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Delayed cervical cancer diagnosis: a systematic review

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Abstract. – OBJECTIVE: Cervical cancer (CC) is a preventable women's cancer. Vaccination and routine Pap smear screening have reduced cervical cancer-related mortality by 70-80% in the world. The eradication of CC depends on identifying the disease early and removing barriers to its timely detection. This review study was designed to determine diagnostic delay and factors related to delayed CC diagnosis in the world.

MATERIALS AND METHODS: A comprehensive search was carried out in databases including Medline, Web of Science, Core Collection (Indexes = SCI-EXPANDED, SSCI, A & HCI Timespan), and Scopus for articles published up to December 2021. Publications were included if they reported data on the delayed CC, and factors related to diagnosis of CC in women. There was no time restriction in this review.

RESULTS: In total, 45 articles were entered into the study. In studies, advanced stages of CC (IIB to IV) varied from 10.2% to 87.9% due to delayed diagnosis. A delayed CC diagnosis was reported in 4.3%-89.1% of patients. The median and mean days of delayed diagnosis were 59-210 days and 2.92-10.5 months, respectively. Factors related to delayed CC diagnosis were categorized into three components including patient, medical history, and health system delay. Patient delay included socio-demographic, husband/ partner, and knowledge. Medical history included medical issues, obstetrics, and family history. Health system delays included health facilities and levels of accessibility.

CONCLUSIONS: There is an urgent need to shorten the diagnostic journey of CC patients by addressing all the components of diagnostic delay and developing strategies to modify the factors associated with these delays.

Key Words:
Barrier, Cervical cancer, Cytology, Diagnosis, Pap smear, Colposcopy.

Introduction

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020[1]. Important co-factors of CC include some sexually transmitted infections (STIs), smoking, a higher number of childbirths, and long-term use of oral contraceptives[2-4]. Early diagnosis of CC is crucial[5], and recently the concept of "delayed diagnosis" has become an important issue in cancer prevention and treatment[6] because cancer in an advanced stage has a poor prognosis and is correlated with lower survival rates[7]. Some reasons have been proposed in the literature[8-11]. Delayed CC diagnosis in women especially in low- and middle-income countries occurs mostly due to poor access to appropriate management[12]. In most studies, being older was a risk factor for the delayed diagnosis, whereas some studies identified younger age as a risk factor[13,14]. In a study by Ashing-Giwa et al[8], women who were employed and could not take time off had a greater risk for delayed diagnosis. While in a cross-sectional study by Ouasmani et al[15], occupation [adjusted odd ratio (aOR) = 0.439, CI: 0.264–0.730, $p< 0.002$] was a protective factor[15]. In a cross-sectional study by

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Traore et al[16], 62.0% of women were living with their partners, and it was reported that not living with a partner increased the risk of delayed CC diagnosis by 2.86 times. Conversely, in the other study living with a partner was reported to be a risk factor for delayed CC diagnosis (OR=1.3; 95% CI 1.2-1.4)[17]. The other factors included: not attending for screening[14]; lack of cancer diagnosis by a screening service[18]; not detecting a symptom of cancer by the individual; not paying attention to healthcare advice; and healthcare providers or the health system to be failed to detect cancer[19]. Since timely cancer diagnosis improves patient's survival and quality of life[20] and delayed diagnosis is a major factor contributing to lower cancer survival[21], in this review, we explored the factors related to delayed CC diagnosis.

Materials and Methods

The present systematic review was conducted over four months (September–December 2021), to identify the period time of delay (median/mean) and factors related to delayed CC diagnosis in the world. The onset of symptoms to the first medical diagnostic consultation was defined as delayed diagnosis.

Search Strategy and Information Sources

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[22]. Three databases PubMed/MEDLINE, Scopus, and Web of Science were searched for relevant articles. The search was performed in December 2021 using the following keywords: "late detection", "late screening," "diagnostic delay," delayed diagnosis," "uterine cervical neoplasms," "cervical neoplasm," "cancer screening tests", "cervical cancer," "cervix cancer," "cervix neoplasm", "Pap smear," "barriers", "challenge", "obstacles", "uterine cervical neoplasms", "cervical neoplasm", "cervical cancer", "cervix cancer", "cervix neoplasm". Boolean (AND, OR) operators and the Mesh terms were used to optimize the selection of records. An example of the search strategy is summarized in Table I.

Then, in order to make the search comprehensive, a manual search of reputable journals was performed followed by a manual search of references in the full text of articles and related systematic reviews.

Table I. Electronic search strategy for PubMed.

	Query
11: 10& 9	((((Late Diagnosis) OR (Delayed Diagnoses)) OR ("Delayed Diagnosis"Mesh)) OR ((((((Time to TreatmentTitle/Abstract) OR (Door to Treatment TimeTitle/Abstract)) OR (Delayed TreatmentTitle/Abstract)) OR (Delayed TreatmentsTitle/Abstract)) OR (Treatment DelayTitle/Abstract)) OR ("Time-to-Treatment"Mesh))) AND (("Uterine Cervical Neoplasms"Mesh) OR ((((((Cervical CancerTitle/Abstract) OR (Cervix NeoplasmTitle/Abstract)) OR (Uterine Cervical CancerTitle/Abstract)) OR (Cancer of CervixTitle/Abstract)) OR (Cervix CancerTitle/Abstract)) OR (Neoplasm, CervixTitle/Abstract)))
10: 3&6	(((Late Diagnosis) OR (Delayed Diagnoses)) OR ("Delayed Diagnosis"Mesh)) OR ((((((Time to Treatment Title/Abstract) OR (Door to Treatment Time Title/Abstract)) OR (Delayed Treatment Title/Abstract)) OR (Delayed Treatments Title/Abstract)) OR (Treatment Delay Title/Abstract)) OR ("Time-to-Treatment"Mesh))
9:7&8	("Uterine Cervical Neoplasms"Mesh) OR ((((((Cervical Cancer Title/Abstract) OR (Cervix Neoplasm Title/Abstract)) OR (Uterine Cervical Cancer Title/Abstract)) OR (Cancer of Cervix Title/Abstract)) OR (Cervix Cancer Title/Abstract)) OR (Neoplasm, Cervix Title/Abstract))
8	"Uterine Cervical Neoplasms"Mesh
7	(((((Cervical Cancer Title/Abstract) OR (Cervix Neoplasm Title/Abstract)) OR (Uterine Cervical Cancer Title/Abstract)) OR (Cancer of Cervix Title/Abstract)) OR (Cervix Cancer Title/Abstract)) OR (Neoplasm, Cervix Title/Abstract)
6: 4&5	(((((Time to Treatment Title/Abstract) OR (Door to Treatment Time Title/Abstract)) OR (Delayed Treatment Title/Abstract)) OR (Delayed Treatments Title/Abstract)) OR (Treatment Delay Title/Abstract)) OR ("Time-to-Treatment"Mesh)
5	((((Time to Treatment Title/Abstract) OR (Door to Treatment Time Title/Abstract)) OR (Delayed Treatment Title/Abstract)) OR (Delayed Treatments Title/Abstract)) OR (Treatment Delay Title/Abstract)
4	"Time-to-Treatment" Mesh
3: 1&2	((Late Diagnosis) OR (Delayed Diagnoses)) OR ("Delayed Diagnosis"Mesh)
2	(Late Diagnosis) OR (Delayed Diagnoses)
1	"Delayed Diagnosis" Mesh

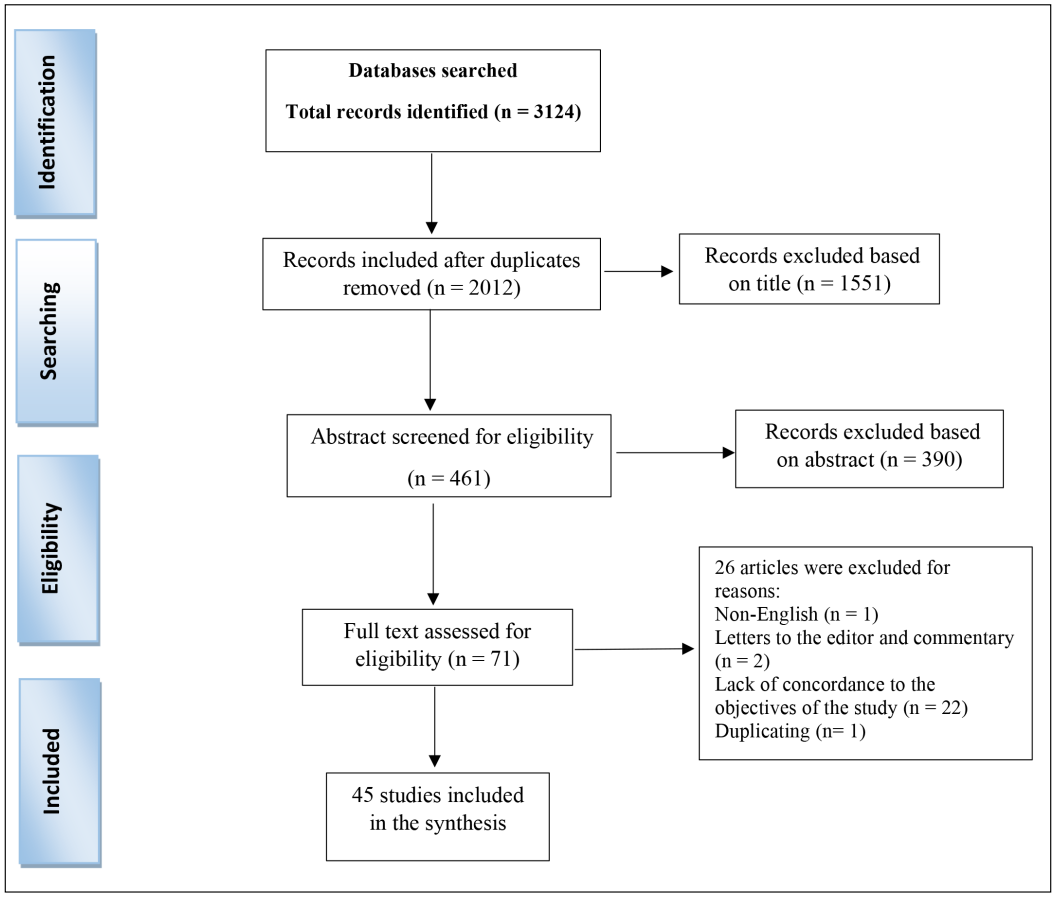

Figure 1. The process of screening and selecting relevant studies based on the Preferred Reporting Items for Systematic Reviews guideline (PRISMA).

Inclusion and Exclusion Criteria

This study reviewed the peer-reviewed papers conducted across the world and considered all kinds of observational studies. Studies that were exclusively in English language and addressed CC cancer screening, diagnosis and factors related to delayed CC diagnosis in women worldwide were included. Articles that used the keywords in their title or abstract were also included in the search. There was no time restriction in this study. Comments, editorials, systematic reviews, conference abstracts, opinion statements, practice guidelines, case studies or reports, and studies with no full text were excluded from this study.

Study Selection

The review process consisted of two screening steps: (1) reviewing the title and summary of the articles, and (2) reviewing the full text of the articles. For the first step of screening, the titles and abstracts of the articles were read and analyzed by two researchers (LA and HS) independently to identify eligible articles. In the second step, two researchers (LA and IA) evaluated the full text of each article independently. All retrieved articles were entered into a database on Endnote X7.

Quality of the Articles

In this study, the quality of studies was assessed by Newcastle-Ottawa Quality Assessment Form[23].

Data Extraction

Details of all articles were extracted and reported from the studies. Data including author and year of the study, country, study type, sample size, diagnostic delay (number/percentage), the diagnostic delay time [mean ± standard deviation (SD), median], and main results were extracted by two independent investigators, as appropriate.

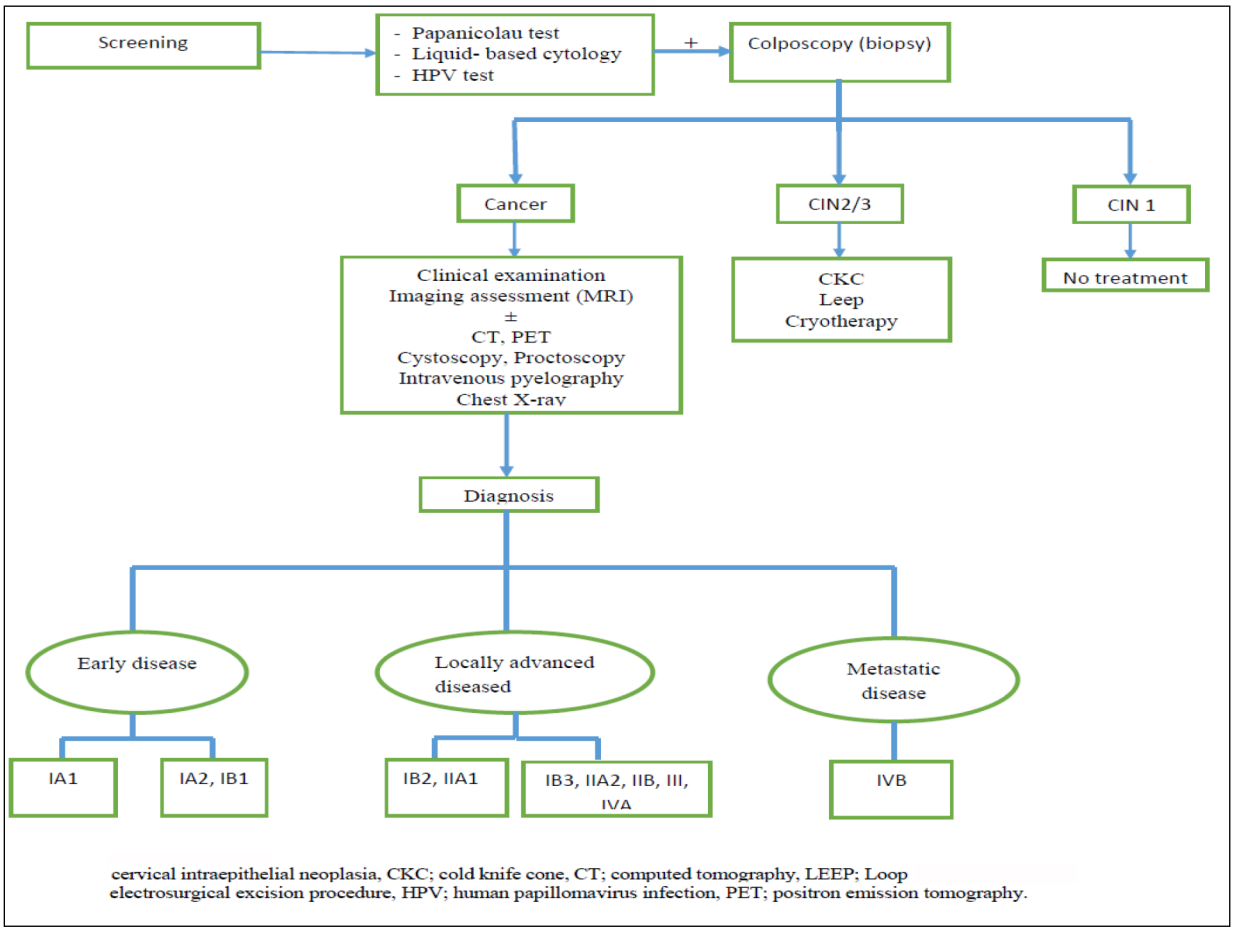

Figure 2. The process of diagnosis of cervical cancer from screening to diagnosis.

Results

At the beginning, 3124 articles were found via electronic different databases, 45 of which met the inclusion criteria (Figure 1). Out of all studies reviewed, 15 studies were cross-sectional, in which data had been collected using a questionnaire or interview[8,13,15-19,24-32]. In total, 11 studies had been done using data registered on the cancer registry database[9,33-42]. Seven[43-49] and four studies[50-53] were cohort, retrospective, and population-based prospective studies, respectively. The remaining studies had descriptive[54,55], descriptive-analytical[56], time series[57], case-control[58], and unknown designs[32,59,60]. The sample size in the articles varied from 55 to 65843. Characteristics of studies included in the review are summarized in **Supplementary Table I**. In total, the results of 45 studies are summarized in two main domains: 1) delayed CC diagnosis, and 2) factors related to delayed CC diagnosis.

Delayed Cervical Cancer Diagnosis

According to included studies, a delayed CC diagnosis was reported in 4.3%-89.1% of patients[15,16,18,19,28,38,39,48,52,54,56,57]. The median diagnostic delay was 59-210 days[14,24,41,43,44,50,57]. The mean time of delayed diagnosis was 2.92-10.5 months[8,13,15,19,39,45,54,59,60]. Advanced stages of CC (IIB to IV) varied from 10.2% to 87.9% due to delayed diagnosis[8,9,14,17,19,24,27,30,31,33-37,39,40,43,44,46,47,51,55,58-60]. The process of diagnosis of CC is shown in Figure 2.

Factors related to delayed cervical cancer diagnosis

According to the result of the studies, factors related to delayed CC diagnosis are categorized into three components patient, medical history, and health system delay (Table II).

Patient delay

Patient delay domain included three categories socio-demographic, husband/partner, and education and awareness.

Socio-Demographic characteristics

Age, race/ethnicity, marital status, and socio-economic status were subcategories of socio-demographic characteristics.

Age

A delayed CC diagnosis has been more common in old women and the odds ratio (OR) of delayed diagnosis in these women varied from 1.98 [95% confidence interval (CI): 1.81-2.16] to 20.2 (95% CI = 12.8, 32.0)[9,14-17,27,34,37,38,40,46,47,49,51,52,54,56,58]. Although in most studies being older was a risk factor of the delayed diagnosis[14], some studies reported that younger age is a risk factor. A national descriptive study by Lim et al[13] reported delay in diagnosis was more common in patients < 25 years compared with women older than >25 years. In a cross-sectional study by Berraho et al[19], an elevated risk was observed for women aged under 50 years (OR=2.44; 95% CI: 1.24-4.76).

Ethnicity

Ethnicity is one of the factors that contributed to the delayed CC diagnosis[8,9,17,27,34,36,46,52]. OR of delayed diagnosis in Black women was in the range of 1.15 (95% CI: 1.10-1.20) to 1.34, (95% CI: 1.15-1.57)[17,36,46,52]. A cross-sectional study by Pelletier et al[27] was revealed that African American women born in outside of the United States had a lower risk of late-stage diagnosis *vs.* women born in the United States (OR= 0.67, p = <0.001), while in a study by Montealegre et al[34], being foreign-born *vs.* U.S.-born increased the risk of delay in CC diagnosis [OR = 1.15 (95% CI: 1.10-1.20), p = <0.001]. In a study by Mitchell et al[52], delay in diagnosis in Hispanic women was higher (OR= 1.528, p = 0.01), and in a study by Barry et al[9] the relative risk ratio (RR) of delayed CC diagnosis in Hispanic women was reported 1.457 (95% CI: 1.031-2.059). In a multivariate analysis by McCarthy et al[36], blacks had similar mortality risk (HR 1.07, 95% CI = 0.95-1.20) to whites while Puerto Ricans had increased risk [Hazard ratios (HR) = 1.31, 95% CI = 1.10-1.55], and non-Puerto Rican Hispanics (HR = 0.54, 95% CI = 0.45-0.63) and Asian/PIs (HR = 0.64, 95% CI = 0.52-0.78) had

Table II. Factors related to delayed cervical cancer diagnosis.

Domain	Categories	Sub-categories		References
Patient	Socio-demographic	Age		9, 13-17, 19, 27, 34, 37, 38, 40, 46, 47, 49, 51, 52, 54, 56, 58
		Race/ethnicity:		8, 9, 17, 27, 34, 36, 46, 52
		Marital status		14, 19, 27, 32, 46, 47
		Socio-economic status	Income level	8, 9, 15, 24, 28, 30, 31, 46, 47, 52
			Occupation status	
	Husband/ partner	Living with husband/partner		16, 17
		Role of husband/ partner		14, 15, 18, 28
	Education and awareness	Education (women/husband)		14-19, 28, 30, 31, 45
		Awareness		8, 15, 24, 25, 31, 41, 58
Medical history	Medical issue	History of sexually transmitted infections		32, 43, 53, 58
		Gynecological examination and screening history		14, 15, 18, 28, 40, 44, 49, 56
		Clinical symptoms		14, 15, 19, 32, 58
	Obstetric history	Gravidity, parity, number of children		26, 31, 56
	Family history	Family history of cancer		19, 30
Health system	Health facility	Level of health facilities		14, 25, 31, 33, 37, 41, 44, 50
		Health care providers		13, 18, 50
	Levels of accessibility	Distance from health centers		15, 16, 19, 36, 40, 54
		Waiting time		43

reduced risk. In a cross-sectional study by Ashing-Giwa et al[8] Latina Americans were more likely to report diagnostic delays (p = 0.003), while Native Americans (HR = 0.60; p = 0.01) and Latinas (HR = 0.65; p < 0.0001) had reduced risk.

Marital status

Based on the results of studies, marital status is one of the determinants to delay the CC diagnosis[14,19,27,32,46,47]. Odds of delayed- *vs.* early-stage CC diagnosis in unmarried women varied from 1.31 (95% CI: 1.15-1.49) to 5.0 (95% CI: 1.43-16.66)[19,27,47]. In a retrospective cross-sectional study by Pelletier et al[27], single, separated/divorced, or widowed women had a significant risk *vs.* married women (OR= 1.26, p = 0.0001), (OR 1.21, p = 0.008), and (OR 1.17, p = 0.07), respectively. Similarly, a cohort study revealed that single, separated/divorced, or widowed women had a significantly higher risk of delayed CC diagnosis than married women: $OR_{S/M}$ = 1.27, (95% CI: 1.18-1.38); $OR_{SDW/M}$=1.97, (95% CI: 1.81-2.14)[46]. In Saghari et al[47] study, delays in diagnosis of CC were highest among unmarried compared with married women (OR= 1.52; 95% CI: 1.07-2.15).

Socioeconomic Status (SES)

Based on the results of studies, the income level and occupation status are two factors that could affect CC diagnosis[8,9,15,24,28,30,31,46,47,52].

Income level

In a cross-sectional study by Behnamfar et al[28], 89.1% of women had delayed diagnosis of CC, and delayed diagnosis of the CC was significantly higher in patients with lower socioeconomic status (p < 0.001). A cohort study by Morgan et al[46], showed that women with lower SES had a more significant risk compared to the highest SES (OR=1.53, 95% CI: 1.38-1.71). In Saghari et al[47] study, women with higher SES with each race/ethnicity (Non-Hispanic black/ Hispanic / or Non-Hispanic white) had a lower risk of delayed diagnosis of CC. In Barry et al[9], women with extreme poverty (RR=1.519, 95% CI: 1.096-2.105) and underclass socio-economic status (RR=1.534, 95% CI: 1.084–2.171) had a significant risk of delay in diagnosis. In a cross-sectional study by Ashing-Giwa et al[8], 10% of women with a delayed diagnosis had a financial issue. Notably, in women with financial problems, the duration of delay in diagnosis was reported higher than that of in women without a financial problem (113.4 ± 141.3 *vs.* 44.3 ± 84.7 days, (p < 0.001). In a population-based study, low income increased delayed CC diagnosis by 19%[52]. In an institution-based cross-sectional study, women with less than 14 USD income had a 3.79-fold higher risk for delayed diagnosis (95% CI: 1.48, 9.67)[24]. Not only does low economic conditions increase the risk of delay in cervical diagnosis, but it also leads to diagnosis at an advanced stage. The odds of advanced-stage cancer among women who self-reported financial problems were 5.7 times (95% CI 1.58 to 20.64), the odds of advanced cancer among the women who did not report financial problems as a reason for non-prompt health-seeking[31]. In a cross-sectional study by Tanturovski et al[30], monthly income of 74% of the patients was below the average. The odds of delayed CC diagnosis among patients who had below average and average monthly income were 13.16 (95% CI: 2.042-84.894) and 10.5 (95% CI: 1.278-87.110) times the odds of women with high average monthly income.

Occupation status

In a study by Ashing-Giwa et al[8], women who were employed and could not get time off from work had a greater risk for delayed diagnosis, whereas in a cross-sectional study by Ouasmani et al[15], occupation (aOR = 0.439, CI: 0.264-0.730, p < 0.002) was a protective factor[15]. Also, in a study by Robinson et al[54], a weak association was found between long total delay and the women who were still working as opposed to being retired.

Husband/partner

Living with the partner/husband and the role of the husband were factors that influenced CC diagnosis[14-18,26,28].

Living with the husband/partner

In a cross-sectional study by Traore et al[16], 62.0% of women were living with their partners and it was reported that not living with a partner increased 2.86 times the risk of delayed CC diagnosis (95% CI: 2.09-3.89). While in the other study, living with a partner was reported as a risk factor for delayed CC diagnosis (OR=1.3; 95% CI 1.2-1.4)[17]. In the study by Silva Rodolfo et al[26], having no steady partner was a risk factor for advanced CC in a major Brazilian city.

Role of husband/partner

In Gyenwali et al[14], women who shared their symptoms late had a more significant delayed diagnosis (aOR=4.272, CI: 1.110-16.440), and wom-

en who shared their symptoms with people other than their husband had more significant odds of the delayed diagnosis (aOR=12.701, CI: 1.132-142.55). Also, having a smoker and an addict's husband increased the probability of delayed diagnosis of CC ($p < 0.001$)[28]. In a cross-sectional study by Panda et al[18], lower education status of the husband was a risk factor for delayed diagnosis of CC (aOR: 2.76, 95% CI: 1.03-7.42). The secondary level of education and a higher level of husband education was also found as a protective factor (aOR= 0.176, CI: 0.085-0.365)[15].

Education and Awareness

Education level and awareness were factors that influenced CC diagnosis[14-19,24,25,28,30,31,41,45,58].

Education level

According to the results of the studies, the low level of education of women and their husband were one of the risk factors for delayed CC diagnosis[14-19,28,30,31,45]. In a cohort study in India, being illiterate was a sole risk factor of delayed diagnosis of CC[45]. In a cross-sectional study, low educational level of women increased the risk of delayed CC (OR=1.2; 95% CI; 1.1-1.3)[17]. Based on studies, being a literate was a protective factor of delayed CC (aOR=0.121, CI: 0.030-0.482)[14]. In a cross-sectional study by Berraho et al[19], illiterate women had 3.85 times more odds of delayed CC diagnosis (95% CI: 1.45-10.00). In a cross-sectional study by Ouasmani et al[15], level of education was a protective factor, respectively, for primary, secondary, and high levels (aOR = 0.430 (CI: 0.25-0.713), and 0.071 (CI: 0.038-0.133). In women with primary and secondary education, the risk of delayed CC diagnosis was 2.69 (95% CI; 1.62-4.47) and 1.82 (95% CI; 1.36-2.44) respectively[16]. Mwaka et al[31] observed that women with secondary and/or tertiary education are less likely to have delayed CC diagnosis (crude OR= 0.16 (95% CI: 0.03 to 0.87). In a cross-sectional study conducted by Tanturovski et al[30], lower degrees of education were a risk factor for delayed CC ($p < 0.001$). Women with no education and elementary education had 9 (95% CI: 1.619 to 50.035), and 7.54 (95% CI: 1.109 to 50.000) times higher risk for delayed diagnosis.

Awareness

A lack of awareness about the symptoms of CC was a risk factor for the delayed diagnosis among young women[15,24,25,31,41,58]. In a cross-sectional study by Ouasmani et al[15], 55.4% of women had more than 90 days delay in CC diagnosis and 48.9% of all women had never heard of CC, 60.3% did not know the abnormal vaginal bleeding as a symptom of CC, and 51.6% had never heard of screening program[15]. In an institution-based cross-sectional by Zeleke et al[24], it was reported that women who were not aware of CC or CC screening had a significant risk for delayed diagnosis (aOR=1.33 (CI: 1.05, 2.71), and 1.64 (CI: 1.16, 4.07) respectively). In a case-control study by Lourençon et al[58], women who did not know the difference between the Papanicolaou test and gynecological pelvic examinations (OR, = 2.5; 95% CI, 1.3-4.9) and did not consider the Papanicolaou test important (OR=4.2; 95% CI, 1.3-13.4) were more likely to have a delayed diagnosis. In a study by Mwaka et al[8], it was reported that if women perceived their illness as a serious disease or cancer, it would decrease the risk of a delayed diagnosis [aOR=0.43 (95% CI 0.20 to 0.96)][31]. Fear of diagnosis of CC was another risk factor for delayed CC diagnosis.

Medical History

The subcategories of medical history included medical issues, obstetric history, and family history[14,15,18,19,26,28,32,40,43,44,49,53,56,58].

Medical issues

The medical issues domain included three categories: history of STIs, gynecological examination and screening history, and clinical symptoms[14,15,18,19,28,32,40,43,44,49,53,56,58].

History of STIs

The OR of delayed diagnosis in women with a positive history of STIs varied from 1.48 (95% CI; 1.05–2.1)[43] to 3.42 (95% CI; 1.18-10.0)[18]. Likewise, Lourenço et al[58], reported that previous treatment for STIs had a significantly converse effect on the delayed CC diagnosis (OR, 0.3; 95% CI, 1.3-13.4). However, in a study by Friebel-Klingner et al[32], HIV was not associated with a diagnosis of late-stage CC.

Gynecological examination and screening history

Gynecological examination and screening history were found to be the factors affecting CC diagnosis[14,15,18,28,40,44,49,56].

Patients who did not have a gynecological examination during the last three years ($p < 0.0001$)[15] and screening tests were more likely to delay[15,18,28,40,56]. In a cross-sectional study by Gy-

enwali et al[14], it was reported that 78.2% of women had no cervical/per-speculum examination in initial consultation with health care providers. Lack of per-speculum examination in initial consultation was found to be associated with late diagnosis.

No prior screening history was recorded in 60.7% of CC cases and its absence increased with age and advanced stage. False-negative smears were identified in 27.1% of women with CC (adenocarcinoma 52.6% *vs.* squamous cell carcinoma 16.2%, $p < 0.05$)[40]. In line with these findings, other studies reported that among all women with CC, 39-58.9% of them had never performed Pap smear test. Furthermore, 19.48-26.1% of women with CC performed screening pap-smear tests more than three years before diagnosis[15,56]. Panda et al[18] reported that women with non-attendance for a CC screening program were more likely to have delayed diagnosis of CC (aOR: 4.59, 95% CI: 1.14-18.51). Additionally, non-attendance of women for screening program (aOR: 3.97, 95% CI: 1.17-13.46) and not performing cervical/per speculum examination during initial consultation significantly increased the odds of a delayed diagnosis (aOR: 4.08, 95% CI: 1.26-13.22).

In a retrospective cohort study by Philp et al[44], across all cancer stages, 5-10% of Pap smear results were low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of undetermined significance (ASCUS). Low-grade cytology increased the average time of diagnosis (HR= 2.3, 95% CI: 1.7-3.1) compared to atypical glandular cells/adenocarcinoma-in-situ (ACG/AIS) or high-grade squamous intraepithelial lesion/atypical squamous cells (HSIL/ASC-H) results. Stage IV and stage 1A disease resulted in the longest time to diagnosis compared to other stages. In a study by Tabnak et al[49], of those women who completed diagnostic work-up about 23% (n = 993) had mild and 18% (n = 781) had a moderate or severe abnormality. Abnormal Pap smear (HR = 0.77; $p < 0.0001$), or minor abnormal Pap smear (HR = 0.71; $p < 0.0001$) had a protective effect on the delayed diagnosis.

Clinical Symptoms

In a cross-sectional study by Ouasmani et al[15], abnormal vaginal bleeding was identified in 65.8% of patients with CC and women who had abnormal vaginal bleeding, such as postcoital bleeding, intermenstrual bleeding, or postmenopausal bleeding, as early symptoms were less likely to have a patient delay. A greater proportion, 87%, of the patients had squamous cell tumor type and 60.1% of total patients were diagnosed at stages IIA-IIB. In Friebel-Klingner et al[32] study, women with abnormal vaginal bleeding had higher odds of late-stage disease at diagnosis (OR: 2.32, 95% CI 1.70-3.16) compared to those without abnormal vaginal bleeding. While, in a study abnormal vaginal bleeding as an earlier symptom was found as a protector factor (aOR = 0.345, 95% CI: 0.218–0.548, $p < 0.001$)[15]. In Gyenwali et al[14], having abnormal vaginal bleeding as an early symptom (aOR=0.160, CI: 0.035-0.741) was a protective factor of delayed CC. Whereas, in a national descriptive study by Lim et al[13], vaginal discharge was more common among the patients who delayed presentation than those who did not; many of patients reported not recognizing this as a possible cancer symptom. In a cross-sectional study by Berraho et al[19], it was reported that not bleeding as the first symptom was a significant risk factor of the delayed diagnosis (OR=25; 95%CI: 1.62-300). While in a cross-sectional by Lourenço et al[58], abnormal vaginal bleeding was a risk factor of a delayed diagnosis (OR, 15.0; 95% CI, 6.5-35.0).

Obstetrics history

In a cross-sectional study by Mwaka et al [56], the number of biological children (5-9) was found to have a protective effect on a delayed CC diagnosis [aOR= 0.27 (95% CI 0.08 to 0.96)][31]. However, in a cross-sectional study, Mosayebi et al [56] observed that patients who underwent Pap smear during the last three years or fewer had fewer deliveries ($p < 0.01$). In the study of Silva Rodolfo et al [26], patients diagnosed with advanced CC in a major Brazilian city were multiparous.

Family History

Family history is one of the most important factors influencing the diagnosis of cancer[19,30]. In a cross-sectional study by Tanturovski et al[30], it was reported that the patients had a higher probability of being diagnosed with the advanced-stage disease if they had no family history of invasive CC in their first-degree female relatives [OR = 6.42 (95%CI: 1.885 to 21.839)]. In Berraho et al[19] study, women without a familial history of cancer had a significant risk of a delayed CC diagnosis (OR=14.28; 95% CI; 2.22-100).

Health System

Health systems are categorized into health facilities and levels of accessibility[13,14-16,18,19,25,31,33,37,40,41,43,44,50].

Health Facilities

Health facilities included two categories: level of health facilities and health care providers[13,14,18,25,31,33,37,41,44,50].

Level of health facilities

The level of a health facility is one of the factors that contribute to the late presentation of CC[14,25,31,33,37,41,44,50]. In a study by Dereje et al[50], the diagnostic delay was 97 days and the delay was significantly associated with the level of first contacted health facilities, the number of different health facilities visited for diagnosis, and the total number of times that patients visited health facilities for diagnosis. The odds of diagnostic delays among patients who contacted primary-level health facilities (including health centers and private clinics) at the first step were 2.6 times higher than among those who first referred to the secondary- or tertiary-level health facilities (aOR = 2.6; 95% CI, 1.33 to 5.27). Also, the odds of diagnostic delays among patients who visited more than four different health facilities for their cancer diagnosis were nearly 3 times higher than among those who visited less than four different health facilities (aOR = 2.7; 95% CI, 1.07 to 6.71). Likewise, the odds of diagnostic delays among patients who made more than five visits to health facilities before receiving histologic diagnostic confirmation were 2 times higher than among those patients who had five visits (aOR, 2.2; 95% CI; 1.05 to 4.43). In a retrospective cohort study by Philp et al[44], it was reported that patients who were evaluated by family physicians compared to obstetrician-gynecologist had more delays in diagnosis ($p = 0.018$). Women living in states with laws that restrict nurse practitioners (NP) full scope-of-practice are twofold more likely to be diagnosed with late-stage cancer (OR 2.08, 95% CI: 1.4 to 3.1). Cancer screening is primarily in the domain of primary care providers, physicians, and NP. However, the USA has a primary care physician shortage, especially among underserved and rural populations. NPs have historically provided quality care for underserved and rural populations[33]. In a cross-sectional study, Mwaka et al[31], reported that pre-referral diagnoses (any visit to a healthcare professional in an established healthcare setting including lower-level healthcare facilities and private clinics before presentation and diagnosis at the study hospital) by primary healthcare professionals increased the risk of a delayed cancer diagnosis [crude OR=11.8 (3.75 to 37.12); aOR=13.04 (3.59 to 47.30)]. In a cross-sectional study by Gyenwali et al[14], it was reported that medical shops (33.6%) and private hospitals (31%) were major first contact points of patients with health care providers. Types of first contact health facilities (sub-health posts, health posts, primary healthcare centers compared to private medical shops, government hospitals, and private hospitals) were one of the determining factors for the delayed CC diagnosis. Women who at the first contact attended the government hospitals had a significantly lower risk of a delayed CC diagnosis than those referred to other health facilities (OR = 0.072, 95% CI; 0.008-0.658). In a study by Mandelblatt et al[37], a public health setting was reported to be associated with an increased risk of late-stage disease (public compared to nonpublic health setting) (OR = 1.28, 95% CI: 1.02-1.60, $p < 0.001$). In a cross-sectional study by Kívés et al[25], the patient delay (PD - the first perception of symptoms to medical visit) was an average of 4 ± 6.1 months. The medical delay (MD–the first medical visit to the start of treatment) was an average of 3 ± 6.1 months. Where three or more symptoms were perceived, MD was significantly ($p = 0.020$) longer (mean 3 *vs.* 9.76 months). Patients who had never used self-medication had significantly longer PD ($p = 0.034$, 8.5 *vs.* 1.2 months). In a study by Yu et al[41], the median time interval between symptoms and diagnosis was nine months (range 3 – 24 months), and failure of healthcare professionals to recognize the significance of disease symptoms was a factor that contributed to the delayed CC diagnosis.

Healthcare Provider

In a study by Dereje et al[50], the median diagnostic interval for the patients was 97 days (95% CI, 81 to 123 days). More than three-fourths (80.5%; 95% CI, 75.8% to 85.3%) of the patients with CC waited for 30 days from their first health care provider consultation to histologically confirmed diagnosis of CC.

In a study by Lim et al[13], provider delay was reported by 60 % of patients (24/40); in some patients, no report was found in primary care records of a visual inspection of the cervix and some of the patients did not re-attend after the first presentation for several months. Provider delay occurred because patients used hormonal or intrauterine contraception or were pregnant at the first attendance. These patients appear to be difficult to diagnose considering that even at colposcopy (including biopsy), malignancy was not easily recognized. In a cross-sectional study by

Panda et al[18], the median (range) of referral delay (it refers to the time duration from the health care provider's referral to the diagnostic center until patient's first appointment in the diagnostic center) was 4.0 (1-115) days.

Distance from health centers

It was reported that the place of residence and distance of the place of the first consultation could affect CC diagnosis[15,16,19,36,40,54]. In a cross-sectional study by Berraho et al[19], 54.5% of CC were diagnosed at a late stage, and living at remote places (travel time ≥ 4 hours) was a risk factor for a delayed CC diagnosis. An elevated risk for delay more than six months was observed in women who lived > 100 km from the center of diagnosis (OR = 4.51; 95% CI: 1.35-15.11). Also, women who lived in rural areas had 2.56 times (95% CI: 1.25-5.26) higher risk for a delayed diagnosis than who lived in an urban area.

Elevated risks for late stage was observed for women who lived in a mixed area[40], small provincial town (OR= 2.20 95% CI: 1.12-4.32)[54], high poverty neighborhoods (OR =1.15, 95% CI = 0.96-1.51)[36], and rural residence (aOR = 1.888, 95% CI: 1.219-2.925, $p < 0.004$), as well as remoteness more than 6 km for the first consultation ($p < 0.05$)[15]. In a study by Traoré et al[16], being foreigners (OR = 2.86; 95% CI 1.74-4.70), and women with daily activities limited to their neighborhood of residence (OR = 1.71; 95% CI 1.19 – 2.45) were found to have a higher risk to report a late cervical screening.

Waiting Time

In a retrospective cohort study by Begoihn et al[43], waiting time (between the date the patient noticed the first symptom and the date of the biopsy report) increased the odds of delayed CC diagnosis (OR=1.004, 95% CI; 1.002-1.006); this means that the odds of being diagnosed in a more advanced stage group increased by 0.004 every week. The patient interval was shortest for the early stages (24 weeks for FIGO I-IIa) and longest for advanced stages (35 weeks for FIGO IV).

Discussion

The present systematic review aimed to review papers in the field of a delayed CC diagnosis. The results of this study showed that advanced stages of CC varied from 10.2% to -87.9% due to a delayed diagnosis, and a delay in CC diagnosis was reported in 4.3%-89.1% of patients. The median days of delayed diagnosis were 59-210 days. The main factors related to delayed CC diagnosis in the study included patient, medical, and health system delay. Based on the result of studies, older, unmarried, and with lower SES women have a significant risk for delayed diagnosis. Several studies confirmed that advanced age is associated with lesser screening and with an advanced stage[40,61]. It appears that older women are less involved in sexual relationships, and they think that it is not needed to do a screening or be under consultation. In addition, poor patients are more likely to be concentrated on poor neighborhoods with a lack of access to health services[9]. Also, Mwaka et al[31] reported that lack of money was a reason for the non-prompt health-seeking of patients that caused CC to be diagnosed at an advanced stage. Race and ethnicity are effective factors in delayed CC diagnosis. Black, African American, and Hispanic women had more risk for delayed diagnosis. Due in part to a higher proportion of diagnostic delays, ethnic minorities endure a greater cancer burden, including poorer survival and survivorship outcomes.

It was also observed that the patients having no knowledge about CC were at a higher risk of a delayed diagnosis[18,58]. It seems that knowledge of patients regarding CC and its symptoms influences access to health care services[62,63], thereby shortening the diagnostic delays. Partner or husband plays an important role in CC diagnosis. Emotional support attributed to a partner/husband may enable and even promote women to consult early[19]. The lack of support from the partner/husband/family can discourage patients from early consulting.

Patients with a history of STDs were at a higher risk of delayed diagnosis than those without a history of STDs. These patients may falsely perceive the earlier symptoms of CC such as vaginal discharge or abdominal pain or vaginal bleeding as a symptom of STD and give less importance to further diagnosis and treatment.

Non-attendance for screening program and not performing cervical/per speculum examination during initial consultation were significantly associated with longer diagnostic delays[18]. Based on the result of studies, almost half of the women did not perform screening tests in their lifetime, or their screening was not timely[15,56]. This study revealed that women having abnormal vaginal bleeding such as post-coital bleeding, intermenstrual bleeding, or postmenopausal bleeding as

early symptoms were less likely to have a delayed cervical diagnosis. This can be explained by the fact that gynecological bleeding is usually perceived as more urgent than gynecological infection or pelvic pain. Women tend to ignore the mild gynecological symptoms such as vaginal discharge considering it as a general problem until they turn into alarming symptoms such as vaginal bleeding. Patients were typically less likely to delay if they experienced a more serious symptom, such as vaginal bleeding. These findings are further corroborated with a study conducted in Morocco, where increased risks for patient delay were observed in women who did not have vaginal bleeding as the first symptom[15]. A similar result was reported in a study from Morocco, where increased risks for late-stage diagnosis were not associated with vaginal bleeding as the first symptom[19]. Regarding the early symptoms such as 'vaginal discharge', it has been pointed out that 'non-recognition of the symptom seriousness' or ignoring the symptoms by the patient ultimately lead to a delayed diagnosis and advanced stage at diagnosis of CC[64].

According to our research, having no family history of the disease is associated with a higher risk of the advanced stage of the disease at diagnosis. These results might be partly due to the fact that patients with no family history of the disease had no first-hand experience of the disease[30] or women with a family history of cancer are more aware of the disease and more motivated to consult earlier and thus be diagnosed at earlier stages[19].

The level of health facilities was associated with a delayed CC diagnosis. In a study by Dereje et al[50], approximately 86.3% of patients with CC who first contacted a primary health care unit were delayed in seeking medical consultation. This is likely because health care providers working at the primary care level are more likely to be nurses or health officers rather than medical physicians and thus less likely to be knowledgeable about CC for prompt referral of patients with CC symptoms[65]. In addition, patients who seek medical care at the primary health care level are more likely to be those with lower educational attainment and poor awareness about CC[50,64]. The longer diagnostic time interval may reflect poor knowledge about CC among health care providers for prompt referral of patients and less developed diagnostic infrastructure including the absence of pathologists in the city for timely diagnosis of the disease[24,50,66]. The study results showed an increased risk of long GP referral delays among women living in smaller towns or rural areas compared with provincial towns or capital areas. This could be explained by differences in the referral patterns, either due to patient characteristics, GP characteristics, or health system characteristics[54].

The findings showed that remoteness of place of the first consultation was found significantly associated with patient delay. Higher risks were observed for patients who were 3 km and farther from the first consultation. Indeed, access to care was an important element in decision making for consultation and thus the diagnosis of cancer. For this population, in addition to the costs of examination, counseling and treatment, there are additional costs and difficulties linked to travel, which represents an economic burden on women[19].

Limitations

The use of English-language articles might have limited the results of this study and caused some information in other languages to be missed. The small sample size of some studies and the use of convenience sampling that reduced the generalizability of these studies can be considered other limitations of this study.

Conclusions

According to the results of this study, the complex relationship between different factors prevents a person from participating in CC screening and diagnosis. An in-depth exploration of patient and health-worker perspectives regarding delayed presentation and reasons for delayed diagnosis right from initial local clinics is worth undertaking for both inpatients and outpatients. Standardized history-taking templates with regard to specific symptom duration may limit inter-clinician variations. Future research should examine a broader array of patients' personal characteristics. The medical community must recognize the impact of existing dimensions on diagnostic care, as well as the personal and healthcare system-level barriers that contribute to therapeutic delays.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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