

Evaluation of the Factors Associated with Delay in Initiation of Treatment of Advanced Stage Cervical Cancer Patients in Bangladesh

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Abstract

Research Background: Cervical cancer is the second most common cancer in women and the third leading cause of female cancer death in Bangladesh. Delay in initiation of treatment in advanced stage cervical cancer patients is an important modifiable risk factor for cancer-related mortality. Identifying elements associated with delay of diagnosis will help reduce barriers to timely treatment of cervical cancer. **Research Objectives:** The objective of this study was to analyze the factors leading to delay in diagnosis and treatment of women with advanced stage cervical cancer. **Methods:** A cross-sectional observational study analyzed the factors associated with delay in initiation of treatment for 138 patients with advanced-stage cervical cancer from November 2019 to October 2020 at the National Institute of Cancer Research and Hospital (NICRH) in Dhaka, Bangladesh. Advanced-stage cervical cancer patients between the ages of 30 to 70 years were included in this study. Face-to-face interviews with the participants used a predesigned data collection sheet. In this study, three components of delay were identified: primary delay due to patient factors, healthcare provider delay, and healthcare-system infrastructure delay. Factors associated with delay were the independent variables and durations of delay were the outcome variables. Descriptive statistics were expressed as mean \pm standard deviation, median, percentage, and frequency. **Results:** One hundred and thirty-eight patients with advanced stage cervical cancer were included in the study. The mean age of the patients was 48.74 (\pm 9.57) years. Thirty-four percent of patients were illiterate. More than half (57.25%)

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of the patients were from lower middle-class families. Delays were categorized as patient-related, healthcare provider delay, and healthcare-system infrastructure related. Patient-related factors included low monthly income, residence in a rural area, embarrassment, fear, lack of knowledge regarding cervical cancer, delay in contacting a spouse, family member or friend prior to the first medical encounter. These elements predicted a primary delay of more than 60 days (P value < 0.05) for 70.29% of patients. Healthcare providers' delay-related factors included not performing a speculum examination at initial consultation, misdiagnosis, and consultation more than three times in different health facilities prior to referral to tertiary care center hospital and were associated with a delay of more than 30 days (P value < 0.05) and were experienced by 83.33% of patients. The major healthcare-system infrastructure delay-related factor was a long distance between the primary healthcare facility and the tertiary care center hospital from the patients' residences (P value < 0.05). Overall, the median duration of patient-related delay was 75.51 days, healthcare provider delay was 44.03 days and healthcare-system infrastructure delay was 47 days to the initiation of treatment. **Conclusion:** Three broad categories of delay in diagnosis and treatment of cervical cancer: patient-related factors, healthcare provider-related factors, and healthcare-system infrastructure factors were analyzed. Illiteracy, lack of awareness regarding cervical cancer, lack of health-seeking behavior, and poor income status were associated with patient-related primary delay. Nonperformance of speculum examination in the initial consultation, misdiagnosis, inappropriate management, and delay in referral to the cancer treatment center by primary healthcare providers were the contributing factors for healthcare provider delay. Lack of availability and accessibility of health services and limitation of radiotherapy resources led to healthcare-system infrastructure delays. All three categories of delay must be addressed through the education of communities, the gynecologic training of community healthcare providers, the improvement of medical infrastructure, and the increase of medical resources.

Keywords

Advanced Cervical Cancer, Diagnostic Delay, Therapeutic Delay, Patient-Related Delay, Healthcare Provider Delay, Healthcare-System Infrastructure Delay

1. Introduction

A delay in the initiation of treatment for advanced-stage cervical cancer patients is associated with significant cancer-related morbidity and mortality. The risk of dying from cervical cancer is directly related to the stage at presentation and inability to receive definitive therapy [1]. Globally, cervical cancer contributes to approximately 604,127 new cases, representing 6.5% of all female cancers and 341,831 deaths, the majority coming from low and middle-income countries (LMICs) [2] [3]. In high-income countries, 75% of cervical cancer cases are

diagnosed at early stages, but in LMICs, 75% of cases are diagnosed with advanced stage [4]. Delay in diagnosis is a major issue in cancer treatment and control. Early identification of advanced stage cervical cancer will result in early initiation of treatment, which will help reduce mortality and morbidity and improve survival [5] [6].

In Bangladesh, cervical cancer is the second most common cancer in women. The actual national incidence of cervical cancer in Bangladesh is unknown as there is no national cancer database [7]. An estimate of the number of annual cases and deaths respectively of cervical cancer in South Asia, excluding India, is 24,221, with 14,637 deaths and 123,907 cases, with 77,348 deaths in India alone [3]. The World Health Organization (WHO) issued a call to action to eliminate the cervical cancer globally by achieving 90% HPV vaccination coverage, 70% screening coverage and 90% treatment for cervical pre-cancer and cancer by 2030 [8]. To achieve this goal, priority has been given to the screening and treatment of precancerous lesions and cancers. In a survey of national databases in Denmark, four characteristics of delay of interventions for patients, and healthcare systems were identified: age of patients, the presence of alarm symptoms, the performance of a pelvic examination by the general practitioner, and notification of suspicion of cancer by the general practitioner on first referral [9]. In Bangladesh, three major factors are responsible for delays in diagnosis leading to advanced-stage cervical cancer. There is a need for a comprehensive approach to address these three major delays: primary delay due to patient factors, healthcare provider delay and healthcare-system infrastructure delay during the different phases of the diagnostic and therapeutic journey. Patient-related factors cause delay due to decision making, resources, and education at the individual and family level. Healthcare provider-related factors cause delay due to a lack of provider training, lack of diagnostic resources including ability to perform a pelvic exam, obtain biopsies and radiologic imaging and make appropriate referrals to cancer centers. Healthcare-system infrastructure-related factors cause delay due to the inability to commence timely treatments [10]. These delays can be described through the social ecology lens of public health [11]. These delays are influenced by different conditions and characteristics related to either patients, healthcare providers or service delivery systems [10] [12]-[15]. Primary delay is defined as the duration between the onset of symptoms and the first presentation to healthcare providers [16]. Primary delay is the major contributor to delay in diagnosis and it is mainly influenced by the patient's characteristics including age, sociodemographic and cultural factors [17]. Secondary delay or healthcare provider delay, which takes place between the first medical consultation and the definite diagnosis and referral for treatment, encompasses inadequate knowledge about cancer, not performing speculum examination during initial consultation, poor communication, and inappropriate treatment [18]. Tertiary delay or healthcare-system infrastructure delay is defined as the time from a confirmed diagnosis to the start of treatment [12]. Healthcare-system infrastructure delay-

related factors include ineffective transfer systems, inaccessibility and lack of infrastructure [12]. Primary delay of more than ninety days and tertiary delay of more than four weeks are associated with increased mortality [13]. Primary delay is of crucial importance because of its longer span; however, tertiary delay is equally important [14]. Treatment initiation time is a decisive factor in the prognosis, survival of the patient and quality of life [15] [19]-[21].

National Institute of Cancer Research and Hospital (NICRH) is the only tertiary care government referral cancer center in Bangladesh where cervical cancer patients from all over the country come to receive treatment [22]. Most cervical cancer patients seen at NICRH are present at advanced stage [23]. This study evaluates the experience of patients receiving care at NICRH and examines the factors associated with late-stage diagnosis of cervical cancer to gain insight into how to overcome the obstacles for timely initiation of treatment. Direct qualitative evaluation through interviews with women with advanced cervical cancer of the barriers and challenges to diagnosis of cancer and to receiving care is the first step to developing infrastructure necessary to reduce presentation at advanced and potentially incurable stages of cervical cancer.

2. Methods

A cross-sectional observational study analyzed the factors associated with delay in initiation of treatment for 138 patients with advanced-stage cervical cancer from November 2019 to October 2020 at the National Institute of Cancer Research and Hospital (NICRH) in Dhaka, Bangladesh. Advanced-stage cervical cancer patients between the ages of 30 to 70 years were included in this study. Terminally ill patients, patients with psychiatric illness (who could not give consent), a history of previous hysterectomy, or prior exposure to chemotherapy were excluded from the study. Ethical approval was obtained from the Ethics Committee of NICRH. No human samples were part of this study's protocol. The tools involved in the process of putting forward the idea, carrying out the research, obtaining and organizing data, statistical analysis, drawing charts and displaying the research in sequence used included questionnaires, surveys, and group discussions [24]. The roadmap of this research included recruiting patients, administering questionnaires, abstracting the data into data sheets, and performing multivariate analyses.

Nonprobability purposive sampling method was used in this study [25]. Cervical cancer patients with histopathological evidence confirmed by biopsy after attending the outpatient department of Gynecological Oncology of NICRH, were evaluated by history and clinical examination to confirm the clinical stage. Computed tomography scan or magnetic resonance imaging, examination under anesthesia, cystoscopy, and intravenous urography were performed to assign the stage of the cancer. One hundred thirty-eight patients were included in this study. The aims and objectives of the study were explained to the patients. Written informed consent was obtained from each participant. Face-to-face interviews with

the participants used a predesigned data collection sheet. In this study, three components of delay were identified: primary delay due to patient factors, healthcare provider delay, and healthcare-system infrastructure delay. Factors associated with delay were the independent variables and durations of delay were the outcome variables. Descriptive statistics were expressed as mean \pm standard deviation, median, percentage, and frequency. Both bivariate and multivariate binary logistic regression analysis were performed to identify the significantly associated factors. A value of $P < 0.05$ indicates a significant association. Health system interval is the time interval between the date of the first presentation to a healthcare provider and the date of initiation of treatment [26]. Primary delay < 60 days and health system delay < 30 days were considered as the reference category. Statistically significant associated factors estimated by bivariate analysis were included in the final model. Multivariate analysis was used to estimate adjusted Odds Ratios (ORs) with 95% confidence intervals using the Wald statistic to estimate adjusted ORs. After cleaning and checking the accuracy of the data, the collected data were coded, transferred and analyzed by using the SPSS for Windows (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY: IBM Corp.).

World Bank data was used to define income levels [27]. Low income is defined as earning less than or equal to 4920 Bangladesh taka (TK) (\$58 USD) per month. Low-middle income is a monthly income ranging from 4920 TK to 24,600 TK (\$290 USD). The middle-income group included those earning 24,600 TK to 49,200 TK (\$580 USD) per month. Upper middle-income levels are between 49,200 TK and 1,230,000 TK (\$1450 USD) per month, and high-income levels are greater than 1,230,000 TK per month in Bangladesh. There were no participants at NICRH in the low or high-income socio-economic category. No external sources of funding were used for this study.

3. Results

The social and demographic characteristics of the 138 advanced-stage cervical cancer patients who attended NICRH during the study period are summarized in **Table 1**. The mean age of the patients was 48.74 (± 9.16) years. About 37.7% (52) had completed primary education while 30.4% of respondents were illiterate. Seventy-seven percent of the participants were unemployed. About one-third (31.9%) of the patients' husbands were unemployed and the husbands of 59 (42.8%) patients were day laborers. Income status was low and middle in 50% (69) of study population. Eighty-eight (63.77%) of participants were residents of rural areas and the remainder lived in urban areas. Only 82 of the 138 women (60%) had a nearby screening facility. Participants' emotional responses and awareness regarding cervical cancer are summarized in **Table 2**. Fifty-three (38.40%) respondents did not attend healthcare facilities due to fear and 29.72% (41) were embarrassed to attend the health facilities. Only 21 (15.22%) patients knew about cervical cancer and only 17 (12.3%) patients had heard about screening for cervical cancer. Only ten of the 138 women (7.2%) knew about HPV vaccination as a preventative measure

against cervical cancer.

Table 1. Social and demographic characteristics of 138 women with cervical cancer.

CHARACTERISTICS	PARTICIPANTS N (%)
<i>AGE</i>	
<45	44 (31.88)
45 - 54	56 (40.58)
55 - 64	26 (18.84)
>65	12 (8.70)
<i>EDUCATIONAL STATUS</i>	
Illiterate	42 (30.4)
Primary Education	52 (37.7)
Secondary Education	31 (22.5)
Higher Secondary	9 (6.5)
Graduate	4 (2.9)
<i>OCCUPATION OF PARTICIPANT</i>	
Unemployed	107 (77.54)
Day Laborer	29 (21.01)
Office Work	2 (1.45)
<i>OCCUPATION OF SPOUSE</i>	
Unemployed	35 (25.4)
Day Laborer	59 (42.7)
Office Work	44 (31.9)
<i>FAMILY INCOME</i>	
Low	19 (13.77)
Low Middle	79 (57.25)
High Middle	40 (28.98)

Table 2. Emotional reaction and awareness regarding cervical cancer among 138 participants.

CHARACTERISTICS	PARTICIPANTS N (%)
Avoidance of seeking medical care due to fear	53 (38.4)
Avoidance of seeking medical care due to embarrassment	41 (29.7)
Aware of cervical cancer	21 (15.2)
Understand there is screening for cervical cancer	17 (12.3)
Aware of HPV vaccination	10 (7.2)

Table 3 summarizes the symptoms presented by the 138 participants. Half of the patients noted intermenstrual bleeding. Approximately one-fourth of the patient presented with postcoital bleeding and foul-smelling vaginal discharge. Postmenopausal bleeding was present in thirty patients. Painful sex, pelvic pain and dysuria were found in seventeen (12.31%) cases. At the initial evaluation of these women at their local health centers: pelvic speculum exam was not performed for 104 (75.36%) patients. The distribution of stage is summarized in **Figure 1**. Fifty-nine (42.75%) patients were suffering from stage IIB disease. Forty-five women

had stage IIIB (32.6%). Ten patients (7.25%) had stage IIIC disease, while thirteen patients (9.42%) were presented with stage IVA disease. The majority of the patients, 106 women, had developed squamous cell carcinoma (76.8%). Adenocarcinoma was diagnosed in 29 patients (21%). Two patients had adenosquamous histology, and one patient had a clear cell carcinoma subtype. The health-seeking behaviors of the participants are summarized in **Table 4**. The husband was the first contact person with which to share the problem for 49 (35.9%) respondents. Another 42.8% and 21.7% of the respondents shared their problems with other family members and friends, respectively.

Table 3. Presenting symptoms of 138 participants with cervical cancer.

SYMPTOMS	PARTICIPANTS N (%)
Postcoital Bleeding	36 (26.09)
Foul Smelling Vaginal Discharge	35 (25.36)
Postmenopausal Bleeding	30 (21.74)
Intermenstrual Bleeding	69 (50)
Painful Sex, Pelvic Pain, Dysuria	17 (12.32)

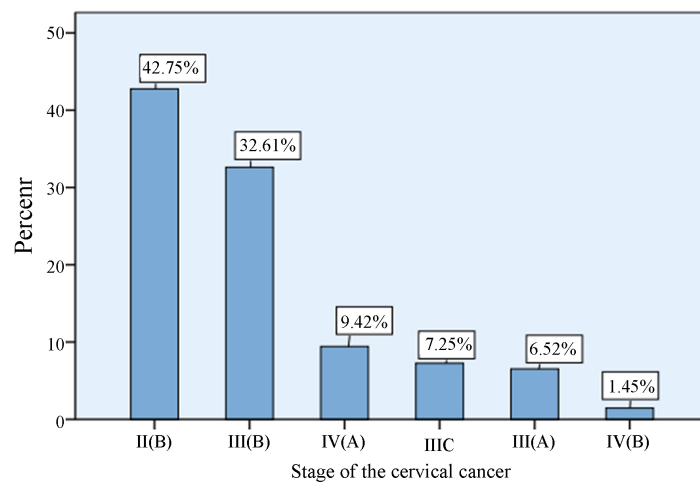


Figure 1. Distribution of 138 patients by stage of tumor.

Table 4. Health seeking behaviors of 138 participants.

RESOURCE	PARTICIPANTS N (%)	PARTICIPANTS N (%)	PARTICIPANTS N (%)
<i>FIRST CONTACT PERSON</i>	<i>Husband</i>	<i>Other Family Members</i>	<i>Friend</i>
	49 (35.5)	59 (42.8)	30 (21.7)
	<i>HEALTHCARE PROVIDER/ FACILITY</i>	<i>Traditional Healer</i>	<i>Government Hospital</i>
52 (37.7)		38 (27.5)	48 (34.8)
<i>NUMBER OF PRE-REFERRAL PROVIDERS/ FACILITIES</i>		<i>One</i>	<i>Two</i>
	22 (15.9)	52 (37.7)	64 (46.4)

Table 5 summarizes the estimated distance between the primary healthcare center and the cancer center, National Institute of Cancer Research and Hospital (NICRH), from the residence of participants. Most of the patients (68.84%) lived more than ten kilometers from the primary healthcare center. The cancer care center was more than 100 kilometers for 67.39% of respondents and most of them lived within 150 - 300 kilometers. Primary delay due to patient-related factors ranged from a minimum of 60 days to a maximum of 125 days, with a median of 75.51 days. healthcare provider delays ranged from a minimum of 13 days to a maximum of 110 days, with a median of 44.03 days. A median of 47 days accounted for delays due to healthcare-system infrastructure factors (minimum 12 days to maximum 70 days). The duration of primary delay was >60 days for 97 (70.29%) respondents. The health system interval (delay from diagnosis to presentation at NICRH) was >30 days in 115 (83.33%) of the participants. **Table 6** summarizes the correlation between a delay of greater than 60 days due to patient factors and stage of cervical cancer at diagnosis with an adjusted odds ratio of 3.8 and 12 for those presenting with Stages III and IV disease, respectively. **Table 7** summarizes the factors significantly associated with delay in treatment initiation. Symptomatic patients with vaginal bleeding, such as postcoital bleeding, intermenstrual bleeding, and postmenopausal bleeding, were less likely to have longer primary delay than patients without these symptoms. Older patients, residents of rural areas, illiteracy, fear and embarrassment were significantly associated with longer primary delays when adjusting for other covariates.

Table 5. Distribution of 138 participants by estimated distance to NICRH.

DISTANCE FROM HOME TO NICRH (KILOMETERS)	PARTICIPANTS N (%)
<40	14 (10.1)
40 - 80	15 (10.9)
80 - 150	24 (17.4)
150 - 300	60 (43.5)
300 - 500	25 (18.1)

Table 6. Patient-related primary delay and stage of cervical cancer at diagnosis for 138 participants.

STAGE	PRIMARY DELAY < 60 DAYS N (%)	PRIMARY DELAY > 60 DAYS N (%)	ADJUSTED ODDS RATIO (95% CI)	P-VALUE
IIB	29 (49.16)	30 (50.84)	1	
IIIA-IIIC	11 (17.18)	53 (82.82)	3.87 (1.672, 9.763)	<0.05
IVA-IVB	1 (0.15%)	14 (99.85)	12.06 (1.573, 100.994)	<0.05

Table 7. Patient-related factors and delays less than or greater than 60 days.

PRIMARY DELAY FACTORS	FACTOR SPECIFICS	PRIMARY DELAY < 60 DAYS N (%)	PRIMARY DELAY > 60 DAYS N (%)	ADJUSTED ODDS RATIO (95% CI)	P-VALUE
Age	<45	3 (7.97)	7 (92.02)	1	
	45 - 54	15 (17.85)	54 (82.15)	4.973 (1.874, 10.454)	
	55 - 64	6 (23.07)	20 (76.93)	3.193 (1.043, 9.765)	<0.05
	>65	2 (16.66)	10 (83.33)	5.109 (1.023, 25.344)	<.05
Symptoms	Intermenstrual bleeding yes/no	Yes 29 (42.02)	Yes 40 (57.98)	0.345 (0.154, 0.845)	
		No 12 (17.40)	No 57 (82.60)	1	
	Postmenopausal bleeding yes/no	Yes 14 (46.66)	Yes (53.54)	0.389 (0.174, 0.967)	<0.05
		No 27 (25)	No 81 (75)	1	
Pain yes/no	Yes 10 (53.34)	Yes 7 (46.66)	0.321 (0.104, 0.965)		
	No 34 (27.64)	No 89 (72.36)	1		
Residency	Urban	21 (51.21)	20 (48.79)	1	
	Rural	26 (27.36)	69 (72.63)	2.25 (1.354, 4.445)	<.05
Husband Occupation	Office work	9 (25.71)	26 (74.28)	1	
	Laborer	4 (6.89)	54 (93.11)	3.11 (2.722, 8.995)	<0.05
	Unemployed	27 (79.41)	17 (20.58)	0.342 (0.093, 0.875)	
Education	Illiterate	12 (28.57)	30 (71.42)	4.993 (1.997, 10.421)	<0.05
	Primary	19 (36.53)	33 (63.46)	3.021 (1.133, 9.823)	
	Secondary	18 (58.06)	13 (41.93)	2.001 (0.965, 6.122)	
	Higher	9 (81.81)	2 (18.18)	1	
Emotional/Cultural Response	Fear yes/no	Yes 9 (16.36)	Yes 44 (83.64)	3.547 (1.967, 7.498)	<0.05
		No 3 (5.35)	No 53 (94.64)	1	
	Embarrassment yes/no	Yes 3 (7.31)	Yes 38 (92.6)	6.004 (2.698,15.131)	<0.05
		No 38 (39.18)	No 59 (60.82)	1	
Knowledge of cervical cancer	Cancer yes/no	Yes 10 (47.61)	Yes 11 (52.39)	1	
		No 29 (24.78)	No 88 (75.22)	1.932 (0.753, 5.723)	
	Screening yes/no	Yes 8 (47.05)	Yes 9 (52.95)	1	
		No 28 (23.14)	No 93 (76.86)	2.311(1.038, 10.53)	
First person to share problem with	Husband	27 (55.11)	22 (44.89)	1	
	Female family	8 (13.55)	51 (86.45)	9.164 (4.724, 14.93)	
	Friend	6 (20)	24 (80)	2.315 (1.038, 10.53)	<0.05
Type of first healthcare contact	Traditional Healer	18 (34.62)	34 (65.38)	1	
	Government Hospital	22 (57.90)	16 (42.10)	0.438 (0.198, 1.126)	
	Private Hospital	16 (33.34)	32 (66.66)	1.769 (0.53, 2.856)	

Table 8 shows factors associated with longer health system intervals. The patients who underwent >3 pre-referral consultations in different health facilities and in whom pelvic and speculum examinations were not performed during initial visits were more likely to have longer health system intervals. Long distances to NICRH from participants' residences, such as 150 - 300 km or greater than 300 km, were more likely to have longer health system intervals, including those who were living greater than 10-kilometer distances from their primary healthcare facilities.

Table 8. Factors associated with longer interval to definitive cancer therapy (Health System Interval).

DELAY RELATED FACTORS		HEALTH SYSTEM INTERVAL < 30 Days N (%)	HEALTH SYSTEM INTERVAL > 30 days N (%)	ADJUSTED ODDS RATIO (95% CI)	P-VALUE
<i>HEALTHCARE PROVIDER</i>					
# of pre-referral visits	<3	27 (36.48)	47 (63.52)	1	<0.05
	≥3	12 (18.75)	42 (81.25)	2.239 (1.7645, 5.835)	
Pelvic & Speculum Exam	Yes	11 (32.35)	23 (67.64)	1	<0.05
	No	12 (11.53)	92 (88.46)	3.351 (1.253, 7.893)	
<i>HEALTHCARE SYSTEM</i>					
Distance to primary healthcare facility	<10 km	20 (43.47)	23 (56.52)	1	<0.05
	>10 km	11 (12.95)	74 (87.05)	2.754 (1.125, 5.594)	
Distance to Cancer Center <i>kilometers</i>	40	2 (50)	2 (50)	1	
	41 - 80	7 (36.84)	12 (63.15)	1.432 (0.15, 13.12)	
	81 - 150	8 (19.51)	33 (80.49)	3.749 (0.46, 31.95)	
	151 - 300	5 (26.31)	44 (73.69)	7.774 (0.965, 73.734)	<0.05
	300 - 500	1 (7.7)	12 (92.3)	22.32 (1.134, 338.927)	<0.05

4. Discussion

Delays in the evaluation of abnormal signs and symptoms concerning cervical cancer and diagnosis increase the proportion of women who present with advanced stages of this malignancy. These delays are associated with poorer prognosis and quality of life [28]. In a recent systematic search of studies from three global regions, the prevalence of late-stage presentation of cervical cancer ranged from 46% in Europe, to 50% in North America, to 62% in Africa, to 69% in Asia [29]. Over forty percent of our advanced stage cervical cancer patients were suffering from stage IIB and over thirty percent had Stage IIIB disease, similar to the findings of other investigators [30]. About seventy-seven percent of our patients had squamous cell carcinoma, as seen in other reports [31]. Our study revealed that primary delays of greater than 60 days were four times and twelve times more likely in Stage III and Stage IV, respectively, than the patients with Stage II cervical cancers (P value < 0.05). This excessive delay unfortunately correlates with progression to the advanced stage and has been identified in other low-resource countries [32].

In our study, delay was classified as a primary delay due to patient factors, healthcare provider (HCP) delay and healthcare-system infrastructure (HCS) delay. Factors associated with the delay in initiation of treatment were identified and related to each of these three delay categories. We found that the median duration of primary delay, HCP delay and HCS delay was 75.51 days, 44 days and 47 days, respectively. Median primary delay was higher than the studies conducted in Morocco and Nepal which were 68 days but lower than in other countries where patient delays were over 60 days in over half of patients [14] [26] [30] [33] [34]. Delays vary due to the influences of patient characteristics such as level of education, health awareness, economic conditions, health-seeking behaviors, and traditional practices.

The demographics of our patients were similar to those in other studies from resource-limited countries. In this study, the mean age of patients was 48.74 years, 30.4% of patients were illiterate and 37.7% completed their primary education. Elevated risks for primary delay were observed for patients who were illiterate (AOR = 4.993, 95% CI (1.997, 10.421) P value 0.002) and in patients with poor income status income (AOR = 3.545; 95% CI (2.456, 11.351)). Similar results were observed in other countries [33]. Our patients older than 65 years were 5.5 times more likely to have a primary delay than the patients less than 45 years old. Comparable observations have documented that treatment refusal rates increased with increasing age of the cancer patient (AOR = 5.109 (1.002, 25.340) P value 0.03) [12].

In our study, patients with higher per capita family monthly income and those with higher education levels might have positive health seeking behaviors when faced with early symptoms of cervical cancer. Most of the families belonged to the low middle income group. These findings are consistent with the experience on the Indian subcontinent [12] [35] [36]. Two-thirds of the patients were residents of rural areas. Our patients who were residents of rural areas were more likely to have primary delays with AOR 2.25, 95% CI (1.35, 4.44). This can be explained by the existence of great inequality in the distribution of healthcare between rural and urban areas and differences in socioeconomic status between urban and rural areas [12] [33]. In a meta-analysis of ten reports from Ethiopia, where 60% of cervical cancer patients present with advanced disease, rural residence was the leading risk factor for delayed presentation (adjusted Odds ratio of 2.07) [37]. The occupations of husbands were day laborers for 42.85% of the patients. This finding is consistent with a study conducted in Morocco [30] [38]. Patients whose husbands were day laborers were three times more likely to have primary delays greater than 60 days than office workers.

The binary logistic regression analysis identified the association of primary delay and related factors, which include symptoms, sociodemographic factors, fear, embarrassment and lack of awareness about cervical cancer. Most of our respondents presented with intermenstrual bleeding (IMB) (50%), postcoital bleeding (PCB) (26%), postmenopausal bleeding (PMB) (22%), and foul-smelling discharge (25%). In a series from Mexico, vaginal bleeding was also the most common

symptom in 65.9% of patients [34]. In a cross-sectional study from India, time from symptoms to seeking care for cervical cancer averaged 80 days and the patients' lack of awareness of cervical cancer was the leading reason for delay [39]. Our study revealed that women with abnormal vaginal bleeding such as PCB, IMB or PMB as early symptoms were less likely to have primary delays, compared to women who did not have the symptoms (P value < 0.05). This indicates that the nature of the early gynecological symptoms may determine the health seeking behavior of women. The present study is consistent with previous studies [33] [38] [40].

In our study, fear (38.40%) and embarrassment (29.78%) were important barriers to timely presentation at local primary care clinics and revealed a significant association between primary delay and psycho-cultural factors (P value < 0.05). In India, these factors were present but less significant with 16% and 10 % of patients reporting fear and shame, respectively [41]. These results may differ due to cultural differences [42].

Awareness regarding cervical cancer may influence the time to help seeking and diagnosis of cancer. We identified a lack of education and awareness of cervical cancer as important factors impeding the timely presentation of medical care. In our study, over eighty percent of patients did not know about cervical cancer and only twelve percent had heard about cervical cancer screening. This finding is parallel with reports from Ethiopia, which revealed only 16.6% of patients had heard about cervical cancer and 9% had knowledge about cervical cancer screening [33] [37]. Lack of population-based screening programs and ineffective mass media campaigns might be the cause of this suboptimal knowledge. Only seven percent of our respondents knew about HPV vaccines. This finding was also reported in Moroccan patients where only 11.2% patients knew about HPV vaccination [30]. In our study, patients who had not heard about cervical cancer or screening were more likely to have primary delays greater than 60 days (P value < 0.05). Similar factors were observed in other studies in Malawi and Ethiopia [33] [43]. A scoping review of cancer screening in Bangladesh also identified lack of education, fear, and shyness as barriers to screening and early diagnosis of cervical cancer [44]. In a survey of households in remote rural areas of Bangladesh, only 20% of respondents knew about HPV [45].

In rural Bangladesh, women are commonly not the decision makers for their own medical care and their husbands or mothers-in-law are responsible for these important decisions [45]. In our study, the husband was the first contact person for thirty-six percent of patients who shared information about their abnormal symptoms. Forty-three percent of patients shared their problems with other family members. The case series from Ethiopia reports similar findings [33]. Our patients who shared their problems with persons other than their husbands or family members and who contacted nonmedical persons or traditional healers prior to seeing healthcare providers were more likely to delay definitive care (P value < 0.05). This risk factor for delay was also identified by other investigators [30] [46].

As was found in Nepal, traditional healers (37.7%) and private hospitals (34.8%) were the main primary contact point with a healthcare provider for our patients [14]. Only twenty-seven percent of our patients visited government hospitals. Government hospitals can provide cheaper and more accessible care to the rural communities of Bangladesh [47].

The distance from residence to the primary healthcare facility was more than ten kilometers for nearly seventy percent of our patients. In Morocco, 44% patients lived greater than ten kilometers from the nearest clinic [30]. In our study, two-thirds of our patients lived more than 100 kilometers, of which 43.5% lived within 150 to 300 kilometers of the cancer center. Patients in Nepal had a similar experience where 40% lived more than 100 kilometers from the cancer facility [14]. Our study supports previous experiences that the increasing distance of healthcare facilities from residence was a significant delay variable for all three domains of delay: Patients who lived within 40 kilometers of a cancer center and within 10 kilometers to a primary healthcare center were less likely to have > 30 days delays [19] [42] [48]. In Bangladesh, inaccessibility may be due to inadequate numbers of both primary health and regional cancer treatment centers. Increasing distances to receive definitive cancer treatment is a major barrier to treatment initiation due to accessibility of transport, costs of travel, and costs of finding local places to stay during treatment. In a review of 27 studies pooling the experiences of over 700,000 cancer patients, there was an association between distance and travel time to the hospital and an increase in more advanced disease at diagnosis, inappropriate treatment, and worse prognosis [49].

Healthcare providers influence women's health seeking behaviors. It was found that the underutilization of knowledge for diagnosis of cervical cancer leads to misdiagnosis and inappropriate management by the healthcare providers and ultimately delays of diagnosis and referral. We found that primary healthcare providers did not perform a pelvic examination in 75.36% patients during the initial consultation. This finding is parallel with reports from India and Nepal [14] [35]. Not performing a pelvic examination during the initial consultation and failure to make an appropriate diagnosis by the primary healthcare provider was also significantly associated with greater than 30 days delay. This important healthcare provider-related delay factor has been well documented in other resource-limited countries as well [30] [33] [46]. The ability and agency of a primary healthcare provider to perform a pelvic examination is complicated by many factors including training and familiarity with this examination on the part of the provider, to obtaining permission from the patient, their husband or other head of household to perform the examination, cultural and religious structure against examination by a member of the opposite gender [50] [51].

In our study, 37.7% of patients visited two, 29.7% of patients visited three and 16.7% of patients went to more than three health facilities before receiving a diagnosis. Other studies revealed that 21% visited two centers in Ghana and 69% of patient visited two to three health facilities in Nepal [14] [31]. In our study,

consultations more than three times in different health facilities prior to referral to study hospital were associated with >30 days delay to referral to a cancer center. We found that only 16.67% of patients started treatment within 30 days of diagnosis. The result is most consistent with the study result conducted in Colombia [15].

Healthcare-system infrastructure delays were usually due to a lack of resources. There are limited radiotherapy centers in Bangladesh and these limitations increase the waiting times to receive radiation at NICRH. Approximately one thousand patients seek appointments for radiotherapy every day at the NICRH. With only six radiotherapy machines, the hospital can offer services to 450 to 500 patients per day [52]. In contrast, health system infrastructure delays are lower when there are more resources in other developing countries such as Brazil [19]. Bangladesh has only 24 radiotherapy machines for a country population of 171 million [53]. In a linear regression model of number of radiotherapy machines per population and cancer mortality, an inverse linear relationship was identified between radiotherapy resources and cancer mortality [54].

In summary, illiteracy, lack of awareness regarding cervical cancer, limited health seeking behavior, and poor income status were all associated with primary delay. Nonperformance of pelvic examination in the initial consultation, misdiagnosis, inappropriate management, and delay in referral to cancer treatment center by healthcare providers were the contributing factors for healthcare provider delays. Lack of availability and accessibility of health services and limitation of radiotherapy resources led to healthcare system delay. In a worldwide meta-analysis of determinants of advanced cervical cancer, education and place of residence were the leading risk factors of late presentation [29].

Correction of these various barriers will require public health education of the population, increased women's reproductive healthcare education of primary healthcare providers, improved outreach of cervical cancer screening and vaccination programs, and investment in cancer care infrastructure at the national level. **Table 9** summarizes recommendations to reduce delay in the initiation of cancer treatment for people with advanced cervical cancer. The multi-sectoral approach is mandatory with needed involvement of the Ministry of Health, training institutions, hospitals, communities, families and individuals to address the cervical cancer condition in Bangladesh [55] [56].

Table 9. Recommendations to improve delays in the initiation of treatment of advanced stage cervical cancer patients.

DELAY RELATED FACTORS	RECOMMENDATION
<i>PATIENT RELATED FACTORS</i>	Health education about cervical cancer causes, symptoms, and treatment
	Literacy programs
	Develop transportation systems from communities to healthcare facilities

Continued

<i>HEALTHCARE PROVIDER</i>	Increase cervical cancer screening and vaccination programs
	Training of healthcare providers in pelvic examination and identification of lesions
	Education programs on signs and symptoms of cervical cancer
	Improvement in healthcare facility resources: exam tables, pathology resources
<i>HEALTHCARE SYSTEM</i>	Development of a National cancer registry
	Decentralization of cancer-related healthcare services throughout the country
	Establishment of chemotherapy and radiation treatment centers in each region of the country
	Effective referral system
	Integration of cancer programs into existing healthcare services in primary healthcare facilities
	Involvement of the Ministry of Health, training institutions and hospitals

5. Conclusion

This study adds to the existing body of inquiry on delay factors for women with advanced cervical cancer. This was a single-institution study. The limitation of this study is its small size. Given that only women who were able to travel to NICRH and be treated were studied, we are only aware of delay factors for this group of women with advanced stage cervical cancer. It is unknown how many women in Bangladesh die from cervical cancer without being able to be treated for their cancers. There may be other important barriers to care that must be identified to intervene for those who are unable to receive care. Another limitation is that this study did not include surveys or interviews with traditional healers, primary care providers or cancer specialists. Specifically, it is important to interview primary care providers to understand better the barriers to performing pelvic examinations, as this factor was an important reason for the delay in definitive cancer care. Future studies should include input from these various healthcare specialists to increase our understanding of the multidimensional barriers to receiving oncologic evaluation and treatment for cervical cancer.

Precis: This qualitative study of a large population in Bangladesh identified the three layers of barriers to early initiation of treatment in cervical cancer patients: patient-related, healthcare provider delay, and healthcare-system-related.

Disclosure of Relationship and Activities

This work was published as an E-Poster (EP039/#692) in the *International Journal of Gynecological Cancer* (Akhter *et al.* 2022) [57].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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