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Patterns of AIDS-defining and Non-AIDS-defining Malignancies in People Living with HIV/AIDS: A 6-Year Retrospective Study from a Tertiary Care Center in South India

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Abstract:

Background: People Living with HIV/AIDS (PLWHA) are at increased risk of developing malignancies, both AIDS-defining and non-AIDS-defining, and trends in incidence and severity have changed since the advent of Antiretroviral therapy (ART). This study aimed to analyze the spectrum of AIDS-defining and non-AIDS-defining malignancies in PLWHA.

Methods: A 6-year retrospective study was conducted in a tertiary care center by reviewing the medical records of PLWHA, which included those diagnosed with cancer. The data obtained were entered into an Excel spreadsheet, and descriptive statistical analysis was performed.

Results: Among the 627 PLWHA, 46 (7.3%) developed cancer, among whom 14 (30.4%) had AIDS-defining cancer, with the most common cancer being Non-Hodgkin Lymphoma (NHL) (71.4%). Non-AIDS-related cancer was reported in 32 patients (69.6%), with the most common factors being oral cavity and upper airway tract malignancies (21.9%), followed by haemato-lymphoid malignancies (18.8%).

Conclusion: The frequency of non-AIDS-defining malignancies mirrors that of the general population, which may be due to the increased survival rate of people living with HIV/AIDS. A multidisciplinary approach for early detection and cancer screening is recommended for people living with HIV.

Keywords: HIV, AIDS-defining malignancies, Non-AIDS-defining malignancies, Tertiary Care Center, Cancer, Anti-retroviral Therapy (ART).

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is a major global pandemic with high morbidity and mortality. The World Health Organization (WHO) estimates that approximately 40.4 million (32.9–51.3 million) people are presently living with HIV, including breastfeeding mothers and children. Worldwide, there were approximately 630,000 (480,000–880,000) deaths in 2022 attributable to HIV [1, 2]. In India, although current trends are declining, there are still 23,48,000 people living with HIV and 69,220 new HIV infections [3].

Anti-retroviral Therapy (ART) substantially reduces

mortality rates in People Living with HIV (PLWHA) [4]. However, this increased longevity has nonetheless led to other challenges, namely the development of other complications, including malignancies, opportunistic infections, and cardiovascular diseases in this cohort of patients, which may be attributable to either ART or HIV infection itself [5]. Traditionally, malignancies in PLWHA have been classified into AIDS-defining and non-AIDS-defining malignancies [2]. Compared to AIDS-defined malignancies, such as Kaposi sarcoma (KS), NHL, and cervical carcinoma, which were traditionally reported in the pre-ART era, there is an increasing trend toward the development of non-AIDS-defined malignancies in PLWHA who are receiving ART. It has been reported that PLWHA are at an increased risk for non-AIDS-defining malignancies, such as Hodgkin Lymphoma (HL) and anal and lung carcinomas. Few studies have described survival outcomes in PLWHA with associated malignancies, and poorer outcomes have been reported [6].

Although the rates of opportunistic infections have declined with the introduction of ART, they still remain an important cause of mortality in PLWHA, particularly owing to late detection as well as lower CD4+ T-cell count. These pathogens include *Pneumocystis jiroveci*, *Toxoplasma*, *Candida*, *Tuberculosis* (TB), and *Cryptococcus* [7, 8]. Some opportunistic infections have oncogenic potential and are implicated in the development of various malignancies, including Kaposi Sarcoma Herpes Virus (KSHV), Epstein–Barr Virus (EBV), and Human Papillomavirus (HPV), leading to KS, NHL, and cervical and anal carcinomas, respectively [9]. In addition, low CD4 counts are associated with an increased risk of malignancies and may even precede a diagnosis of HL [10].

The majority of studies on the prevalence of AIDS-defining and non-AIDS-defining malignancies are from the Western literature. There is a paucity of literature on AIDS-related cancers from India, despite having one of the largest global burdens of HIV/AIDS. Knowledge about the patterns and emerging trends of cancers in PLWHA may provide crucial insight into the pathobiology of HIV and may be of vital importance in the prediction, risk stratification, screening, early detection, and management of cancers in people living with HIV [9, 11].

The aim of the present study was to study the emerging patterns and current trends of AIDS-defining malignancies and non-AIDS-defining malignancies in PLWHA.

2. MATERIALS AND METHODS

The present retrospective observational study was conducted at the Department of Pathology. The study included consecutive HIV-infected individuals who were enrolled in the Department of Internal Medicine and were subsequently diagnosed with AIDS-defining or non-AIDS-defining cancer. The study was performed between January 2014 and December 2019 after clearance from the institutional ethics committee (IEC KMC MLR 4-19/186) was obtained. Patients who developed cancer prior to HIV seroconversion, those without documented positive HIV tests, and those without histopathological confirmation of malignancy were excluded from the present study. In selected cases, after confirming the presence of malignant tumors *via* histopathology, the required data were recorded from digital records and the patient's case files obtained from the medical records department. The data included demographic details, clinical history, examination findings, and treatment details. The relevant laboratory investigations included HIV viral loads, CD4 lymphocyte counts, and histopathology reports. The data obtained were entered into an Excel spreadsheet, and descriptive statistical analysis was performed.

3. RESULTS

The present 6-year retrospective study included 627 PLWHA with a mean age of 42.9 years and an age ranging from 1 to 75 years; the majority were male (60.9%), accounting for 382 patients, and 245 patients were female (39.1%). In this study, out of 627 PLWHA, 46 were diagnosed with malignancy, accounting for 7.3% of all PLWHA. The mean age of the PLWHA who developed cancer was 48.16 years (age range: 7–67 years). Of these, 26 were male (56.6%) and 20 were female (43.4%). Table **1** shows the distribution of the types of malignancies across the different age groups. The majority of the patients were in the 40–60 years age group.

3.1. ART Therapy

Among the 356 PLWHA on first-line ART, 22 (6.2%) subsequently developed cancer, whereas among the 47 PLWHA on second-line ART, 1 (2.1%) developed cancer. A total of 121 PLWHA who visited the hospital did not receive ART. Among these patients, 21 (17.3%) went on to develop cancer. After initiating ART, 10 PLWHA discontinued treatment; among them, 2 (20%) went on to develop cancer. Treatment details were not available for the remaining patients.

3.2. CD4 Cell Count

Of the 46 patients who developed malignancy, details of the CD4 cell count at the time of initial diagnosis with HIV were available for 16 patients. The mean CD4 cell count at the time of diagnosis of HIV was 407.31/µL. Among these patients, 3 (18.8%) had a CD4 cell count <50/µL at the time of diagnosis, 3 (18.8%) had a CD4 cell count of 150–200/µL, and 10 (62.4%) had a CD4 cell count >1000/µL at the time of diagnosis.

Details of the CD4 cell count at the time of diagnosis of malignancy were available for 29 patients. The mean CD4 cell count at the time of diagnosis with malignancy was 502.4/µL. Among these patients, 4 (13.8%) had a CD4 cell count of <50/µL, and 3 (10.3%) had a CD4 count of 400–450/µL.

3.3. Opportunistic Infections

The most common opportunistic infection among PLWHA and those with malignancies was TB, which was detected in 4 patients (8.6%, n=46); 3 patients each were diagnosed with CNS tuberculoma, herpetic skin lesions, and *Pneumocystis jiroveci* pneumonia (6.5%, n=46).

Among the 46 patients diagnosed with HIV and malignancies, 14 patients (30.4%) had AIDS-defining malignancies, and 32 patients (69.6%) had non-AIDS-defining malignancies.

3.4. AIDS-defining Malignancies

Among the 14 AIDS-defining malignancies, the mean age at the time of diagnosis was 45.14 years (age range: 7–67 years). Among these 14 patients, 8 (57.1%) were male, and 6 (42.9%) were female. Table **2** shows the spectrum of AIDS-defining malignancies.

3.5. Non-AIDS-defining Malignancies

Among the 32 patients with non-AIDS-defining malignancies, the mean age at the time of diagnosis was 49.33 years (range: 34–67 years). Among these patients, 18 (56.2%) were male, whereas 14 (43.8%) were female. Table **3** shows the spectrum of non-AIDS-defining malignancies.

Among the 46 patients, 28 (60.9%) were diagnosed with malignancy within the first 5 years of being diagnosed with HIV, and 16 patients (34.8%) were diagnosed with HIV within 5–10 years. Details about the exact date of diagnosis of HIV were not available for 2 patients (4.3%).

3.6. Metastasis

Six patients (13%, n=46) had evidence of distant metastasis at the time of diagnosis, whereas 40 patients (87%, n=46) did not have metastasis.

3.7. Young HIV Patients with Malignancies

Diffuse large B-cell lymphoma of the stomach was the only case of cancer among HIV-infected children in the present study. There were no cases of any malignancies among young adults aged 18–25 years.

3.8. HPV-linked and Non-HPV-linked Malignancies

Among the patients with malignancies, 13 (28.3%, n=46) had HPV-linked malignancies, whereas 33 (71.7%, n=46) had non-HPV-linked malignancies. Table **4** shows the spectrum of HPV-linked malignancies.

Table 1. Distribution of AIDS defining and non-AIDS defining malignancies based on different age groups.

Type of Malignancy	Age Group				Number of Cases(%)
	≤ 20 years	21-40 years	41-60 years	61-80 years	
Non-hodgkin lymphoma	1(2.17%)	2(4.36%)	6(13.04%)	1(2.17%)	10(21.74%)
CNS lymphoma	-	-	1(2.17%)	-	1(2.17%)
Squamous cell carcinoma	-	1(2.17%)	16(34.78)	2(4.36%)	19 (41.31%)
Endometrial stromal sarcoma	-	-	2(4.36%)	-	2(4.36%)
Ovary- serous papillary carcinoma	-	-	1(2.17%)	-	1(2.17%)
Ovary- serous cystadenocarcinoma	-	-	1(2.17%)	-	1(2.17%)
Breast-Infiltrating ductal carcinoma	-	2(4.36%)	-	-	2(4.36%)
Multiple myeloma	-	-	2(4.36%)	1(2.17%)	3(6.53%)
Hodgkin lymphoma	-	1(2.17%)	1(2.17%)	-	2(4.34%)
Acute leukemia	-	-	1(2.17%)	-	1(2.17%)
Lung adenocarcinoma	-	-	1(2.17%)	-	1(2.17%)
Esophageal adenocarcinoma	-	-	-	1(2.17%)	1(2.17%)
Hepatocellular carcinoma	-	-	1(2.17%)	-	1(2.17%)
Renal cell carcinoma	-	-	-	1(2.17%)	1(2.17%)
Total	1(2.17%)	6(13.04%)	33(71.75%)	6(13.04%)	46(100%)

Table 2. Spectrum of AIDS defining malignancies.

Type of Malignancy		Number of Cases (%)
Lymphoid malignancy -Nodal	NHL	3 (21.44%)
	B lymphoblastic lymphoma	1 (7.14%)
	DLBCL	1 (7.14%)
Lymphoid malignancy-extra nodal	DLBCL stomach	1 (7.14%)
	DLBCL Ileocecum	1 (7.14%)
	NHL jejunum	1 (7.14%)
	NHL submandibular salivary gland	1 (7.14%)
	NHL oral cavity	1 (7.14%)

(Table 2) contd.....

Type of Malignancy		Number of Cases (%)
Squamous cell carcinoma	Cervix	3 (21.44%)
Lymphoma	CNS	1 (7.14%)
Kaposi sarcoma		0
TOTAL		**14(100%)**

Table 3. Spectrum of non-AIDS defining malignancies.

Type of Malignancy		Number of Cases(%)
Oral cavity and upper airway	Maxilla SCC	2 (6.25%)
	Tongue SCC	3 (9.4%)
	Alveolus SCC	1 (3.13%)
	Lip SCC	1 (3.13%)
Female genital tract	Endometrial stromal sarcoma	2 (6.25%)
	Ovary serous papillary carcinoma	1 (3.13%)
	Ovary serous cystadenocarcinoma	1 (3.13%)
Breast-Infiltrating ductal carcinoma		2 (6.25%)
Haematolymphoid	Multiple myeloma	3 (9.4%)
	Hodgkin lymphoma	2 (6.25%)
	Acute leukemia	1 (3.13%)
Lung	Squamous cell carcinoma	2 (6.25%)
	Adenocarcinoma	1 (3.13%)
GIT and liver	Oesophagus adenocarcinoma	1 (3.13%)
	Anal canal SCC	3 (9.4%)
	HCC	1 (3.13%)
MGT	Penile SCC	2 (6.25%)
Urinary tract	RCC Kidney	1 (3.13%)
Eye	SCC	1 (3.13%)
Metastasis with occult primary	SCC lymphnode	1 (3.13%)
TOTAL		**32(100%)**

Table 4. Spectrum of HPV linked malignancies.

HPV Linked Malignancies	Type of Malignancy	Number of Cases(%)
AIDS defining malignancies	Invasive cervical cancer	3 (23.1%)
Non-AIDS defining malignancies	Anal SCC	3 (23.1%)
	Tongue SCC	3 (23.1%)
	PNS SCC	2 (15.3%)
	Alveolus SCC	1 (7.7%)
	Lip SCC	1 (7.7%)
TOTAL		**13 (100%)**

3.9. Treatment Modalities

The most common treatment modality for those diagnosed with cancer was chemotherapy, which was given to 13 patients (28.2%, n=46), followed by surgery, which was performed in 9 patients (19.5%, n=46), and concurrent chemoradiation, which was given to 7 patients (15.2%, n=46). The details of treatment were not available in other cases, or the patient refused medical advice regarding treatment.

3.10. Follow-up Data

Follow-up data were available for only 24 patients. Seven patients (29.1%) recovered after treatment, 5 patients (20.8%) developed complications linked to chemoradiation, 6 (25%) patients developed other complications unrelated to treatment, 4 patients (16.6%) refused treatment, and 2 patients (0.08%) succumbed to their illness.

4. DISCUSSION

People living with HIV are at increased risk of developing cancer. In the early 1980s, reports of a cluster of cases of *Pneumocystis jiroveci* and an unusually aggressive malignancy, KS, in homosexual men drew attention to the rising AIDS pandemic. It soon spread throughout the globe, and soon worldwide, there were increasing reports of certain specific cancers, namely, KS, aggressive lymphomas, and cervical cancers, which are now termed AIDS-defining cancers [12].

The present study included 627 PLWHA, among whom 46 were diagnosed with cancer. The majority of the patients were male, and the mean age was 48.16 years. The average age of developing cancer in the general population is over 60 years. Early development of malignancy is due to HIV-associated immunodeficiency and persistent oncogenic viruses [13]. In a study by Venkatesh *et al*., 42 patients with HIV and malignancy were included; the majority of the patients were male. The median age of the patients in the study was 35 years [11].

The proportion of malignancies in PLWHA in the present study was 7.3% (n=627). As the hospital is a major government district hospital that also serves as a referral center, the incidence of patients with cancer is higher than that of other general hospitals. However, in a study done by Sachdeva *et al*., which included 2880 PLWHA aged 3 years from a tertiary care center in North India, the frequency of cancer was found to be 1% [14].

For the 46 patients, details of the CD4 cell count at the time of diagnosis of malignancy were available for 29 patients, with a mean CD4 count of 502.45/µL, which is within the normal range, and similar findings were reported in a study by Madu *et al*. [15]. Moreover, 29.2% of the patients had a CD4 count <500/µL. In a study by Monforte *et al*., [7] researchers reported lower CD4 cell counts to be associated with higher mortality. They reported that doubling the CD4 count led to a reduction in mortality to approximately half. Even among patients who receive ART, the latest CD4+ T-cell count and nadir CD4+ T-cell count are independent predictors of mortality in HIV patients with AIDS, indicating the presence of malignancies [7]. Other researchers have also similarly described the association of lower CD4+ T-cell counts with the risk of malignancy, particularly for infection-related cancers, including HL, cervical carcinomas, HCC, and anal carcinomas [16].

In the present series, the majority of the patients (69.5%) had non-AIDS-defining malignancies, similar to the findings of Traore *et al*. [16]. Compared to individuals without HIV, PLWHA have a two- to four-fold greater risk of head and neck carcinomas and double the risk of oral cavity and pharyngeal carcinomas as cancer. This may be attributable to HPV, with studies showing a prevalence of oncogenic HPV ranging from 12–26% among HIV-infected individuals. Among the various subtypes, HPV 16 has been implicated in over 80% of malignancies of the oropharynx [17]. In our study, we found that 29.2% of non-AIDS patients had malignancies in the oral cavity and upper airway.

In a study performed in Guinea, the authors reported breast cancer as the most common malignancy, accounting for 26% of non-AIDS cases, whereas lung malignancy was more common in developed countries [16, 18]. In contrast to the present study, where oral malignancies were found to be more common, we found 9.3% and 6.2% lung and breast malignancies, respectively. In another study by Venkatesh *et al*., researchers reported HL as the most common malignancy among non-AIDS-defining malignancies, followed by breast carcinomas [11].

AIDS-related malignancies accounted for only a minority of the cases in the present study (30.4%, n=14). Among these cases, the most common was NHL, accounting for 71.4% of cases, followed by cervical cancer, accounting for 21.4% of cases. These findings were similar to those reported by Venkatesh *et al*. and Traore *et al*. [11, 16]. The increased risk of cervical cancer in PLWHA is attributed to the increased prevalence of co-infection with HPV and associated immunodeficiency. Lymphoma accounts for 74% of all HIV-associated malignancies. However, the pathogenic mechanism is unclear, possibly because coinfection with EBV can induce mutations in oncogenes and tumor suppressor genes [19]. The discovery of KSHV, which is responsible for the development of KS, led to an understanding of the oncogenic potential of other viruses, including EBV and HPV [9].

There were no reported cases of KS in the present study. This is in accordance with studies performed in Indian tertiary care centers [12, 14, 20]. The authors also did not observe KS in their study. In contrast, another study from Nigeria reported an increased risk of developing KS, but not NHL or cervical carcinomas, among PLWHA. This low incidence of KS in India highlights significant demographic differences with respect to malignancies among HIV-infected individuals in different parts of the world [21, 22].

In a study by Clifford *et al*., the authors followed 7304 HIV patient records from the Swiss HIV cohort study and Swiss cantonal cancer registries. They reported that the standardized incidence ratio for KS and NHL had an inverse association with CD4+ T-cell count. However, this association was not observed for other malignancies, including cervical carcinomas, or for cancers of the lip, mouth, pharynx, trachea, lung, bronchus, or non-melanomatous skin. They concluded that patients who were on ART had a lower risk of KS as well as NHL. However, the benefit of ART does not reduce the risk of developing HL or other non-AIDS-defining malignancies [22].

Among the patients with malignancies, 13 patients (28.3%) had HPV-linked malignancies. Studies have reported a high incidence and prevalence of HPV as well as precursor lesions in patients with HIV compared to the general population. These include anogenital malignancies, including cervical and anal carcinomas. The authors reported that the risk of anal carcinomas is greater in homosexual men and recommended screening the at-risk population. Similarly, current guidelines for women recommend cytology screening once every six months for 2 consecutive negative cytology results and thereafter yearly. Researchers have recommended colposcopy examination with acetic acid for cervical carcinoma screening in resource-strapped countries to reduce the incidence of these cancers [23]. The risk of HPV-related malignancies at other sites, including the oropharynx, penis, vulva, and vagina, has also been predicted to increase, although at present, data are limited with respect to these factors [20, 24].

Researchers have documented a relatively high incidence of malignancies caused by oncogenic viruses attributable to high-risk behavior, such as cervical carcinomas, anogenital carcinomas, and Hepatocellular carcinoma (HCC), in sexually active adolescents and adults. There remains a greater risk in individuals who have perinatally acquired HIV infection, which is attributable to various factors, including a longer duration of infection with HIV, immune dysregulation, and coinfection with HBV, HCV, or both. Thus, it is recommended that this unique cohort of young patients be diagnosed earliest and start ART, and access to HPV vaccination as well as individualized cancer screening facilities should be provided in multidisciplinary services [25, 26].

Presently, cancer screening plays a crucial role in the routine management of PLWHA, which includes an assessment of individual risks and benefits of screening as well as its potential outcome. Although successful interventions in the form of cancer screening in the general population have proven beneficial, data on similar interventions in PLWHA are lacking. Sigal *et al*. provided a conceptual framework for screening for cancer in patients with HIV. This included a Pap test for cervical carcinomas, an anal cytology test for anal carcinomas, abdominal ultrasound, and alpha-fetoprotein estimation for HCC. In addition, other screening modalities, including mammography for breast carcinoma, fecal occult blood testing and sigmoidoscopy for colonic carcinoma, prostate-specific antigen tests for prostatic carcinoma, and CT scans in heavy smokers for lung carcinoma, have been recommended by other authors [27-29].

5. LIMITATION OF THE STUDY

This was a retrospective study with limited control over the data collection.

CONCLUSION

Malignancies in people living with HIV constitute an emerging global health issue, particularly in young patients. In the present study, non-AIDS-defining malignancies were more common than AIDS-defining malignancies, which may be due to the increased survival rate of PLWHA receiving ART. A multidisciplinary approach for early detection and cancer screening facilities is recommended for people living with HIV.

DISCLOSURE

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AUTHORS' CONTRIBUTION

C.S.P., S.S., J.T.R., and S.K.M.: Contributed to the study conception and design, data collection, analysis and interpretation of results, and drafting of the manuscript; S.R. and R.M.: Performed the analysis and interpretation of results and drafted the manuscript. All the authors have reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

PLWHA	=	People Living with HIV/AIDS
ART	=	Antiretroviral Therapy
HIV	=	Human Immunodeficiency Virus
NHL	=	Non-Hodgkin Lymphoma
WHO	=	World Health Organization
KS	=	Kaposi Sarcoma
HL	=	Hodgkin Lymphoma
KSHV	=	Kaposi Sarcoma Herpes Virus
EBV	=	Epstein–Barr Virus
HPV	=	Human Papillomavirus
HCC	=	Hepatocellular Carcinoma

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The following study was approved by the institutional ethics committee Kasturba Medical College, Mangalore India (IEC KMC MLR 04-19/186).

HUMAN AND ANIMAL RIGHTS

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

The institutional ethics committee (Institutional Ethics Committee, Kasturba Medical College, Mangalore; approval number: IEC KMC MLR 04-19/186) waived the need for written informed consent from the patients to collect, analyze, and publish the retrospectively obtained and anonymized data for this non-interventional study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are openly available in a repository; figshare at https://figshare.com/articles/dataset/Patterns_of_ AIDS-defining_ and_Non-AIDS defining_Malig nancies_ in_People_Living_with_HIV_AIDS_A_6-_Year_Retros pective_Study_from_a_Tertiary_Care_Center_in_South_Indi a/28100549 [30].

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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