8	60.5 (53.3-67.0)	40 (18.7)	1	0.5	35.9 (28.9-43.1)	11 (5.1)	24.5 (17.5-32.1)	0.8 (0.07-3.3)
Kenya, Eldoret[a]	145	48.9 (13.6)	35 (24.1)	74	51.0	67.6 (57.9-75.5)	13 (9.0)	6	4.1	41.0 (28.5-53.0)	3 (2.1)	31.1 (18.4-44.8)	0.1 (0.0-1.0)
Kenya, Nairobi[a]	144	49.4 (12.5)	20 (13.9)	69	47.6	81.7 (73.1-87.8)	16 (11.1)	12	8.3	55.1 (42.6-65.9)	4 (2.8)	44.0 (30.4-56.9)	0.5 (0.08-2.0)
Mauritius[a]	428	55.7 (13.9)	42 (9.9)	0	0	90.1 (86.8-92.6)	52 (12.3)	0	0	77.8 (73.5-81.4)	16 (3.8)	73.6 (69.0-77.5)	5.7 (3.9-7.4)
Mozambique, Maputo	112	48.2 (12.0)	25 (22.3)	76	67.9	66.2 (54.2-75.7)	1 (0.9)	10	8.9	55.2 (31.6-73.6)	—	—	0.1 (0.04-0.4)
Namibia[a]	74	54.6 (16.3)	11 (15.5)	28	39.4	80.7 (67.9-88.8)	8 (11.3)	6	8.5	58.4 (42.0-71.7)	3 (4.2)	45.0 (27.0-61.4)	0.6 (0.07-2.7)
SA, Eastern Cape[a]	931	56.1 (15.2)	256 (27.5)	336	36.1	66.5 (63.0-70.0)	122 (13.1)	45	4.8	40.8 (36.7-44.9)	30 (3.2)	32.1 (27.9-36.4)	0.4 (0.01-1.9)
Seychelles[a]	43	53.1 (16.5)	11 (25.6)	0	0	74.4 (58.6-84.9)	7 (16.3)	0	0	58.1 (42.1-71.2)	4 (9.3)	46.2 (30.2-60.8)	3.6 (0.9-4.7)
Uganda, Kampala[a]	151	44.9 (13.6)	33 (21.9)	83	55.0	69.9 (60.3-77.5)	17 (11.3)	7	4.6	32.2 (20.0-45.0)	3 (2.0)	21.4 (10.2-35.5)	0.1 (0.0-1.0)
Zimbabwe, Bulawayo	58	53.0 (15.7)	21 (36.8)	24	42.4	53.3 (37.9-66.6)	11 (19.3)	1	1.8	2.3 (0.0-16.1)	—	—	0.1 (0.02-0.8)
Zimbabwe, Harare[a]	197	53.5 (13.7)	105 (53.8)	1	0.5	46.0 (38.9-52.8)	30 (15.4)	0	0	30.5 (24.2-37.1)	8 (4.1)	25.6 (19.6-32.1)	0.8 (0.1-3.9)

Abbreviation: LFU, lost to follow-up.

[a]Registries with a potential follow-up time of 5 years (or more).

3.1.1. | Assessing LFU

LFU was highest in the first year of follow-up after cancer diagnosis compared to subsequent years. Maputo and Cotonou had the highest LFU in the first year, with LFU of 67.9% and 57.9%, respectively (Table 2). When assessed in a Cox Model, LFU at 1 year was random with no association with age or known stage, with the exception of age-groups 55 to 64 for Addis Ababa and Bulawayo, and age-group 75+ for Eastern Cape, where these age-groups were less likely to be LFU compared to the 15 to 44 age-group.

Out of the 13 registries, 10 had potential for 5-year follow-up time (Table S1). Among cases with potential for 5-year follow-up time, the proportion with complete 5-year follow-up and known vital status ranged from 77.7% in Mauritius to 5.5% in Kampala.

3.1.2. | Survival statistics for all ages by registry

In the study cohort, the overall observed survival in SSA women with cervical cancer was 67.5% (65.5-69.5) at 1 year, 46.2% (43.9-48.4) at 3 years and 40.2% (37.9-42.5) at 5 years (Figure 1A). The 75+ age-group had a much lower survival than all other age-groups (log-rank test $P < .001$; Figure 1B). Figure S3 shows the KM survival by registry, the 5-year observed survival was lowest in Kampala (16.4% [7.0-29.2]) and highest in Mauritius (74.2% [69.8-78.1]).

Overall relative survival for all registries combined was 72.7% (70.7-74.5), 52.5% (50.0-55.0) and 47.3% (44.6-50.0) at 1, 3 and 5 years, respectively. Generally, registries from high and medium HDI countries had the highest survival, while the lowest survival was found in low HDI registry areas. The relative survival at Year 1 ranged from 91.9% in Mauritius to 47.5% in Harare, Zimbabwe (Figure 2). Similarly, at 5 years after diagnosis, relative survival was highest in Mauritius at 82.1% and lowest in Kampala, Uganda at 24.0% (Figure 2). Women with cervical cancer had a much lower survival compared to women in the general population (Figure S5).

Age-standardised relative survival (ASRS) also varied greatly across registries, the 5-year ASRS ranging from 25.3% (18.0-33.4) in Addis Ababa to 85.6% (78.8-90.4) in Mauritius (Table S2). Even within the same country, there were large disparities between survival in registry areas in smaller cities/towns vs capital cities with better survival observed for patients diagnosed in the capital cities of Zimbabwe (Harare) and Kenya (Nairobi).

The estimated average relative survival for the 11 countries (taking into account the size of the study sample from each) was 69.8%, 44.5% and 33.1% at 1, 3 and 5 years, respectively.

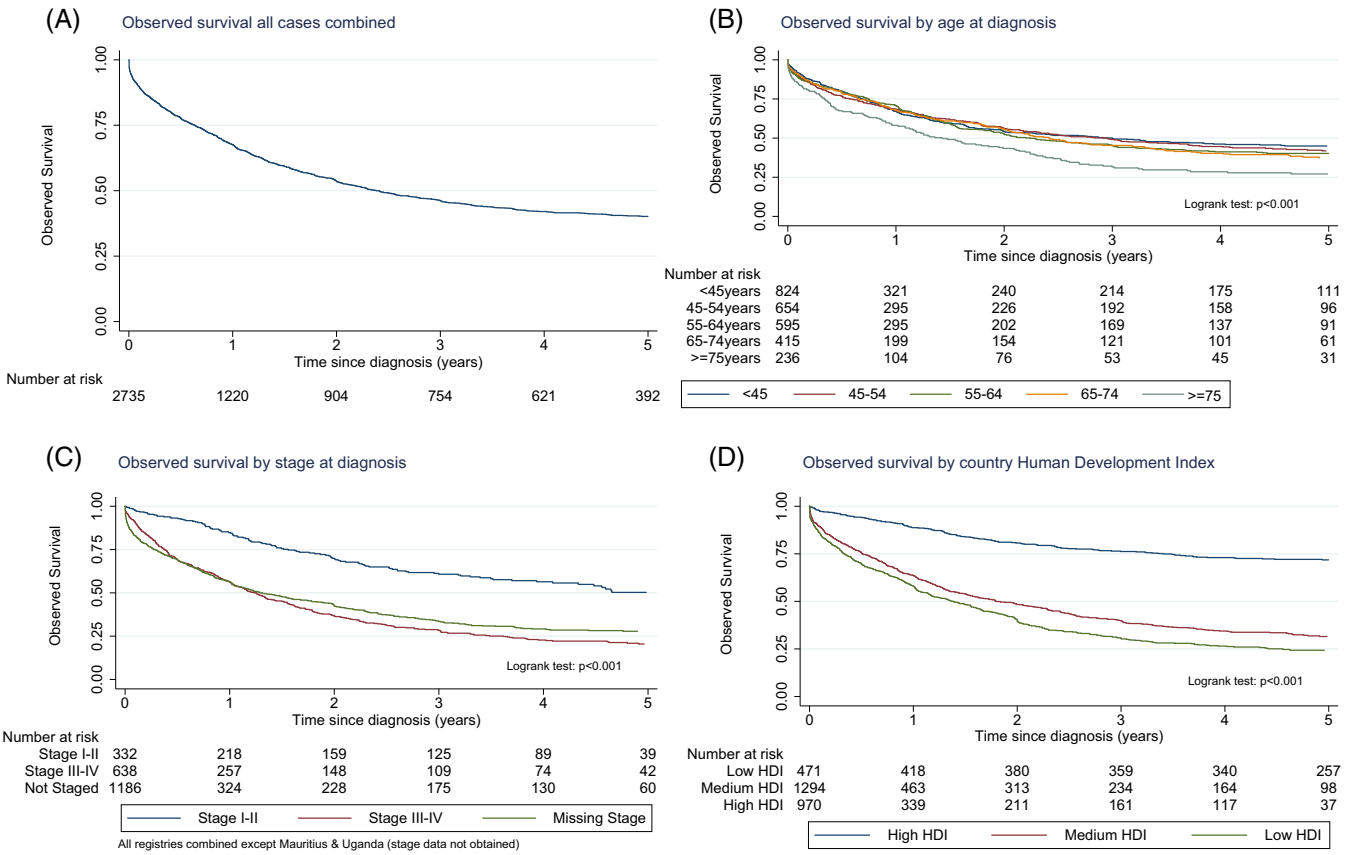

FIGURE 1 A, Overall Kaplan-Meier (KM) survival for all registries combined, B, by age, C, stage, and D, country-level Human Development Index (HDI) [Color figure can be viewed at wileyonlinelibrary.com]

3.1.3. | Survival by age at diagnosis and registry

There were no consistent patterns in age-specific relative survival by registry and these data are presented in Table S2.

3.1.4. | Survival by stage at diagnosis

Patients with Stage I-II cervical cancer had a much better KM survival probability than those diagnosed with Stage III-IV cervical can-

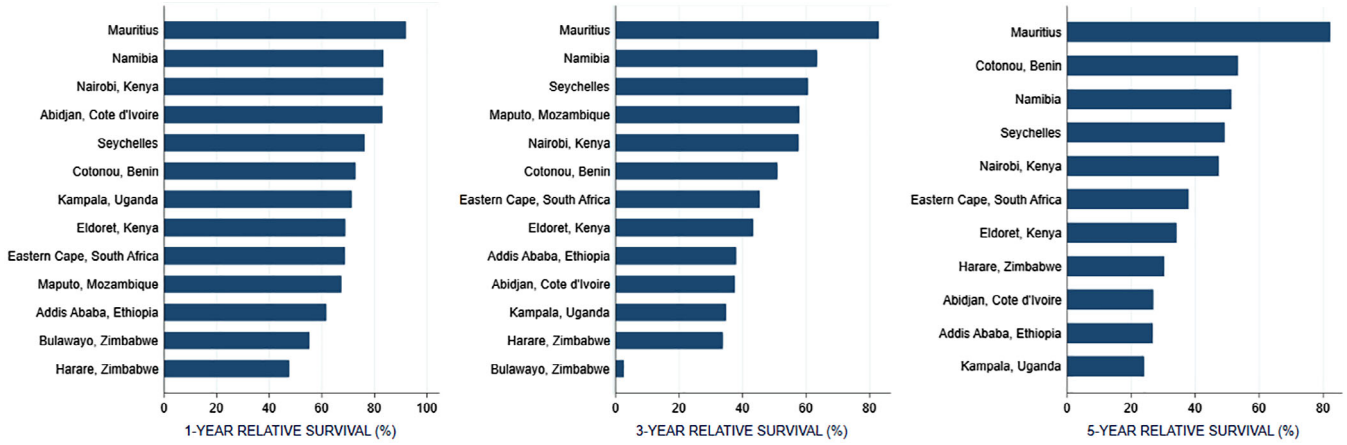

FIGURE 2 Relative survival (RS) from cervical cancer at 1, 3 and 5 years after diagnosis, by registry [Color figure can be viewed at wileyonlinelibrary.com]

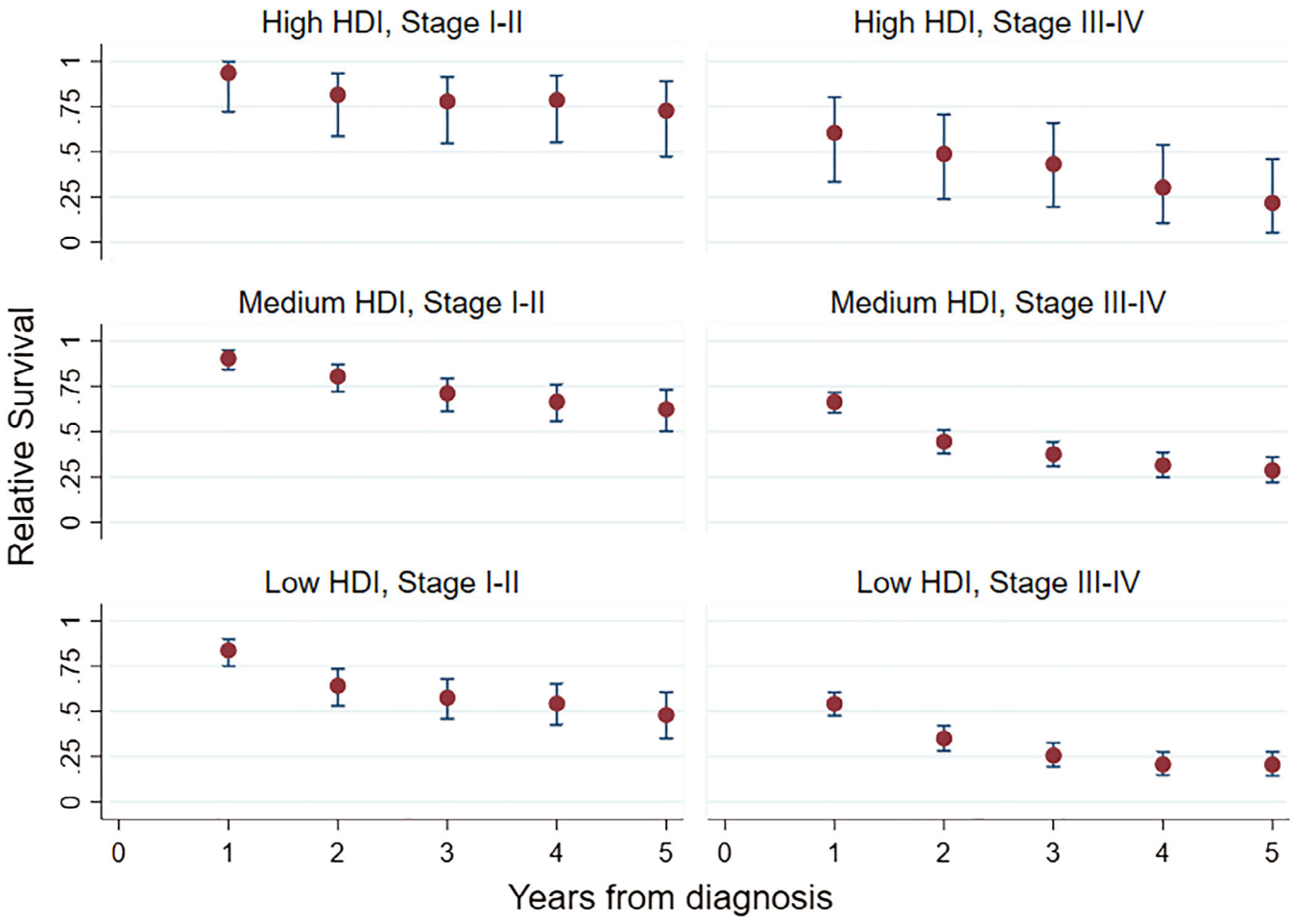

FIGURE 3 Relative survival by country-level Human Development Index (HDI) and stage at diagnosis [Color figure can be viewed at wileyonlinelibrary.com]

cer (Figure 1C). The overall 5-year KM survival probability (excluding Mauritius and Kampala) for SSA women with Stage I-II cervical cancer was 50.3% (42.9-57.2) while it was only 20.5% (16.5-24.6) for Stage III-IV cervical cancer (log-rank test $P < .001$; Figure 1C). Within the same stage, there were differences in relative survival by registry, with lower 5-year relative survival for low HDI countries even for Stage I-II disease (Table S3). Similarly, KM survival for Stage I-II disease was lower in low HDI countries than in high HDI countries (Figure S4).

3.1.5. | Survival by country-level HDI

The 5-year KM survival probability was much higher in high HDI than in low and medium HDI registry areas (Figure 1D; log-rank test $P < .001$). Figure 3 shows stage-specific relative survival by HDI. The 5-year relative survival for Stage I-II cervical cancer patients from high HDI registries was 67.5% (42.1-83.6) while it was much lower (42.2% [30.6-53.2]) for low HDI registries. However, the 5-year relative survival estimates for Stage III-IV cervical cancer for high HDI registries (21.2% [5.6-43.4]) and low HDI registries (15.8% [11.0-21.4]) were not dissimilar and had overlapping confidence intervals. Overall survival was lowest in low HDI registries (Figure S3).

3.1.6. | Excess Hazard ratio; incorporating the effect of age, stage, country-level cervical screening coverage and country HDI

We modelled mortality in women with cervical cancer in SSA adjusting for age, stage and country HDI (Model 1, Table 3). Independent predictors of mortality in SSA women with cervical cancer were Stage III-IV disease, medium to low country-level HDI and age older than 65 years at diagnosis (Table 3). Women with Stage III-IV cervical cancer were 2.4 (1.9-3.0) times more likely to die than those with Stage I-II disease after adjusting for age at diagnosis and country-level HDI (Table 3). Cervical cancer patients from medium HDI registry areas were four times (HR 4.0 [3.3-4.9]) more likely to die than those from high HDI registry areas, while those from low HDI areas had a five times (HR 4.9 [4.0-6.0]) greater hazard of dying (Model 1, Table 3).

TABLE 3 Cervical cancer excess mortality hazard by stage, country-level HDI, age at diagnosis and screening coverage

		Univariable analysis		Multivariable adjusted Model 1		Multivariable adjusted Model 2	
Prognostic factors	Number of cases	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age at diagnosis (years)							
<45	824	Reference		Reference		Reference	
45-54	654	1.0 (0.9-1.2)	.50	1.1 (0.9-1.3)	.14	1.1 (1-1.3)	.14
55-64	595	1.1 (0.9-1.3)	.18	1.1 (0.9-1.3)	.16	1.1 (0.9-1.3)	.16
65-74	415	1.1 (1.0-1.4)	.12	1.3 (1.0-1.5)	.012	1.3 (1.0-1.5)	.01
75+	236	1.6 (1.3-1.9)	<.0001	1.6 (1.3-2.0)	<.0001	1.6 (1.3-2.0)	<.0001
Country-level HDI							
High HDI	471	Reference		Reference		Reference	
Medium HDI	1294	3.7 (3.0-4.4)	<.0001	4.0 (3.3-4.9)	<.0001	4.0 (3.3-4.9)	<.0001
Low HDI	970	4.5 (3.7-5.5)	<.0001	4.9 (4.0-6.0)	<.0001	5.1 (4.1-6.3)	<.0001
Stage at diagnosis							
Stage I-II	332	Reference		Reference		Reference	
Late Stage III-IV	638	2.5 (2.0-3.1)	<.0001	2.4 (1.9-3.0)	<.0001	2.4 (1.9-2.9)	<.0001
Unknown Stage	1765	1.5 (1.2-1.8)	<.0001	2.2 (1.8-2.7)	<.0001	2.2 (1.8-2.8)	<.0001
Country-level screening coverage							
<5%	615	Reference				Reference	
5 < 15%	1814	0.8 (0.6-0.9)	<.0001			1.0 (0.9-1.2)	.63
15% or more	117	0.7 (0.5-0.9)	.0007			1.2 (0.8-1.6)	.42
No screening data available	189	1.2 (0.9-1.5)	.28			1.0 (0.7-1.3)	.81

Note: Model 1: adjusted for stage at diagnosis, country-level Human Development Index (HDI) and age at diagnosis. Model 2: adjusted for adjusted for stage at diagnosis, country-level HDI, age at diagnosis and country-level screening coverage. Uganda and Benin had no available data on screening.
Abbreviation: 95% CI, 95% confidence interval.

Women aged 65 to 74 had an excess hazard of 1.3 times (1.0-1.5) and women older than 75 had an excess hazard of 1.6 times relative to women diagnosed before the age of 45 years. In Model 2, we adjusted for age, stage, country-level HDI and screening coverage. While women in countries with high screening coverage were less likely to die (HR 0.8 [0.6-0.9] for 5% to 15% screening coverage, HR 0.7 [0.5-0.9] for screening coverage >15%), after adjusting for age, stage and country-level HDI, screening coverage had no effect on mortality. We explored the interaction between country HDI and stage (Tables S4 and S5) and found that patients diagnosed with cervical cancer at a late stage have a higher risk of dying, independent of the HDI. Patients with missing stage in medium and low HDI countries were more likely to die compared to those in high HDI and earlier stage. Missing stage had a strong interaction with HDI; patients with missing stage were more than four times more likely to die when in medium and low HDI (Table S5).

4 | DISCUSSION

Cervical cancer is a significant cause of cancer morbidity and mortality in the SSA region.[1] We present the first study to compare population-based cervical cancer survival across 13 PBCRs taking into account country-level HDI, disease stage and age at diagnosis.

In the cohort of women from 13 cancer registries, the overall observed survival of women with cervical cancer was 67.5% (65.5-69.5) at 1 year, 46.2% (43.9-48.4) at 3 years and 40.2% (37.9-42.5) at 5 years. The estimated average relative survival for the 11 countries (taking into account the size of the study sample from each) was 69.8%, 44.5% and 33.1% at 1, 3 and 5 years, respectively.

FIGO Stage I-II are cancers that have not spread beyond the cervix (not to the pelvic wall, or lower 1/3 of the vagina[12]). Observed and relative survival estimates in women with Stage I-II cancers were much higher than in women with Stage III-IV disease. Survival was also superior in high HDI countries compared to medium or low HDI countries, and in registry areas that include capital cities than in provincial areas within the same country. Factors independently associated with an increased hazard of death in SSA women with cervical cancer were Stage III-IV disease, medium to low country-level HDI and age older than 65 years at diagnosis.

For the 11 countries studied, the estimate for relative survival at 3 years was 44.5% in other words, more than half of women with cervical cancer will die from the disease within 3 years of diagnosis. This may be compared to 3-year relative survival of 73.7% for women diagnosed with cervix cancer in the United States in 2012.[23] It is regrettable that SSA women still endure so many unnecessary deaths from a largely preventable disease whose natural history offers multiple opportunities to intervene and halt cervical cancer progression.[24,25] A recent study estimated that in England, screening currently prevents 70% of cervical cancer deaths and potentially 83% could be prevented if all eligible women attended screening regularly.[26] Previous population-based studies reported a 5-year relative survival of 17.7% and 26.5% in Kampala and Harare respectively, in the period 1993 to 1997.[27,28] In the current study, for the period 2009 to 2013, 5-year relative survival estimates in Kampala and Harare were 24.0% (11.4-39.7) and 30.3% (23.2-37.9; Table S2). These estimates show that over 16 years later, there has not been much improvement in the survival of women with cervical cancer in these low HDI countries.

Population-based cervical cancer survival reflects the cumulative effect of a multitude of factors.[5,24,25] These include secondary prevention measures (pap smears, HPV DNA testing, visual inspection with acetic acid and appropriate treatment of cervical precancer) and timely appropriate radiation, surgical and chemotherapeutic treatments.[24,25] The situation with respect to services for diagnosis and treatment of cervix cancer in SSA can only be described as poor; there is a huge disparity between calculated need and actual availability of radiotherapy services,[29,30] effective and affordable surgery[31], and access to chemotherapy and skilled oncology personnel.[30,32] The differences in survival between registries in capital cities and other registries within the same country possibly reflect the need for decentralisation of cancer screening services and efficient referral pathways for cancer treatment.

The HDI collectively measures life expectancy, education level and gross *per capita* income of a country or region.[16] The HDI was identified as a key measure in the changing patterns of cancer morbidity and mortality globally.[33] Predominantly low HDI regions like SSA have a higher burden of infection-related cancers such a cervical cancer.[33] We found that the 5-year relative survival for Stage I-II cervical cancer patients from high HDI registry areas was 67.5% (42.1-83.6) while it was much lower (42.2% [30.6-53.2]) for low HDI registry areas. This showed that Stage I-II tumours still have unsatisfactory survival outcomes in low HDI countries. Our findings underscore the importance of the factors contributing to the HDI (notably education and *per capita* income) in cervical cancer control. Higher levels of education may translate to better screening uptake, early diagnosis and improved survival. Countries with higher gross *per capita* income likely have functional health systems, availing screening services and effective treatment programmes. Only 10% of the population in low income countries has access to radiation treatment,[34] an essential component of cervical cancer treatment. Where radiation treatment services exist in SSA, poor machine maintenance, machine breakdowns and long treatment waiting periods are commonplace.[35,36] The low gross *per capita* income in these countries is consistent with the lack of affordable and accessible cancer treatment services to the general populace. Cervical cancer patients from medium and low HDI registry areas were at least four times more likely to die than those from high HDI registry areas. This suggests that in SSA, the health systems of both medium and low HDI countries are similar and severely inadequate in cervical cancer control.

We found that nearly two-thirds (65.8%) of patients with known stage, were diagnosed at a late stage (FIGO Stages III and IV). Similarly, a hospital-based cross-sectional study exploring the factors associated with advanced stage at diagnosis in Northern Uganda, found that 66% of all patients with cervical cancer had late stage disease.[2] Factors associated with late-stage disease in

Northern Uganda were early sexual debut in women of low socioeconomic status, financial difficulties, low education levels and health system factors such as referral delays from primary health care centres.[2] As expected, Stage III-IV disease and age at diagnosis >65 years were independently associated with an excess hazard of death in the current study. A recent study in Ethiopia found that cervical cancer patients older than 60 years had a two-fold higher risk of death than younger patients (HR = 2.02, 95% CI: 1.01-4.05).[3] This can be explained by other competing causes of mortality that increase with age.

In univarible analysis, we found that higher screening coverage was associated with lower mortality. However, after adjusting for age, stage and HDI, screening coverage had no effect on mortality.

In sensitivity analyses, we explored the interaction of country-level HDI and stage at diagnosis. Missing stage had a strong interaction with HDI; patients with missing stage were more than four times more likely to die when in medium and low HDI registry areas (Table S5). We had very few high (Mauritius and Seychelles only) and medium (Kenya, South Africa and Namibia only) countries included in our study because the majority of SSA countries are of low HDI. Large proportions of missing stage in high (Mauritius-no staging information available) and medium (65% missing stage in Eastern Cape, 55% missing stage in Kenya), might explain the interaction seen between missing stage and HDI (Figure S2). Staging information is not part of the mandatory variables collected by cancer registries, which is why it was largely missing for some registries.

Our study had several strengths. We used data from 13 PBCRs from 11 SSA countries, which approximates real life scenarios allowing for generalizability in the context of available resources and limitations in the region. We used random sampling to select included cases and most registries had MV% of at least 74%. Patients were actively traced using telephones and/or home visits with the exception of Mauritius where linkage with the death registry was used to ascertain vital status. Mauritius has an estimated 100% completeness of cause-of-death registration[11] and our random check on 10% of cases with no matching death certificate confirmed them to be alive, which gives us confidence with our estimates. Despite these strengths, our study also had some limitations. While every effort was made by registry staff to trace patients, a significant number of patients could not be traced, for example, Maputo had LFU of 67.9% at 1 year after diagnosis. However, when assessed in a Cox Model, LFU at 1 year was random with no association with age or known stage, with the exception of age-groups 55 to 64 for Addis Ababa and Bulawayo, and age-group 75+ for Eastern Cape, where these age-groups were less likely to be LFU compared to the 15 to 44 age-group. Due to high loss to follow up in many registries, some of the estimates of cervical cancer survival at 3 to 5 years were imprecise (Table 2). Staging information was not available for Mauritius and Kampala. Staging information was only available for 45% of all included patients. For the registries with staging information, cancer registrars relied on documentation of staging information in patient records by attending clinicians and could only abstract that which was available. Observed survival is multifactorial, reflecting the combined effect of both patient factors (eg age, disease stage, co-morbidities such as HIV and socioeconomic factors such as level of education) and health system factors (such as availability screening programmes and access to timely treatment).[4-6] While we were able to adjust for disease stage, age and country-level screening coverage, factors such as level of education and HIV status were not available. HIV infected women with cervical cancer have a higher risk of dying compared to HIV-negative women (HR, 1.95 [1.20-3.17]).7 We were also not able to evaluate whether or not specific treatment was received. Nonetheless, country HDI is a composite indicator which takes into account education levels, life expectancy and a country's financial resources which allowed us to control for education and health system factors at country-level. The current study covers over a period of 11 years and compared registries at different time points. This might bias the results if there were significant changes in survival over time.

Women in SSA are still diagnosed with cervical cancer at advanced stages with unacceptably poor survival outcomes. Patients from SSA countries with high HDI were diagnosed at earlier disease stages and had more favourable survival outcomes than low and medium HDI countries. Cervical cancer patients from medium and low HDI registry areas were at least four times more likely to die than those from high HDI registry areas, reflecting that health systems in both low and medium HDI countries in SSA are severely inadequate in cervical cancer control. Patients with Stage I-II tumours still have unsatisfactory survival outcomes in low HDI SSA countries. Factors contributing to the HDI (such as level of education and a country's financial resources) are critical for cervical cancer control in SSA and there is need to strengthen health systems with timely and appropriate prevention and treatment programmes.

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ETHICS STATEMENT

Our study was approved by the AFCRN and used anonymized secondary data. Informed consent was not feasible since secondary registry data was used for the study. Permission to use data was sought and granted from each participating registry.

CONFLICT OF INTEREST

E. S. received grants from Janssen Pharmaceutica, outside the submitted work. All other authors have no conflict of interest to declare.

DATA ACCESSIBILITY

The data that support the findings of our study are available on request. All data requests will be evaluated by the AFCRN research committee. Details of the data application process are outlined on the AFRCN website (http://afcrn.org/index.php/research/how-to-apply/76-research-collaborations).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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