Association Between Distance and Stage at Breast Cancer Diagnosis Among Patients at Butaro Cancer Center of Excellence, Rwanda

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A thesis submitted to the Faculty of the Department of Global Health and Population, Harvard T.H. Chan School of Public Health in partial fulfillment of the requirements for the degree of Master of Science

Harvard T.H. Chan School of Public Health
Boston, Massachusetts
May 2021

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Abstract

Objective
Travel distance to health facilities can be an important barrier to timely breast cancer diagnosis, particularly in low-income rural regions where patients often live far from cancer facilities. Rwanda's first public cancer facility, Butaro Cancer Center of Excellence (BCCOE), provides highly subsidized cancer care to low-income patients. We sought to determine if longer travel distances to local health centers (HCs) and BCCOE are associated with advanced-stage disease at diagnosis.

Methods
Using a database of all patients treated for breast cancer at BCCOE from 2012-2016, we included 446 patients receiving no prior treatment. We calculated patients' travel distances to HCs and BCCOE using AccessMod5, a spatial analytic software, and examined distance as a continuous variable and in quartiles. Following descriptive analysis, we used Chi-square tests and multivariable logistic regression to examine the association of distance and other patient characteristics with advanced-stage presentation.

Results
Median age of patients in the cohort was 49.5 years (IQR=40.0-58.0); median sector-level poverty rate was 41.3% (IQR=29.2-48.8). Three-quarters were diagnosed with stage III or IV disease. Median distance to local health center was 2.97 km (IQR=1.68-5.05). Univariate analyses showed no association between distance quartile from the HC and stage (p=0.38). Median distance to BCCOE was 90 km (IQR=55-139). In multivariable logistic regression, odds of late-stage diagnosis were 2.35 (95% CI: 1.14–4.96) times higher among those in distance quartile four versus distance quartile one (>139 km versus < 55 km) from BCCOE. Poverty was also significantly associated with advanced-stage presentation, with each percent increase in sector-level poverty associated with a 1.03 times higher odds of late-stage diagnosis (95% CI: 1.01–1.05).

Conclusions
In Rwanda, longer travel distance to tertiary facilities, but not HCs, is associated with late-stage presentation. Optimizing travel distance through decentralized diagnostic testing or transport subsidies should be prioritized in early detection interventions.

Background

Theoretical framework

Reducing health disparities and ensuring equitable health care access are major objectives of national health systems. The World Health Organization's (WHO) Commission on Social Determinants of Health has defined three core contextual factors impacting population health that extend beyond the health sector: the socioeconomic and political context; the structural determinants of health inequities; and the intermediary determinants of health [1–3]. These social and contextual determinants, including levels of education and income, standards of living, access to transportation, and food security, have both direct and indirect impacts on health outcomes. Therefore, addressing these "upstream" determinants can lead to large improvements in population health [4].

Conceptual health-seeking behavioral models can help address such social determinants. For instance, Andersen initially developed a model to describe households' motives in using health services and their equitable access, so to guide policy and promote health equity [5]. The model conceptualizes relationships and points to three categories of factors underpinning health services utilization: "predisposing characteristics" such as sociodemographic characteristics; "enabling resources" such as differences in resources available through family or community; and "need" or individuals' unique perceived needs [5,6]. Walter later built upon Andersen's model and proposed to use time intervals to document transitions between symptom recognition, diagnosis, and initiation of treatment [7].

Distance to health facilities, and subsequent travel time to and from facilities, have been widely identified as major contextual determinants of health that impede access and use of health services [8,9]. There is evidence across low- and middle-income countries (LMICs) that distance and time to health facilities play a critical role in delaying seeking treatment; they have also been associated with higher out-of-pocket (OOP) costs to patients and families, and ultimately with worse health outcomes [8,10,11]. Facility distance and time transitions across recognition, diagnosis, and treatment, as highlighted by the Walter model, are essential to understand in LMIC settings, where often higher levels of care, such as those delivering services for non-communicable diseases (NCDs), are located in major urban centers and capital cities [12,13].

Growing buden of non-communicable diseases

A rapid epidemiological transition from communicable diseases and childhood illnesses to chronic NCDs has already occurred in LMICs [14]. As a result, a significant challenge has emerged as the great majority of health systems in low-income settings have been initially designed to respond to infectious disease burdens, neonatal and maternal concerns, and reproductive health issues, and thus are often ill-equipped to address the rising tide of NCDs. This is especially evident in many sub-Saharan African countries where there has been a growing burden of diabetes, chronic respiratory diseases, cardiovascular diseases, and cancers, and where the greatest rise in NCD-related mortality over the next ten years is expected [14,15].

In particular, the burden of cancer is steadily increasing in LMICs where the mortality rates are much higher than in richer countries [16–18]. Breast cancer is the most common cancer among women globally, with 62% of global breast cancer deaths estimated to occur in less economically developed countries (including all regions of Africa, Asia [excluding Japan], Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia) [19,20]. Primary reasons for high breast cancer case fatality ratios in LMICs include late-stage diagnoses and limited access to early detection and high-quality treatment [19,21,22]. The Walter model appropriately highlights the critical time intervals between symptom recognition and diagnosis, and between diagnosis and initiation of treatment – two intervals that, when reduced, have been shown to improve breast cancer survival rates. This is indeed a major focus of this study, which intends to explore the time intervals between symptom recognition and diagnosis, as proposed by Walter, with a focus on distance to health facility and clinical stage at presentation at a referral hospital in the country of Rwanda.

Health in Rwanda

Rwanda is a low-income country located in East Africa that has a population of roughly 12.5 million inhabitants [23]. The country has significantly strengthened its health system and has made remarkable improvements in population health over the past 20 years, [24] notably, achieving the health-related Millennium Development Goals 4 (to reduce child mortality), 5 (to improve maternal health), and 6 (to combat HIV/AIDS, malaria, and other diseases) [25]. The under-five mortality rate decreased from 179 per 1,000 live births in 2000 to 42 per 1,000 live births in 2015; and the maternal mortality ratio decreased from 1,160 per 100,000 live births in 2000 to 275 per 100,000 live births in 2015 [26,27]. In addition to steep declines in maternal and child mortality, Rwanda has also greatly enhanced its response to many NCDs, including cancers [28].

In Rwanda, there is a hierarchical provision of public health services with a focus on decentralized primary care. Patients first present to one of the roughly 500 health centers (often located within their sector of residence) for access to routine services. If additional services are needed, such as Cesarean section or treatment of complicated cases, they are referred to their district hospital. Finally, if the patient is in need of specialized care, they are referred to one of the five national referral and teaching hospitals providing specialized services and which are intended to serve the entire country [29].

In the mid-2000s, a community-based health insurance (CBHI) program, the so-called "Mutuelles de Santé", was rolled out nationally and now covers about 90% of the Rwandan population [30–32]. While the implementation of CBHI has proven to be a significant milestone toward universal health coverage (UHC) in Rwanda, many challenges still remain, particularly around disproportionate inequities in financial contributions toward CBHI premiums [32]. As NCDs and cancer control is increasingly integrated within the national health policy agenda, determining how to fairly finance NCD diagnosis and treatment while simultaneously protecting those affected individuals from medical impoverishment and "catastrophic" health expenditures [33] will be a major undertaking for the Rwandan health sector.

Butaro Cancer Center of Excellence

Prior to 2012, availability of cancer care throughout Rwanda was limited, with few specialists and only one district hospital providing limited services [34]. However, in 2012, Rwanda's Ministry of Health, in collaboration with Partners In Health and the Dana Farber Cancer Institute, launched the Butaro Cancer Center of Excellence (BCCOE) which became the first center to provide comprehensive, and highly subsidized, cancer care throughout the country while targeting the rural poor. BCCOE is a public, rural-based tertiary level facility located at Butaro Hospital, a district hospital in the Burera District [34]. Burera is a rural and mountainous district in the Northern Province that shares a boarder with Uganda.

Today, BCCOE remains the only public facility providing comprehensive cancer diagnosis and care and is able to do so largely free of charge to the patient as a result of generous philanthropic support [28,35]. Breast cancer has since been the most common cancer diagnosed at BCCOE where the majority of patients often present with late stage disease [22]: indeed, significant delays in breast cancer diagnosis and access to timely treatment and surgery have been persisting at BCCOE [36,37].

Delays in breast cancer detection

Diagnosing breast cancer early is essential since early stage breast cancer can be treated and stage at diagnosis is a strong predictor of survival [38–40]. Treatment of early-stage breast cancer is also more cost-effective compared to treating late stage breast cancer [41]. With the majority of breast cancer patients in Rwanda presenting with late stage disease, understanding barriers to accessing diagnoses early is critical to guide early detection strategies [22]. Known barriers to accessing breast cancer care early in sub-Saharan Africa include communities' lack of knowledge of breast cancer, overreliance on traditional medicine, not practicing self-breast examination, geographical distance to cancer services, and costs associated with both transport to referral hospitals and specialized care [42–44]. Although studies have shown geographic proximity and urban residence to be associated with early stage diagnosis, there has been little analysis of the geographical determinants of care seeking at BCCOE and of the relationship between travel distance and stage at diagnosis [45–48].

BCCOE is purposefully located among the rural poor rather than within the capital city, Kigali, where much of the county's wealth is concentrated [34,49]. Given that specialized health services are often located in capital regions across similar settings, Rwanda has developed a unique cancer care delivery model. Therefore, understanding factors associated with late stage presentation in this setting, shedding light on care-seeking delays, can guide further development of cancer care systems throughout sub-Saharan Africa.

Notably, in South Africa, Dickens and colleagues found that, among breast cancer patients diagnosed at the largest public referral hospital in the country, those who lived farther were diagnosed at later stages compared to patients who lived closer [45]. Moreover, Togawa et al. explored distance and stage at presentation among more than 1,500 patients included in the African Breast Cancer–Disparities in Outcomes (ABC-DO) prospective study across Namibia,

Nigeria, Uganda, and Zambia. They found a significant association between travel distances to cancer diagnosis and/or treatment facilities and clinical stage at diagnosis but no association between travel distances to first provider and stage [50]. In Rwanda, among breast cancer patients, Pace and colleagues have documented how long patient and system delays have been associated with late stage at presentation and found that living within the same district as BCCOE was associated with shorter delays in presentation [51].

Research aims

This study builds upon the work of Pace and colleagues to quantify the relationship between long travel distances and delayed diagnoses. Given the location of BCCOE, and its function as the only free-of-charge cancer hospital in Rwanda, this thesis explores the relationship between distance and stage at presentation hypothesizing that longer distances are associated with later stage presentation adjusting for contextual and socioeconomic determinants. Building on the Walter and Andersen conceptual frameworks, we develop a quantitative model for identifying and measuring the barriers to early cancer detection. This can help strengthen the evidence base to inform policy and guidelines for integrating cancer care into existing health systems in Rwanda and beyond.

Methods

Data sources

Data for this analysis were obtained using structured extraction forms and were manually collected from electronic and paper medical records from BCCOE. De-identified detailed clinical histories and patient demographics were available including: age; year of presentation; pre-existing conditions; stage at diagnosis; hormone receptor status; treatment details; and residential area. Residential sector poverty level was based on a relative poverty index, i.e. the percentage of households living below the poverty line of the residential sector (taken from the 2013-14 Poverty Mapping Report from the National Institute of Statistics of Rwanda) [52]. Distance and time estimations were based on residential cell – administrative entity that provides basic services to the people (total of 2,148 cells) – for which computation methods are outlined below [53]. In 2015, a breast cancer early detection intervention was randomly assigned to 12 health centers in the Burera district. This intervention consisted of training community health workers and nurses on signs and symptoms of breast cancer, and how to perform clinical breast exams and diagnostic breast ultrasounds [54]. We merged data from this trial with de-identified patient demographics to determine which patients were exposed to the early detection intervention based on their residential area and timing of diagnosis.

Study population

Patients with breast cancer diagnosed at BCCOE between 2012-2016 (N=687) were included. Patients were excluded if there was incomplete data on either age or residence (N= 13), if they were male (N=25), if they resided outside of Rwanda (N=37), if they were missing data on clinical stage at diagnosis (N=84), or had received treatment for breast cancer prior to being diagnosed at BCCOE (N=82). After excluding these patients, there were a total of 446 patients

included in the analytic cohort. At BCCOE, breast cancer is staged according to the American Joint Committee on Cancer (AJCC) staging system [55]. Cases were categorized into either early or late stage. Early stage included stage 0, stage I, and stage II. Late stage included stage III, when curing disease is extremely difficult but not impossible, and stage IV when disease is incurable in this setting.

Geographical analysis

All data used for the geographical analysis were downloaded from open source websites. Rwandan subnational administrative boundary shapefiles were from the World Health Organization's Humanitarian Data Exchange database and were developed for the 2012 Census and updated in 2018 [56]. A shapefile of cell boundaries was downloaded from World Bank databases, and geographic centroids at the cell level were calculated in ArcMap [57]. A road shapefile was downloaded from OpenStreetMap (2020 update), and a digital elevation model (DEM, of 90 meters) was used from the ArcGIS hub (2018 update) [58,59]. A land use landcover dataset was obtained from Google Earth Engine [60]. Health facility geolocations of 486 health centers and BCCOE were taken from Maina et al. (2019) [61]. Speed limits for land cover use and land cover type were taken from Google Earth Engine, and road speeds were taken from Munoz et al. (2012) [62]. Before importing into AccessMod5 (AM5), all files were re-projected using World Geodetic System 1984 Universal Transverse Mercator 36S (WGS 1984 UTM 36S).

After generating a merged landcover in AM5, a total of six health centers and 50 centroids were located on a water barrier, either a river or lake, and were manually moved to the nearest cell. First, accessibility analyses to BCCOE and to the nearest health center were run. Then, two referral analyses were run with the cell centroids as the origin points; first with BCCOE as the destination, and second with the health centers as the destination points, limiting the analysis to the nearest health center. Distance and time outputs to BCCOE and the nearest health center from the referral analysis were merged with the residence data in the study cohort.

Statistical analysis

First, descriptive statistics were used to report general characteristics of the study population overall and by cancer stage (early vs. late). Univariate analyses were conducted to examine associations between these characteristics and late stage presentations, using chi-squared tests. Patient characteristics were also reported across distance quartiles and distinguishing Kigali (the capital city) to the rest of the country. Second, generalized linear models were run to assess the associations between distance and stage at diagnosis. Stage was categorized as a binary outcome, either early or late, with a logit function for odds ratios (ORs). The independent variable, i.e. distance to BCCOE, was included firstly as a categorical variable using distance quartiles and secondly as a continuous variable. A univariate logistic regression was used to report the crude association between distance to BCCOE and stage at diagnosis. Then a multivariable logistic model was run adjusting for age, year of diagnosis, sector level poverty, pre-existing comorbidities, distance to nearest health facility, receiving early detection intervention, and hormone receptor status – variables that were either statistically significant in univariate analysis or previously determined to be *a priori* confounders. Lastly, a sensitivity test was conducted; the

AM5 referral analysis was re-run with alternate speed limits based on a previous study by Ouma and colleagues [63].

All analyses were conducted using R statistical software (version 4.0.3).

Ethical approval

Ethical approval was obtained from the Partners HealthCare Institutional Review Board [2012P002016] (Boston, MA), the Rwanda National Ethics Committee, and the Harvard University Institutional Review Board [IRB20-0699] (Boston, MA).

Results

Of the 446 patients diagnosed with breast cancer at BCCOE included in this study, the median age at first visit to BCCOE was 49.5 years (Interquartile range (IQR): 40.0-58.0 years); 44 lived in Burera, 211 lived in regions with a poverty score between 1-3, 235 lived in regions with a poverty score between 4-6, and 13 resided in areas in which health centers participated in the early detection intervention. Overall, 24% (N=108) of all cases were diagnosed with early stage breast cancer while 76% (N=338) were diagnosed with late stage disease. Sixty-one percent (N=270) had hormone receptor positive tumors. In univariate analyses (Table 1), year of presentation, residing in Burera district, health center participation in early detection intervention, hormone receptor status, and distance/time to BCCOE were all significantly associated with stage at diagnosis ($p<0.05$).

As for the residential location of patients (Figure 1), 32% of all patients resided in the Northern Province (N=143). Travel time to BCCOE is shown in Figure 2 with the median travel time estimated at about 127 minutes (IQR: 85-188). Density plots of the relative distributions of travel times to either BCCOE or the nearest health center are shown in Figure 3.

Stage was marginally significantly associated with distance quartile ($p=0.07$): the percentage of patients increased with distance quartile among those who presented late stage, while the percentage of patients decreased with distance quartile among those who presented early stage. Patients from different distance quartiles also varied by year of presentation (marginally significant), hormone receptor status, and sector level poverty (Appendix Table A1). Further (Table A2), a higher proportion of those living outside Kigali presented at late stage (69%) compared with those living in Kigali (66%) (marginally significant). Patient characteristics also differed among those living in Kigali (vs. not living in Kigali) including year of presentation, presence of comorbidities, and sector level poverty.

Results from the multivariable logistic regression are reported (Table 2). The odds of late stage diagnosis were 2.35 (95% CI: 1.14–4.96; $p=0.02$) times higher among those in distance quartile 4, living more than 139 km from Butaro (compared to those in quartile 1, living within 55 km from Butaro). Poverty index was also significantly associated with increased odds of late stage diagnosis with each increase in poverty index associated with a 1.03 times higher odds (1.01–1.05; $p<0.01$). Receiving early detection intervention (in 2015) was also found to have a

protective association as did positive hormone receptor status. No association was found between distance or time to nearest health center and stage at presentation.

Table A3 reports a multivariable model with distance as a continuous variable, assessing the association of each additional kilometer a patient lives from Butaro with the likelihood of late stage diagnosis. The odds of late stage at breast cancer diagnosis were higher per kilometer further a patient lives from BCCOE (p=0.02). As whether the effect of distance was different among the wealthier compared to the poorer, results from a stratified model did not suggest a different association between distance and stage at presentation among those in sector poverty levels 1-3 vs. those in sector poverty levels 4-6 (Table A4).

After estimating distances to BCCOE using alternate travel speeds from Ouma and colleagues [63], ultimately increasing travel speed on major roads, the median travel distance stays relatively constant at 93 km (compared to 92 km); however, the median travel time is reduced from 131 to 95 minutes. We find the results of the multivariable model to change: the updated OR (Table A5) of late stage diagnosis that compares those living in distance quartile 4 to those living in distance quartile 1 being 1.99 (0.99–4.07; p=0.06) is no longer statistically significant.

Discussion

We explored the association between the distance patients had to travel to get to BCCOE and breast cancer stage at presentation to determine if longer distances were associated with late stage presentation, adjusting for other variables. The majority of patients in our study (75%) presented with late stage breast cancer. We found a significant association between distance and stage, confirming our hypothesis that those living further from BCCOE were at a higher risk for presenting with late stage disease. After adjusting for key variables, the threshold at which distance appeared to have the most significant impact on stage was 139 km (beyond which the odds of late stage diagnosis were more than two times higher than the odds of late stage diagnosis for those living within 55 km of BCCOE).

Our study also finds that poverty was associated with later stage at presentation, with patients from poorer sectors having higher odds of presenting with late stage disease. Patients coming from Kigali were more likely to present with early stage disease, as those residing in Kigali are relatively wealthier than the rest of the country. BCCOE is located in the Burera district, and a higher proportion of those living in this district presented with earlier stage disease. In addition to living closer to BCCOE, those living in Burera can be referred from their health center directly to BCCOE. Those residing outside of Burera must be referred from health centers to district hospitals, and then to BCCOE. Further, those who lived in districts in which health centers participated in the 2015 pilot early detection intervention, presented more than half of the time (54%) with early stage disease. Interestingly, no association was found between distance to nearest health center and stage at diagnosis indicating that travel distance to local health facility is less predictive compared to travel distance to referral facility.

Our results are consistent with the literature on breast cancer delays and confirm that living further from referral facilities, but not health centers, is associated with presentation with late stage disease and therefore with more likely adverse outcomes from breast cancer. A review by Ambroggi and colleagues summarized the findings from studies exploring this association and

concluded that increased travel burden was associated with late stage cancer diagnosis and poorer health outcomes [64]. However, the majority of the studies reviewed were from high-income countries, and only one of all 27 studies included was from Africa.

Our findings are consistent with other studies conducted in sub-Saharan Africa including from Dickens and colleagues who examined the effect of distance on stage at diagnosis among over 1,000 patients diagnosed with breast cancer in South Africa. The study found that risk of late stage diagnosis was 1.25-fold higher (1.09-1.42) per 30 km [45]. More recently, Togawa and colleagues conducted the largest scale analysis of distance and stage in sub-Saharan Africa through the African Breast Cancer–Disparities in Outcomes study where they explored this relationship among more than 1,500 patients across four countries (Namibia, Nigeria, Uganda, and Zambia). Similar to our findings, they found that distance to first provider was not associated with late stage at diagnosis, but found that distance to diagnostic/tertiary facility was associated with greater delays (1.56-fold; 1.08-2.27) [50]. To our knowledge, our study is the first analysis of breast cancer in sub-Saharan Africa that uses a rasterized referral analysis to measure distance and time rather than Euclidean distance.

Our study utilizes a raster-based referral analysis to model physical accessibility to health care (through distance and time travel estimations) taking into account road networks, elevation, landcover and travel speeds. Both Dickens et al. (2014) [45] and Togawa et al. (2021) [50] utilize Euclidean, or straight line distance, in their models, a less robust distance estimation technique. Although these different estimation techniques have been found to be highly correlated with each other, Euclidean estimates routinely underestimate true travel distances and raster-based approaches represent a relatively more accurate measure of a patients true travel route [8,65–67]. Given the high levels of correlation between the techniques, the effect size is likely not impacted, however the threshold at which distance is significantly associated with late stage may be less refined and therefore hold less policy relevance.

Understanding breast cancer delays is critical for guiding early detection interventions and breast cancer control strategies. In Rwanda, Pace et al. (2015) [51] showed that long patient and system delays were associated with late stage at presentation among breast cancer patients. This study confirms these findings: living within the same district as BCCOE was associated with shorter delays in presentation; and with additional data, it pointed at how distance, which can be interpreted as both a system and patient delay, can impact stage at presentation [51].

Limitations

Our study has several limitations. First, our sample size is relatively small, and given that this was a retrospective study, we were not able to test for all the possible determinants that might be associated with stage at presentation (e.g. educational level). Second, we did not have complete information on all patients' prior referral pathways to examine in detail all the health facility interactions each patient had before presenting at BCCOE. Third, patients presenting with breast cancer at BCCOE may not be representative of all patients with breast cancer throughout Rwanda. For example, those who could afford private health services in Kigali might prefer to receive care and treatment there. Burera district residents were also overrepresented within our study given the location of BCCOE. The patients included were also relatively less wealthy than

the rest of the country with the median sector level poverty index in 2013/14 (the percentage of households living in poverty) being 41.3 compared to the national average of 39.1 [68].

Finally, the distances and times included in our analysis were estimates, and not patient-reported distances and times. We did not account for mode of transportation or associated costs within these estimates, which likely played a major role in the barriers distance could play in accessing diagnosis in a timely manner. The findings associated with the sensitivity analysis using alternate travel speeds highlights the vulnerability of distance and time estimations, being only as accurate as their model inputs. Faster travel speeds resulted in alternate travel routes, slightly increasing, on average, the distance traveled but decreasing the travel time. These faster travel speeds were taken from a study that utilized travel speeds generalized across sub-Saharan Africa and therefore should be interpreted with caution when applied to a specific study setting [63]. The travel speeds utilized in the main analysis were taken from a study in Rwanda and took into account the Rwanda national guidelines for roads and are therefore more appropriate for this analysis [62].

Conclusion

The burden of breast cancer is increasing throughout sub-Saharan Africa, including Rwanda. The majority of patients are presenting with late stage disease, and strategies to facilitate earlier detection are critical. Travel distance impacts stage at presentation, suggesting that careful consideration should be given to the location of available facilities. Optimizing travel distance through decentralizing cancer diagnostic testing, transport subsidies, or social support should be prioritized in early detection interventions. Additional research exploring the mechanisms by which distance may lead to delays such as costs, lost time working, or lack of awareness of facility is needed in order to inform more targeted health policy.

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Tables

Table 1. Patient characteristics by stage at presentation at Butaro Cancer Center of Excellence.

	All Patients (n=446)	Early Stage (n=108)	%	Late Stage (n=338)	%	p-value
Age (years)						
Median (IQR)	49.5 (40.0, 58.0)	49.5 (39.8, 59.0)	-	49.5 (41.0, 58.0)	-	0.48
Age group (years)						
<30	20	7	6.5	13	3.8	0.34
31-40	94	23	21.3	71	21.0	
41-50	119	26	24.1	93	27.5	
51-60	123	32	29.6	91	26.9	
61-70	55	16	14.8	39	11.5	
70+	35	4	3.7	31	9.2	
Year of presentation						
2012	76	9	8.3	67	19.8	0.05
2013	116	27	25.0	89	26.3	
2014	94	24	22.2	70	20.7	
2015	95	30	27.8	65	19.2	
2016	65	18	16.7	47	13.9	
Residence in Burera district						
No	402	91	84.3	311	92.0	0.03
Yes	44	17	15.7	27	8.0	
HIV positive						
No	418	101	93.5	317	93.8	1
Yes	28	7	6.5	21	6.2	
Comorbidities						
No	361	84	77.8	277	82.0	0.41
Yes	85	24	22.2	61	18.0	
Health center participation in early detection intervention						
No	433	101	93.5	332	98.2	0.03
Yes	13	7	6.5	6	1.8	
Hormone receptor positive						
No	176	29	26.9	147	43.5	<0.01
Yes	270	79	73.1	191	56.5	

Sector poverty index						
Median (IQR)	41.3 (29.2, 48.8)	38.1 (23.3, 46.5)	-	41.8 (31.0, 49.0)	-	0.05
Sector poverty level						
1 -2	115	35	32.4	80	23.7	0.18
3 - 4	247	56	51.9	191	56.5	
5 - 6	84	17	15.7	67	19.8	
Distance to BCCOE (kms)						
Q1 (<=55.2)	113	33	30.6	80	23.7	0.07
Q2 (55.3-90.3)	110	29	26.9	81	24.0	
Q3 (92.4-139.3)	111	29	26.9	82	24.3	
Q4 (>139.3)	112	17	15.7	95	28.1	
Distance to BCCOE (kms)						
Median (IQR)	90 (55, 139)	91 (45, 122)	-	107 (57, 148)	-	0.01
Time to BCCOE (mins)						
Q1 (<=84.5)	112	32	29.6	80	23.7	0.04
Q2 (84.6-126.5)	111	32	29.6	79	23.4	
Q3 (126.6-187.8)	111	28	25.9	83	24.6	
Q4 (>187.8)	112	16	14.8	96	28.4	
Time to BCCOE (mins)						
Median (IQR)	127 (85, 188)	126 (68, 168)	-	131 (89, 196)	-	0.01
Distance to health center (kms)						
Q1 (<=1.68)	112	33	30.6	79	23.4	0.38
Q2 (1.68-2.97)	111	22	20.4	89	26.3	
Q3 (2.98-5.05)	111	25	23.1	86	25.4	
Q4 (>5.05)	112	28	25.9	84	24.9	
Time to health center (mins)						
< 10	203	53	49.1	150	44.4	0.46
>= 10	243	55	50.9	188	55.6	

Sector poverty level 1 - 2: richest
Sector poverty level 5 - 6: poorest

Table 2. Results of the multivariable model to assess the effect of distance from Butaro Cancer Center of Excellence on likelihood of late stage at breast cancer diagnosis

Variable	OR	95% CI	p-value
Distance to BCCOE (km)			
Quartile 1 (<=55.2)	Reference	-	-
Quartile 2 (55.3-90.3)	1.21	(0.61 - 2.45)	0.58
Quartile 3 (90.4-139.3)	1.14	(0.58 - 2.26)	0.70
Quartile 4 (>139.3)	2.35	(1.14 - 4.96)	0.02
Age group (years)			
< 40	Reference	-	-
40 - 60	1.09	(0.63 - 1.86)	0.75
> 60	1.26	(0.63 - 2.56)	0.51
Year			
2012	Reference	-	-
2013	0.50	(0.20 - 1.12)	0.10
2014	0.37	(0.14 - 0.86)	0.02
2015	0.31	(0.13 - 0.70)	0.01
2016	0.43	(0.16 - 1.09)	0.08
Percent of households in poverty at sector level	1.03	(1.01 - 1.05)	<0.01
Comorbidities	0.80	(0.46 - 1.44)	0.45
Health center participation in early detection intervention	0.28	(0.08 - 0.99)	0.05
Hormone receptor positive	0.49	(0.29 - 0.80)	0.01
Distance to nearest health center	0.96	(0.88 - 1.04)	0.28

Figures

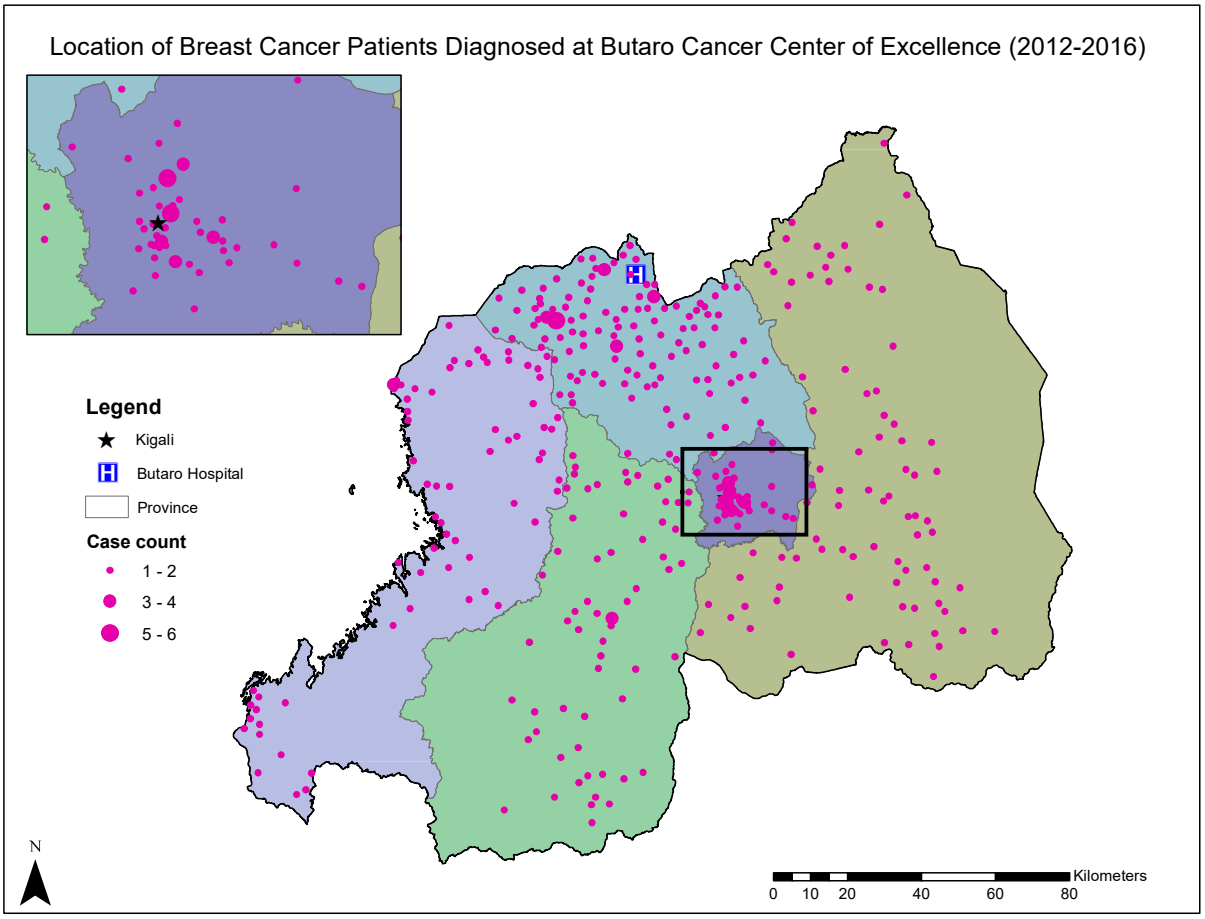

Figure 1. Location of breast cancer patients diagnosed at Butaro Cancer Center of Excellence from 2012-2016 and included in our study.

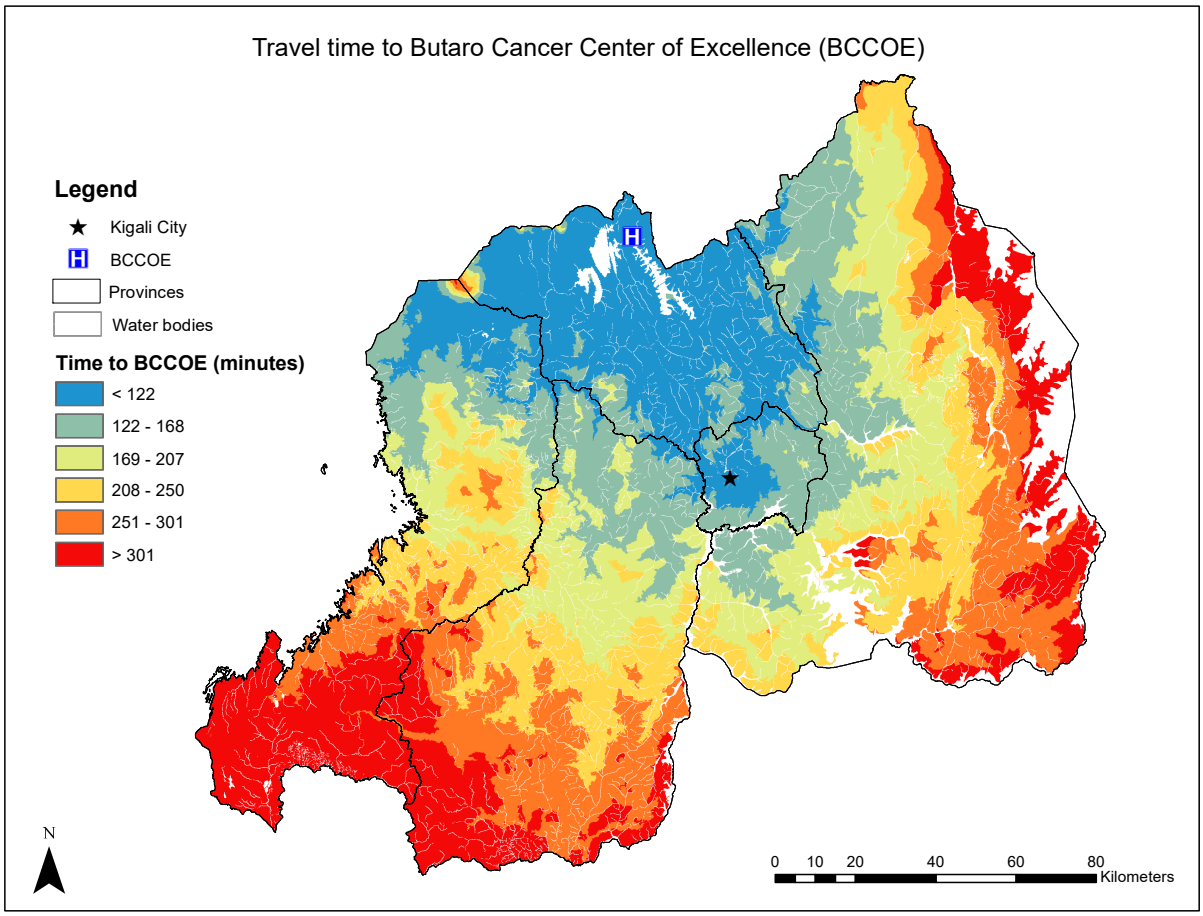

Figure 2. Travel time to Butaro Cancer Center of Excellence based on AccessMod5 estimates.

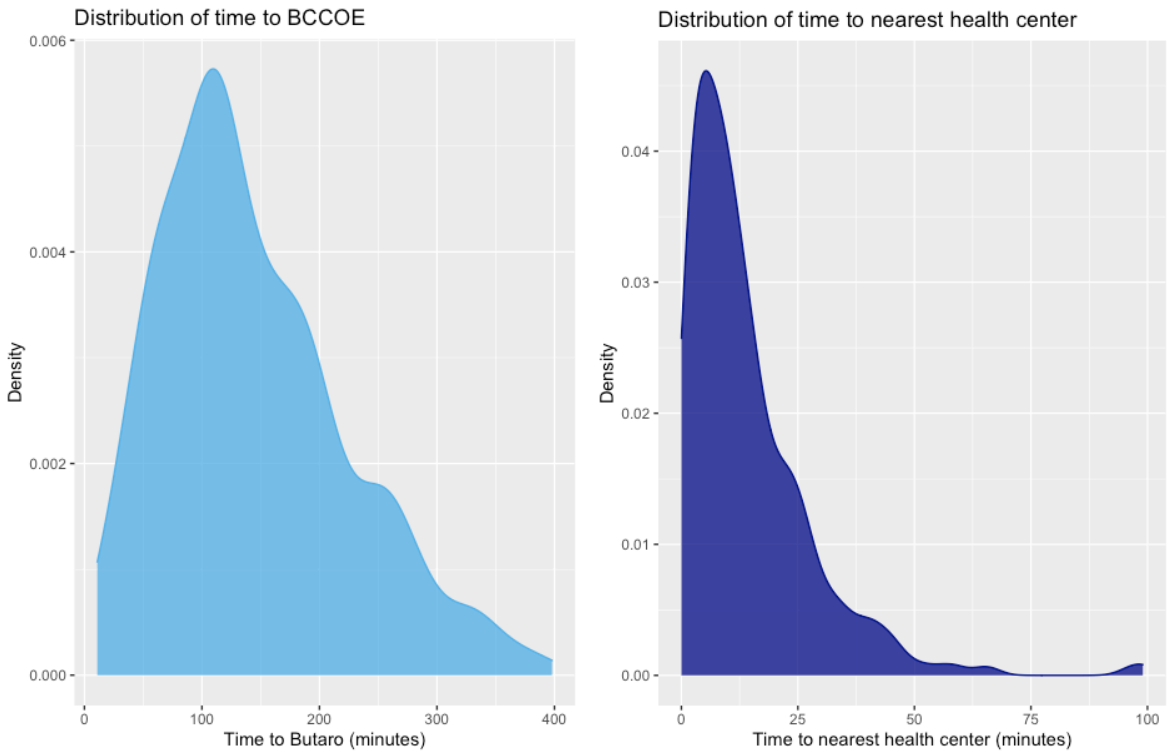

Figure 3. Density plots describing the distribution of time to to Butaro Cancer Center of Excellence and time to nearest health center.

Supplementary appendix tables

Table A1. Patient characteristics by distance quartile.

	All Patients (n=446)	Q1	%	Q2	%	Q3	%	Q4	%	p-value
Stage										
Early	108	33	29.2	29	26.4	29	26.1	17	15.2	0.07
Late	338	80	70.8	81	73.6	82	73.9	95	84.8	
Age group (years)										
< 40	114	31	27.4	26	23.6	34	30.6	23	20.5	
40 - 60	242	54	47.8	63	57.3	57	51.4	68	60.7	0.40
> 60	90	28	24.8	21	19.1	20	18.0	21	18.8	
Year of presentation										
2012	76	13	11.5	21	19.1	19	17.1	23	20.5	
2013	116	24	21.2	41	37.3	26	23.4	25	22.3	
2014	94	31	27.4	15	13.6	20	18.0	28	25.0	0.06
2015	95	26	23.0	21	19.1	26	23.4	22	19.6	
2016	65	19	16.8	12	10.9	20	18.0	14	12.5	
HIV positive										
No	418	105	92.9	103	93.6	104	93.7	106	94.6	0.96
Yes	28	8	7.1	7	6.4	7	6.3	6	5.4	
Any comorbidities										
No	361	92	81.4	86	78.2	92	82.9	91	81.3	0.84
Yes	85	21	18.6	24	21.8	19	17.1	21	18.8	
Hormone receptor positive										
No	176	33	29.2	40	36.4	56	50.5	47	42.0	0.01
Yes	270	80	70.8	70	63.6	55	49.5	65	58.0	
Sector Poverty level										
1 -2	115	10	8.8	46	41.8	36	32.4	23	20.5	
3 - 4	247	52	46.0	51	46.4	68	61.3	76	67.9	<0.001
5 - 6	84	51	45.1	13	11.8	7	6.3	13	11.6	

Table A2. Patient characteristics, for patients living in Kigali vs. rest of the country.

	All Patients (n=446)	Non-Kigali	%	Kigali	%	p-value
Stage						
Early	108	87	30.6	21	33.9	0.08
Late	238	197	69.4	41	66.1	
Age group (years)						
< 40	114	93	24.2	21	33.9	
40 - 60	242	210	54.7	32	51.6	0.20
> 60	90	81	21.1	9	14.5	
Year of presentation						
2012	76	65	16.9	11	17.7	
2013	116	86	22.4	30	48.4	
2014	94	91	23.7	3	4.8	<0.001
2015	95	84	21.9	11	17.7	
2016	65	58	15.1	7	11.3	
HIV positive						
No	418	363	94.5	55	88.7	0.14
Yes	28	21	5.5	7	11.3	
Any comorbidities						
No	361	318	82.8	43	69.4	0.02
Yes	85	66	17.2	19	30.6	
Hormone receptor positive						
No	176	149	38.8	27	43.5	0.57
Yes	270	235	61.2	35	56.5	
Sector poverty level						
1 - 2	115	65	16.9	50	80.6	
3 - 4	247	237	61.7	10	16.1	<0.001
5 - 6	84	82	21.4	2	3.2	

Table A3. Results of the multivariable model to assess the effect of distance from Butaro Cancer Center of Excellence on likelihood of late stage at breast cancer diagnosis, assessing distance as a continuous variable

Variable	OR	95% CI	p-value
Distance to BCCOE (km)	1.01	(1.001 - 1.009)	0.02
Age group (years)			
< 40	Referent	-	-
40 - 60	1.07	(0.62 - 1.83)	0.80
> 60	1.27	(0.64 - 2.58)	0.50
Year			
2012	Referent	-	-
2013	0.49	(0.20 - 1.10)	0.10
2014	0.37	(0.15 - 0.85)	0.02
2015	0.30	(0.12 - 0.68)	0.01
2016	0.42	(0.16 - 1.05)	0.07
Percent of households in poverty at sector level	1.03	(1.01 - 1.05)	<0.01
Comorbidities	0.82	(0.47 - 1.47)	0.49
Health center participation in early detection intervention	0.29	(0.08 - 1.02)	0.05
Hormone receptor positive	0.50	(0.30 - 0.81)	0.01
Distance to nearest health center	0.96	(0.88 - 1.04)	0.31

Table A4. Comparing results of multivariable logistic models stratified by wealth status to assess if poverty mitigates the effect of distance from BCCOE on likelihood of late stage at breast cancer diagnosis

	*Poverty level 1 -3 (N=211)**			*Poverty level 4 - 6 (N=235) **		
	OR	95% CI	p-value	OR	95% CI	p-value
Distance to BCCOE (km)						
Quartile 1 (<=55.2)	Reference	-	-	Reference	-	-
Quartile 2 (55.3-90.3)	0.88	(0.26 - 2.86)	0.83	2.05	(0.76 - 6.26)	0.18
Quartile 3 (90.4-139.3)	1.22	(0.36 - 3.95)	0.74	0.91	(0.36 - 2.38)	0.85
Quartile 4 (>139.3)	2.20	(0.63 - 7.54)	0.21	2.01	(0.71 - 6.41)	0.21

* Adjusted for age, year, poverty, comorbidities, distance to health center, health center participation in early detection intervention, and hormone receptor status.

Table A5. Sensitivity test using alternate travel speeds

Variable	OR	95% CI	p-value
Distance to BCCOE (km)			
Quartile 1 (<62)	Reference	-	-
Quartile 2 (62 - 93)	1.18	(0.54 - 2.38)	0.63
Quartile 3 (94-149)	1.52	(0.78 - 3.00)	0.21
Quartile 4 (>149)	1.99	(0.99 - 4.07)	0.06
Age group (years)			
< 40	Reference	-	-
40 - 60	1.11	(0.64 - 1.90)	0.70
> 60	1.31	(0.66 - 2.65)	0.45
Year			
2012	Reference	-	-
2013	0.50	(0.20 - 1.11)	0.10
2014	0.38	(0.15 - 0.88)	0.03
2015	0.31	(0.13 - 0.69)	0.01
2016	0.42	(0.16 - 1.05)	0.07
Percent of households in poverty at sector level	1.03	(1.01 - 1.04)	<0.01
Comorbidities	0.81	(0.46 - 1.45)	0.47
Health center participation in early detection intervention	0.29	(0.08 - 1.00)	0.05
Hormone receptor positive	0.50	(0.30 - 0.82)	0.01
Distance to nearest health center	0.96	(0.88 - 1.04)	0.32

Supplementary appendix figures

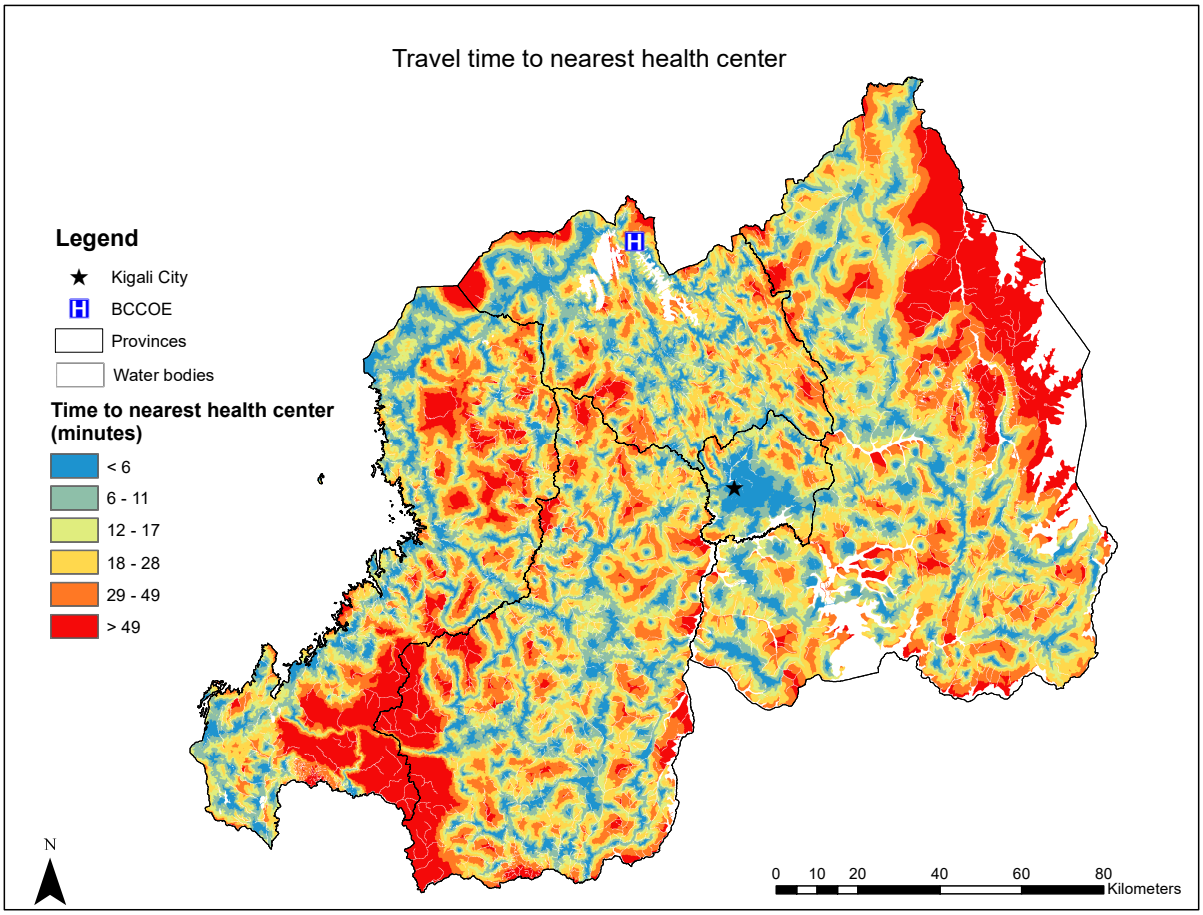

Figure A1. Time to nearest health center based on AM5 estimates.

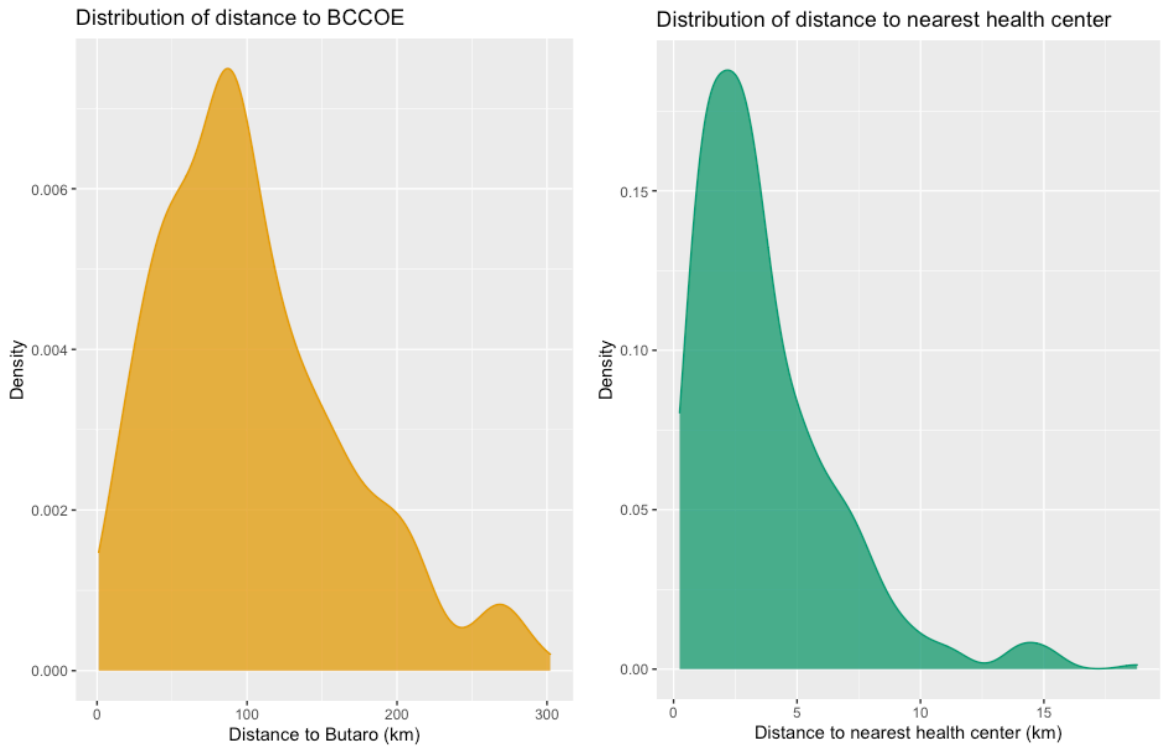

Figure A2. Density plots describing the distribution of distance to Butaro and distance to nearest health center, among patients in the study.

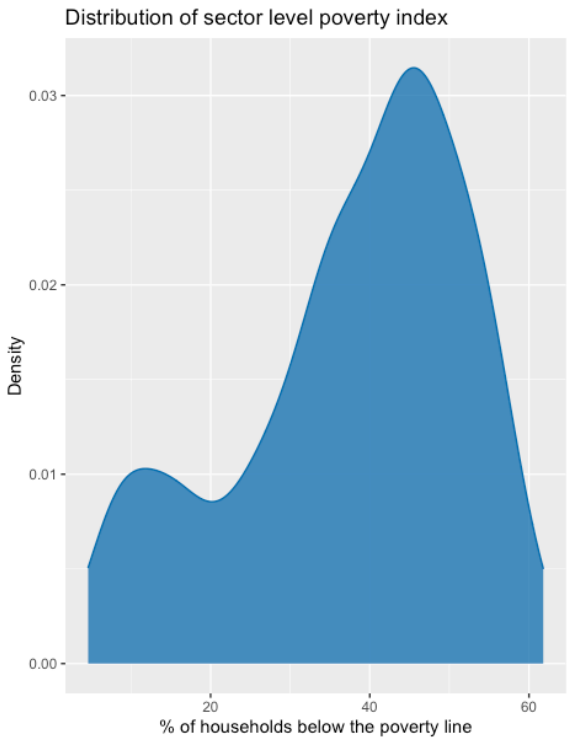

Figure A3. Density plot describing the distribution of sector level poverty index, among patients in the study.

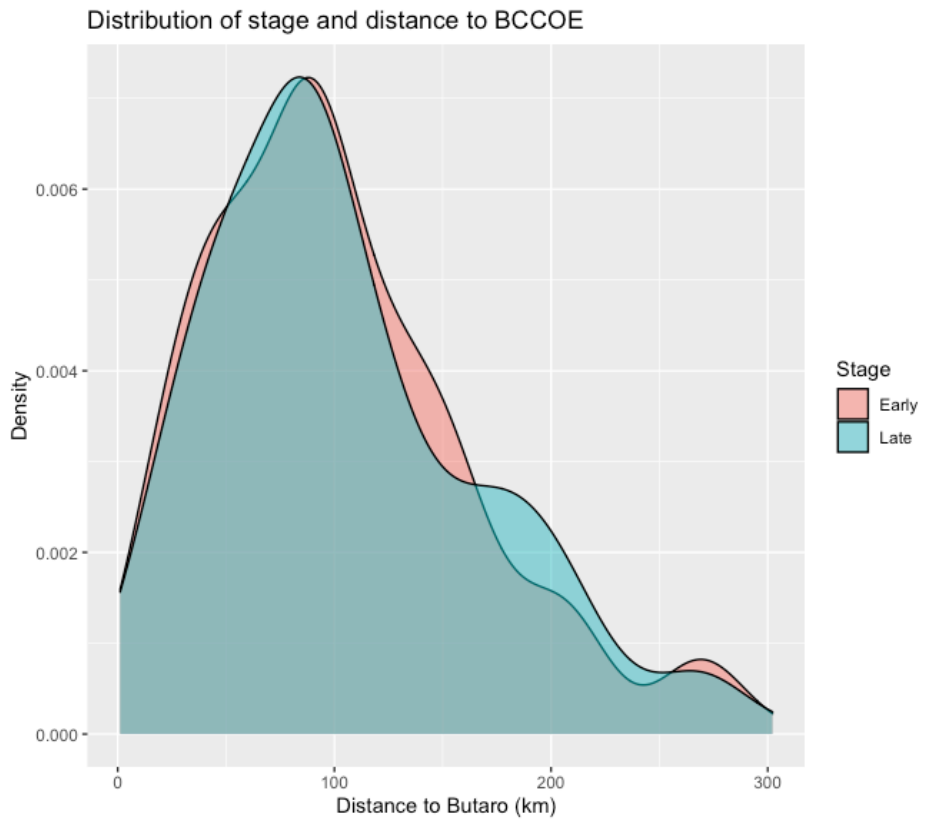

Figure A4. Comparing the distributions of distance to BCCOE by stage at presentation, among patients in the study.