

Comorbidity Clusters and Immune Profiles in Hospitalized People with HIV: A Retrospective Analysis at a Tertiary Care Center in Eastern China

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Background: Antiretroviral therapy (ART) has shifted hospitalization causes in people with HIV (PWH) from AIDS-related to non-AIDS-related events. Data on comorbidity profiles and clinical characteristics of hospitalized PWH remain limited. Therefore, this study analyzes comorbidities and clinical characteristics of PWH in eastern China to understand the regional burden of comorbidities and inform clinical practice and regional hospital management.

Methods: This retrospective study included 593 hospitalized PWH. Demographic, clinical, and laboratory data, along with HIV-related medical history, were extracted from medical records. Diagnoses of comorbidities were based on established criteria. Clinical characteristics were compared across comorbidity groups.

Results: Among 593 participants, comorbidities were categorized into three groups: Non-AIDS-Defining Diseases (NADs, n=241), Opportunistic Infections (OI, n=204), and Malignancies (n=111). PWH with malignancies were significantly older (median age 58 years) than those with OI (43 years, $p=0.001$) or NADs (42 years, $p=0.001$). Patients with OIs had a significantly shorter duration since HIV diagnosis and ART initiation compared with the NADs and malignancy groups. Immunological analysis showed that the NADs group had higher median CD4⁺ T cell counts [413.5 (234–584) cells/ μ L] and CD4/CD8 ratios [0.75 (0.41–1.18)] compared with the OI and malignancy groups. AIDS-Defining Malignancies (ADMs) cases had significantly lower CD4⁺ T cell counts than Non-AIDS-Defining Malignancies (NADMs) cases [134.5 (97–313.75) vs 306 (200.25–503.00) cells/ μ L, $p=0.002$]. Multivariate logistic regression analysis established that a CD4/CD8 ratio below 0.5 independently associated with ADMs [adjusted OR 3.47 (95% CI 1.37–8.77), $P=0.004$].

Conclusion: NADs have emerged as the leading cause of hospitalization among PWH. For PWH who receive stable ART, remain at risk for NADs, warranting regular screening to prevent advanced disease. Routine monitoring of CD4⁺ T cell counts and CD4:CD8 ratios may facilitate improved cancer and OI screening strategies for individuals with persistently low ratios of CD4/CD8 or ART-naïve.

Keywords: human immunodeficiency virus, comorbidities, malignancies

Introduction

The Human immunodeficiency virus (HIV) epidemic poses one of the greatest challenges to global public health. According to the latest data of the Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome (AIDS), there were an estimated 39.9 million persons living with HIV (PWH) in the world at the end of 2023, with 1.3 million new infections reported in 2023.¹ Fortunately, with the introduction of modern antiretroviral therapy (ART), the incidence of AIDS related events has declined, and the life expectancy of PWH has drastically increased.² AIDS-

related mortality has decreased by 69% since its peak in 2004 and by 51% since 2010.¹ However, as PWH age, the relative burden of Non-AIDS-Defining Diseases (NADs) such as cardiovascular disease (CVD), renal impairment, metabolic disorders, and malignancy has increased, and the hospitalization rates among PWH remain high.^{3,4}

The development of these comorbidities is likely associated with immune suppression, chronic inflammation, and adverse effects of ART,⁵ with distinct distribution patterns across different geographic regions and populations. Shah et al reported that, the global burden of HIV-associated cardiovascular diseases has tripled over the past 2 decades, predominantly affecting sub-Saharan Africa and the Asia-Pacific region.⁶ Moreover, previous reports have highlighted the burden of comorbidities such as metabolic syndrome and renal disease in HIV patients,^{7,8} although much of the existing research has focused on populations outside China. The comprehensive data on clinical comorbidity profiles, temporal trends of hospitalization causes, and outcomes of PWH remain scarce in Eastern China, a rapidly developing region with unique socioeconomic and healthcare access patterns. Understanding the spectrum of comorbidities and their regional distribution among PWH is essential for optimizing healthcare resource allocation, enhancing patient care, and developing effective prevention strategies. Therefore, a cross-sectional study by retrospectively extracting patients' medical histories and comorbidity profiles from the hospital electronic health record system was conducted to quantify the comorbidity burden of PWH in Eastern China. Unlike prior reports from tertiary HIV centers, our data reflect real-world practices in a general hospital serving a socioeconomically diverse population. This could uncover unique comorbidity clusters influenced by regional healthcare access disparities, thereby providing valuable insights for tailored resource allocation.

Method

Study Design and Participant Selection

This is a retrospective observational study conducted at the National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU). The study included all HIV-positive patients hospitalized at FAHZU between July 2023 and June 2024. HIV infection was defined by the detection of HIV-1 antibodies by an enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot (WB), which is in accordance with the Chinese Guidelines for the Diagnosis and Treatment of HIV/AIDS.⁹ Patients with a positive initial screening result but a negative confirmatory test of HIV were excluded from the study. Given the census design encompassing all hospitalized PWH meeting inclusion criteria during the study period, formal pre-study sample size calculation was not performed. Demographic, clinical, and laboratory data, along with HIV-related medical history, were extracted from medical records and databases. The study protocols were carried out in accordance with the 1975 Declaration of Helsinki and received ethical approval from the Ethics Committee of FAHZU (Approval Number: 20241472). With all data analyzed in an anonymized format, the committee waived the necessity for obtaining written informed consent from the participants.

Data Collection and Clinical Assessment

Demographic information and medical history were obtained by a face to face questionnaire. The nutritional status was assessed using the nutritional risk screening 2002 (NRS 2002). The diagnoses of comorbidities, including Opportunistic Infections (OIs), Non-AIDS-Defining Diseases (NADs), malignancies, and other conditions, were based on established disease-specific criteria and were documented from the patients' discharge summaries. Immunological indicators like CD4 + and CD8 + T cells counts were determined by 4-color flow cytometry. Individuals who had no prior exposure to antiretroviral therapy were classified as ART-naïve. OIs refer to infections that exploit impaired immunity, including *Pneumocystis pneumonia* (PCP), Recurrent bacterial pneumonias, tuberculosis or non-tuberculosis mycobacteria (NTM) infections, active cytomegalovirus (CMV) infection, herpes simplex virus or varicella zoster virus infections, cerebral toxoplasmosis, deep fungal infections.⁹ NADs in this study encompassed cardiovascular diseases, cerebrovascular diseases, liver disease, chronic kidney diseases and other conditions not classified as opportunistic infections or malignancies. For malignancies, Non-AIDS-Defining Malignancies (NADMs) are typically defined in contrast to the three AIDS-Defining Malignancies (ADMs)—Kaposi sarcoma, non-Hodgkin lymphoma (NHL), and cervical cancer.¹⁰

Statistical Analysis

Continuous variables with a normal distribution are presented as mean \pm standard deviation (SD), while those with a non-normal distribution are reported as median [interquartile range (IQR)]. Categorical variables are summarized as percentages (numbers). Comparisons of continuous variables were conducted using either the Student's *t*-test or the Mann–Whitney *U*-test, as appropriate, while categorical variables were compared using the Chi-square test or Fisher's exact test. Multivariate analysis was performed using a stepwise logistic regression model, including all variables with a *p*-value <0.200 in the univariate analysis. A two-tailed *p*-value < 0.05 was considered statistically significant. Data analysis was carried out using SPSS software (IBM SPSS version 26.0, SPSS Inc). Figures were generated using GraphPad Prism (version 9.0, GraphPad Software Inc.) and Origin (Origin 2021, OriginLab Co).

Result

Baseline Characteristics of Patients

A total of 593 HIV-positive patients hospitalized at the First Affiliated Hospital of Zhejiang University School of Medicine between July 1, 2023, and June 30, 2024, were included in this study. The median age of the study population was 46 years (IQR 34–58) with 253 (42.7%) patients aged 50 years or older, and 86.3% of the studied population were male. Regarding marital status, 324/593 (54.6%) patients were married. And most of individuals resided in rural areas (312/593). For HIV related medical record, the median time since diagnosis for the overall population was 36.0 (IQR 3.5–96.0) months and the median duration of ART was 24.0 months (IQR 2.0–75.3) with 107 (18.0%) subjects being ART-naïve. In terms of the current ART regimen, 355 patients (59.8%) were on INSTI-based regimens, 108 (18.2%) on NRTI-based regimens, and 16 (2.7%) on PI-based regimens. The median CD4+ T cell count was 238.0 cells/ μ L (IQR 89.3–459.8), while the median CD8+ T cell count was 481.0 cells/ μ L (IQR, 306.0–722.5). The median hospital stay was 6 days (IQR, 3–13). The detailed characteristics of the participants are presented in [Table 1](#).

Table 1 Clinical and Demographic Characteristics of Participants

Parameter	N=593
Age (y)	46 (34–58)
<50	340 (57.3)
\geq 50	253 (42.7)
Gender	
Male	512 (86.3)
Female	81 (13.7)
Marital status	
Married	324 (54.6%)
Single	205 (34.6%)
Divorced	44 (7.4%)
Others	20 (3.4%)
Residence	
Urban	281 (47.4%)
Rural	312 (52.6%)
Time since HIV diagnosis (months)	36.0 (3.5–96.0)
ART-naïve	107 (18.0%)
ART duration (months)	24.0 (2.0–75.3)
Nutritional Status	
<3	509 (85.8)
\geq 3	79 (13.3)
Unknown	5 (0.9)

(Continued)

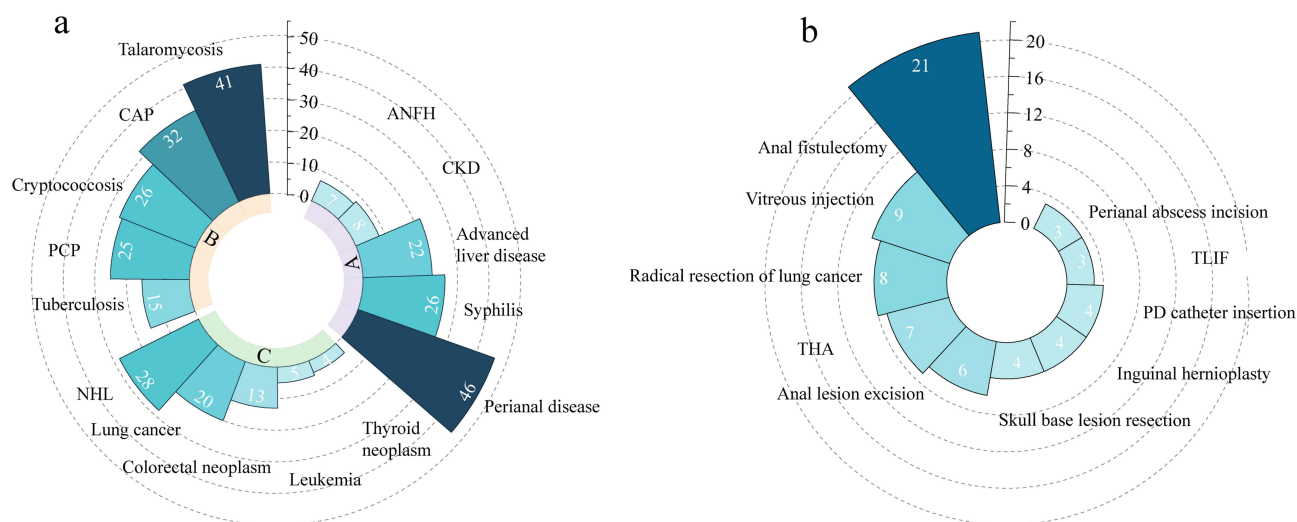


Figure 2 Comorbidity Spectrum and Surgical Spectrum of PWH. (a) Top five most common diseases in different comorbidity groups, A= non-AIDS-defining diseases group, B= opportunistic infections group, C= malignancy group. (b) Top ten most common non-AIDS-defining diseases in hospitalized people with HIV.

Abbreviations: ANFH, avascular necrosis of the femoral head; CAP, community-acquired pneumonia; CKD, chronic kidney disease; NHL, Non-Hodgkin lymphoma; PCP, Pneumocystis pneumonia; PD, Peritoneal dialysis; THA, Total Hip arthroplasty; TLIF, Transforaminal lumbar interbody fusion.

$p=0.001$). Sex distribution showed significant heterogeneity across groups, with malignancy cases showing a higher proportion of female patients ($p<0.05$). Notable geographical disparities were observed: OIs and malignancy cases were predominantly from rural areas, whereas NADs cases showed a higher urban predominance (NADs vs OIs, $p=0.001$; NADs vs malignancy, $p=0.112$). Analysis of HIV-related parameters revealed that patients with OIs had significantly shorter duration since HIV diagnosis and ART initiation compared with NADs and malignancy groups (Tables S1–S3). Moreover, the proportion of ART-naïve individuals was substantially higher in the OIs group. Immunological status, as measured by CD4+ T cell counts and CD4/CD8 ratio, showed that the NADs group maintained significantly higher median CD4+ T cell counts [cells/ul; 413.5 (234–584)] and CD4/CD8 ratio [0.75 (0.41–1.18)] compared with both OI and malignancy groups. Consistently, the NADs group demonstrated shorter hospital stays [days; 6 (3–9)].

Data presented as median (IQR) or n (%). Abbreviations: ART, antiretroviral therapy; NADs, non-AIDS-defining diseases; OIs, opportunistic infections.

Table 2 Comparison of Clinical Characteristics Among Different Comorbidities Subgroups

	NAD (n=241)	OIs (n=201)	Malignancy (n=111)	P value
Median age (y)	42 (33–57)	43 (34–54)	58 (43–67)	0.001
Age (y)				
<50	154 (63.9)	127 (63.2)	34 (30.6)	0.001
≥50	87 (36.1)	74 (36.8)	77 (69.4)	
Gender (%)				
Male	215 (89.2)	174 (86.6)	88 (79.3)	0.042
Female	26 (10.8)	27 (13.4%)	23 (20.7)	
Residence (%)				
Urban	137 (56.8)	74 (36.8)	53 (47.7)	0.001
Rural	104 (43.2)	127 (63.2)	58 (52.3)	
Time since HIV diagnosis	60 (23–108)	8 (0–60)	48 (12–108)	0.001
ART naïve	27 (11.2)	70 (34.8)	5 (4.5)	0.001
ART duration (months)	48 (12–96)	3 (0–24)	48 (11.75–108)	0.001
CD4+ T cell count (cells/μL)	413.50 (234–584.00)	86.00 (19.50–182.50)	278 (134.25–424.50)	0.001
CD4/CD8 ratio	0.75 (0.41–1.18)	0.18 (0.08–0.39)	0.68 (0.29–1.01)	0.001
Length of hospital stay (days)	6(3–9)	10 (4–18.50)	7 (3–13)	0.001

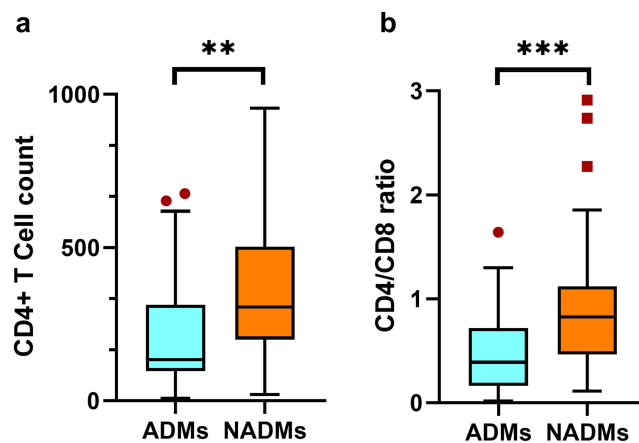


Figure 3 Distinct immunological profiling between ADMs and NADMs patients. (a) Significantly lower CD4+ T Cell Counts in ADMs group. (b) Depressed CD4/CD8 ratio in ADM group. ** $P < 0.01$, *** $P < 0.001$.

Abbreviations: ADMs, AIDS-defining malignancies; NADMs, non-AIDS-defining malignancies.

Distinct Clinical Features Between ADMs and NADMs

Exploratory analysis of subjects with malignancies revealed distinct clinical and immunological patterns between ADMs and NADMs group. Patients with NADMs were older than those with ADMs, although the difference was not statistically significant [59 (43–68.50) vs 53 (41.75–63.75), $P = 0.180$]. Additionally, the median time since HIV diagnosis was shorter in NADMs group than ADMs group, but this difference was also not significant (Table S4). However, no significant differences were observed between groups in sex, urban-rural distribution, or length of hospital stay. Immunological profiling revealed that ADMs cases demonstrated significantly compromised CD4+ T cell counts compared to NADMs cases [cells/ μL ; 134.5 (97–313.75) vs 306 (200.25–503.00), $P = 0.002$]. More strikingly, the median CD4/CD8 ratio was substantially lower in the ADMs patients [0.39 (0.16–0.72)] relative to NADMs patients [0.82 (0.46–1.12), $p = 0.001$] (Figure 3). Multivariate logistic regression identified a CD4/CD8 ratio < 0.5 as an independent predictor of ADMs development, remaining significant after adjusting for confounders (age, ART-naïve status, ART duration, time since HIV diagnosis, and CD4+ T-cell count) [adjusted OR 3.68, 95% CI 1.55–8.74; $P = 0.003$].

Discussion

This is a single-center retrospective study demonstrating that NADs have become the main reason for hospitalization. Besides, there was a high percentage of patients with malignancies (18.7%), with a prevalence 1.4 times higher than previously reported.¹¹ In addition, it was observed in this study that patients with different comorbidities exhibited distinct clinical characteristics and immunological patterns. PWH in the OI and ADMs groups showed lower CD4+ T cell counts, lower CD4/CD8 ratios and longer hospitalizations.

With the aging of the global population and the HIV epidemic, there has been an exponential increase in the number of elderly HIV patients in selected countries and regions over the past decade.¹² Globally, it was reported that the total number of PWH over the age of 50 years increased from 5.4 million to 8.1 million between 2015 and 2020.¹ In the United States and Australia, half of all PWH are older than 50 years old.¹³ This is due in large part to the fact that successful antiretroviral therapy has prolonged life expectancy.¹⁴ Past studies have shown that incidence and prevalence of HIV in older people in China are increasing.^{15–17} In this study, the median age of patients was 42 years and the percentage of patients older than 50 years was 42.7%, with a predominantly rural population (148/253, 58.5%). This relatively high prevalence of older patients is clinically significant and likely contributed to the observed study outcomes, particularly concerning NADs, OIs, and malignancies. Age and immunological status are closely interrelated. In the context of ART, the recovery of CD4+ T cells is slower in older patients compared to younger individuals, potentially impacting immune reconstitution and control of OIs.¹⁸ Additionally, aging is associated with immunosenescence, chronic inflammation and a higher incidence of age-related comorbidities,¹⁹ including hepatic and renal dysfunction, osteoporosis, and cardiovascular disease. These age-associated

factors collectively increase the risk for NADs events and malignancies, providing a plausible explanation for the patterns observed in our cohort where nearly half of the participants were aged 50 or older.

In this study, 241 patients were diagnosed with NADs, including 22 with liver disease, 8 with renal insufficiency, and 7 with femoral head avascular necrosis. Buskin et al²⁰ noted that the mortality in PWH with liver disease was significantly higher than those with HIV alone. In addition, PWH with comorbid chronic kidney disease are at an increased risk of cardiovascular disease and have a poor prognosis.²¹ However, it is noteworthy that the present study indicates perianal disorders constituted the largest proportion (19.1%) in the NADs group. This finding aligns with previous studies demonstrating a high prevalence of perianal lesions among HIV-infected individuals. In a study of 384 PWH,²² ano-rectal pathology was observed in 50 patients (13%), with anal acrocyanosis and hemorrhoidal disease being the most common conditions. These data highlight the importance of early recognition and timely intervention for NADs in HIV patients to enhance their quality of life and long-term prognosis.

Opportunistic infections (OIs) continue to be a significant cause of increased hospitalization and mortality among HIV-infected individuals. In this study, OIs accounted for 33.9% of the cases, with the most prevalent infections being *Penicillium marneffeii*, community-acquired pneumonia, cryptococcosis, pneumocystis pneumonia (PCP), and tuberculosis. A survey conducted at a hospital in northern China revealed that the most common opportunistic infections (OIs) among hospitalized PWH were tuberculosis (43.5%), candidiasis (29.3%), and PCP (22.4%).²³ A retrospective study on HIV-associated opportunistic infections (OIs) in Lebanon reported that the most common OIs were cerebral toxoplasmosis (21%) and fungal infections (17%). These findings suggest that the prevalence and spectrum of OIs among PWH vary by geographic location and socioeconomic conditions.

Over the past 20 years, an increasing cancer burden has been observed among PWH. Improvements in immune function resulting from ART have contributed to a shift in the predominant cancer type in PWH from AIDS-defining malignancies to non-AIDS-defining malignancies. It was demonstrated in this study that NADMs accounted for the majority of PWH with malignancies comprising 77 out of 111 cases (69.4%), which is in line with past research.²⁴ In addition, the study revealed that four of the five most common tumors (NHL, Lung cancer, colorectal neoplasm, leukemia, thyroid neoplasm) were NADMs. Lung cancer, colorectal neoplasm and leukemia should be the main targets for prevention due to their high incidence rates. Prevention research efforts in the setting of HIV infection should include smoking cessation,²⁵ validation of computed tomography screening for lung cancer and colorectal cancer, and primary routine physical examination for leukemia. Additionally, nearly a quarter of the patients underwent surgical treatment within the past year, including 17 grade IV procedures indicating a high operative treatment need. Strengthening HIV viral load testing is crucial to timely detection and control of HIV activity, ensuring the safety of both patients and surgeons during surgical procedures.

In this retrospective study, the clinical characteristics of HIV patients with varying spectrums of comorbidities were analyzed and described. Compared to the NADs and OI groups, PWH with malignancies were older, with a higher proportion of elderly individuals. Further analysis indicated that the median age of PWH with NADMs was higher than that of those with ADMs, although this difference was not statistically significant. Immunological analysis revealed that CD4+ T cell counts of PWH in the malignancies group were comparable to those in the NADs group and significantly higher than those in the OI group. This finding may be attributed to the higher proportion of NADMs patients within the malignancies group. In a cohort of PWH with oropharyngeal cancer, it was reported that these patients showed higher levels of CD4+ T cells.²⁶ Similarly, FJ Zhang²⁷ highlighted that the median CD4+ T cells count was significantly higher in the subjects with NADMs compared with ADMs, which is consistent with our findings.

Furthermore, the CD4/CD8 ratio also varied significantly across disease groups, with the OIs group exhibiting a much lower ratio compared to the NADs and malignancy groups. In the OI group, the median ART duration was only 3 months, with 30% of PWH being ART-naïve. In the early stages of HIV infection, CD8 T cell counts increase as CD4 T cell counts decline,²⁸ which may largely explain the low CD4/CD8 ratio observed in the OI group. Notably, it was found in our study that patients with ADMs exhibited a lower CD4/CD8 ratio compared with those with NADMs. Moreover, a low CD4/CD8 ratio was independently associated with a significantly increased risk of ADMs, irrespective of CD4 cell count, aligning with findings from prior studies. Previous European RESPOND cohort study reported that a CD4/CD8 ratio below 0.5 was associated with a markedly higher risk of ADMs and infection-related malignancies.²⁹ Similarly, Caby et al highlighted a link between a low CD4/CD8 ratio and an elevated risk of Kaposi's sarcoma and non-Hodgkin's lymphoma.³⁰ In addition,

over the past decade, numerous studies have reported an association between a low CD4/CD8 ratio and an increased risk of non-AIDS events.³¹ However, our study did not identify an association between CD4/CD8 ratio and NADs, which may be attributed to the characteristics of the study population and the small sample size. In conclusion, given the consistent association between low CD4/CD8 ratios, OIs and ADMs, early initiation of ART remains essential, which represent the most effective strategy to mitigate immune dysfunction and chronic inflammation.

This study has several limitations that should be considered. First of all, as a retrospective, cross-sectional analysis of hospitalized patients over a one-year period, our study is inherently limited in its ability to establish causality. The findings can only explain the correlation between the observed clinical data and the different comorbidities. Additionally, regarding data collection, we relied on historical administrative databases and primarily collected major comorbidities, which may underestimate the full comorbidity spectrum, potentially impacting the reliability and comprehensiveness of our findings. Third, although our census approach ensured complete sampling of hospitalized PWH in this setting, the single-center design may limit generalizability to outpatient or rural populations. While the overall sample size (n=593) provided adequate power (>95%) for primary comparisons (e.g. CD4+ T cells count), subgroup analyses (eg, ADMs vs NADMs, n=111) warrant cautious interpretation. To gain a more nuanced understanding of the comorbidity profile and clinical characteristics among people living with HIV and to provide stronger evidence for the care and management of the HIV positive population, larger, prospective, multicenter studies are necessary.

Conclusion

This study demonstrates that non-AIDS-related diseases have emerged as the leading cause of hospitalization among PWH, accompanied by a notable demand for surgical interventions. Additionally, the findings highlight the geographical and clinical characteristics of HIV-positive inpatients in Zhejiang Province, underscoring the importance of targeted comorbidity screening and management in specific high-risk populations and regions. Despite achieving high CD4+ T cell counts following stable ART, older PWH (≥ 50 years) remain at high risk for NADs and NADM, warranting regular comorbidity screening to prevent advanced disease. Conversely, for PWH with low level of CD4+ T cell, particularly ART-naïve individuals, OIs and ADMs should be prioritized. Furthermore, this study reinforces the association between a CD4:CD8 ratio < 0.5 and an elevated risk of ADMs. Accordingly, PWH whose CD4:CD8 ratio persistently remains below 0.5 should trigger intensified cancer screening with biannual tumor marker panels.

Abbreviations

ADM, AIDS-Defining Malignancies; AIDS, Acquired Immune Deficiency Syndrome; ART, Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; INSTI, Integrase Strand Transfer Inhibitor; NADs, Non-AIDS-Defining Diseases; NADMs, Non-AIDS-Defining Malignancies; NRTI, Nucleoside reverse transcriptase; OIs, Opportunistic Infections; PI, Protease Inhibitor; PWH, People With HIV.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. The trial protocol was granted by the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (Approval Number: ITT20241472). With all data analyzed in an anonymized format, the committee waived the necessity for obtaining written informed consent from the participants.

Consent for Publication

All the authors declare their consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare there are no competing interests in this work.

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