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Keywords: Burundi; Mpox (monkeypox); prospective studies; resource-limited settings; conjunctivitis; risk assessment.

Article

Clinical Predictors and Determinants of Mpox Complications in Hospitalized Patients: A Prospective Cohort Study from Burundi

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Abstract: (1) Objectives: Studies on mpox patterns, severity predictors, and public health impacts in Burundi remain limited. Therefore, we aimed to identify the clinical predictors and determinants of mpox complications among hospitalized patients in Bujumbura, Burundi, during an active outbreak. (2)Methods: We conducted a prospective cohort study of laboratory-confirmed mpox cases across three treatment centers (July-October 2024). Clinical characteristics and outcomes were assessed through a systematic review of medical and laboratory records supplemented by structured interviews with patients or caregivers. Risk factors for disease complications were evaluated using multivariate Firth penalized logistic regression. (3)Results: Complications developed in 3.1% of 850 patients (54.4% male; median age, 20.3 years). Conjunctivitis (odds ratio [OR]: 27.30; 95% confidence interval [CI], 7.67–122.23) and sore throat (OR: 12.63; 95% CI, 5.78–30.21) were significant predictors of severe disease progression. Conversely, generalized rash (OR, 0.10; 95% CI, 0.04–0.24) and lymphadenopathy (OR, 0.24; 95% CI, 0.08–0.62) were associated with a mild disease course. Sexual transmission was the predominant route of infection. (4)Conclusions: Noncutaneous manifestations, particularly conjunctivitis and sore throat, are early indicators of mpox severity. These findings inform clinical risk stratification in resource-limited settings and highlight the need for further investigation of pathophysiological mechanisms.

Keywords: Burundi; mpox (monkeypox); prospective studies; resource-limited settings; conjunctivitis; risk assessment

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1. Introduction

Mpox (formerly monkeypox) is caused by Orthopoxvirus monkeypox (MPXV) and has evolved from a regional concern to a global health challenge [1]. The virus transmits through close contact and fomites, with African outbreaks leading to international spread, emphasizing the need for enhanced surveillance and control measures [1, 2]. Despite increased global attention, African nations remain disproportionately affected, with outbreaks straining their resource-limited health care systems [3].

Following the first Public Health Emergency of International Concern declaration for mpox in 2022 and its termination in May 2023 [4], the emergence of a new MPXV subclade (clade Ib) in the Democratic Republic of the Congo (DRC) in September 2023 led to the second Public Health Emergency of International Concern declaration by the World Health Organization (WHO) in August 2024. Concurrently, the Africa Centres for Disease Control and Prevention issued its first declaration of a Public Health Emergency of Continental Security as the outbreak had spread to multiple neighboring countries, including Burundi [5, 6].

Burundi reported its initial mpox case on July 25, 2024, with Bujumbura city becoming the national epicenter, accounting for 59% of the confirmed cases by October 26, 2024 [Unpublished Burundi mpox situation report # 093, Ministry of Health. October 26, 2024]. While substantial research has been conducted in low-resource settings, such as Nigeria and the DRC [7, 8], understanding of mpox patterns, severity predictors, and public health impact remains limited in Burundi, which has not been reported before 2024. The current literature describes common manifestations, including fever, lymphadenopathy, and pustular rash [9, 10]; however, the prognostic significance of noncutaneous symptoms remains poorly understood.

This study aimed to identify the clinical predictors and determinants of mpox complications among hospitalized patients in Bujumbura, Burundi, to enhance early detection and clinical management in resource-limited settings during an active outbreak.

2. Patients and Methods

2.1. Study Design and Settings

This prospective cohort study was conducted at three primary treatment centers in Bujumbura, Burundi: the Centre Hospitalo-Universitaire de Kamenge, Clinic Prince Louis Rwagasore, and Hôpital Militaire de Kamenge. This study was conducted between July 25, 2024, and October 26, 2024, coinciding with the initial peak of the ongoing mpox outbreak in Burundi.

2.2. Participant Selection and Case Definitions

All 850 patients with laboratory-confirmed mpox who were hospitalized at the three selected mpox treatment centers in Bujumbura during the defined period were included, with no exclusion criteria. No exclusion criteria were applied to maintain study representativeness. Standardized case definitions based on WHO criteria were adopted by the Burundi Ministry of Health and implemented across all participating centers. A suspected case was defined as an individual presenting with an unexplained acute skin rash, mucosal lesions, or lymphadenopathy, accompanied by fever (> 38.5°C) and associated symptoms, following the exclusion of measles, varicella zoster, and other skin lesion-related diseases. A probable case was defined as a suspected case presenting with skin lesions and an established epidemiological link (contact with a confirmed or probable case within 21 days of symptom onset) without laboratory confirmation. A confirmed case was defined as a suspected case with positive laboratory results through a generic real-time reverse transcription-polymerase chain reaction. Regular monthly audits were conducted to ensure consistent application.

In Burundi, all laboratory-confirmed mpox cases required mandatory hospitalization, regardless of disease severity. With the provision of free health care services, all patients completed their hospital stay and underwent a standardized 28-day post-discharge follow-up. Of the 1441 laboratory-

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confirmed mpox cases in Burundi, 850 (59%) from Bujumbura's three treatment centers were enrolled in this study (Burundi Ministry of Health, unpublished situation report #093, 2024).

Disease severity was evaluated using two standardized approaches: (1) a modified Mpox Severity Scoring System [11] that incorporates skin lesions, mucosal involvement, and systemic symptoms and (2) WHO clinical criteria, which categorized cases as mild (≤ 5 skin lesions), moderate (6–100 lesions or mild complications), or severe (> 100 lesions and/or serious complications, such as secondary bacterial infections, encephalitis, pneumonia, genital necrosis, or ocular involvement). Conjunctivitis was classified as a mild condition, whereas keratitis and sight-threatening conditions were categorized as severe ocular complications. Lymphadenopathy, a characteristic feature of mpox, was analyzed as a presenting clinical feature rather than as a severity indicator or complication.

2.3. Data Collection

For mpox laboratory confirmation, we performed both generic real-time and clade Ib-specific reverse transcription-polymerase chain reaction amplification using the TaqMan Fast Advanced Master Mix. We used various TaqMan-based assays for MPXV detection. This mpox confirmation was performed at the National Reference Public Health Laboratory of the *Institut National de Santé Publique* [12, 13].

We used a mixed-methods approach combining structured interviews with patients or their parents/caregivers performed by clinicians and surveillance officers, data from electronic health records at "Open Clinics," national surveillance databases, case investigations, contact tracing, and records of laboratory polymerase chain reactions. Physicians used a WHO-adapted structured questionnaire to collect confidential patient information, including demographics, symptoms, complications, treatments, and outcomes. Clinicians' training included human immunodeficiency virus (HIV) screening according to Burundi's guidelines (unpublished), which required informed consent. The center protocols were harmonized, and treatment variations were analyzed as covariates.

2.4. Statistical Methods

Analyses were conducted using R (version 4.2.0; The R Foundation for Statistical Computing, Vienna, Austria) with descriptive statistics for demographic and clinical data. Continuous variables were presented as mean (standard deviation) or median (interquartile range [IQRs]). Categorical variables were presented as frequencies (%). Kolmogorov–Smirnov tests were used to assess data distributions. Missing data were managed using multiple imputations by chained equations with subsequent sensitivity analyses to determine imputation robustness and validate missing data assumptions.

Firth's penalized logistic regression was used to identify severe disease risk factors while addressing small-sample bias. Predictors were selected based on clinical relevance and significance in univariate analysis ($P < 0.20$). Sensitivity analyses confirmed these findings, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for balanced and unbalanced datasets. Adjustments for multiple comparisons were implemented using the Benjamini–Hochberg correction with a false discovery rate of 0.05. All significant associations persisted in the postadjustment analysis.

Validation showed reliable performance (Hosmer–Lemeshow test, $P = 0.82$; area under the curve, 0.83). Overfitting was reduced using LASSO, cross-validation, and the selection of strong predictors. Bootstrapping (1000 resamples) confirmed the effect stability, whereas sensitivity analyses and stratification validated the high ORs. A joint research team from the WHO and the Ministry of Health, comprising clinicians and epidemiologists, convened to review and validate the mpox data and to develop evidence-based control recommendations.

2.5. Ethics Approval

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The WHO African Region Ethics Review Committee (AFR/ERC/2024/9.6) approved the generic WHO Mpox Transmission Investigation Protocol developed by the mpox technical team at the WHO headquarters in collaboration with partners. The Burundi National Ethics Committee (*Décision* CNE/33/2024 *du Comité National d'Ethique*) authorized this study with the use of a modified version of the protocol that ensures participant rights and data confidentiality through anonymization of data. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

3. Results

3.1. Participant Characteristics

Between July 25, 2024, and October 26, 2024, there were 850 laboratory-confirmed cases of mpox in Bujumbura, Burundi. The distribution of cases was as follows: 452 (53.1%) from Clinic Prince Louis Rwagasore, 349 (41.1%) from Centre Hospitalo-Universitaire de Kamenge, 46 (5.4%) from Hôpital Militaire de Kamenge, and 3 patients (0.4%) under home-based care. The affected population comprised 462 males (54.4%) and 388 females (45.6%), resulting in a male-to-female sex ratio of 1.2:1. Among females, 7 (1.8%) were pregnant. The median duration of hospital stay was 10 days (IQR: 7–14 days).

The median age was 20.3 years (IQR, 22.0; range, 3 months–71 years). Age distribution analysis showed that children aged < 5 years (13.6%, n = 115) and school-age children (5–15 years; 25.2%, n = 213); that is, pediatric cases (< 16 years) constituted 38.8% (n = 328) of the total cases. Young adults (16–29 years old) represented 33.1% (n = 280) of the total patient population. Among the 522 patients aged > 16 years, individuals reported were single (50.6%, n = 264) or married (34.7%, n = 181), with an unknown status in 77 patients (14.7%).

Occupational data were available for 465 individuals, with the largest group comprising primary and secondary students (34.8%, n = 162), followed by merchants and traders (14.0%, n = 65). Health care professionals, military/police, and university students accounted for 0.9% (n = 4), 3.4% (n = 16), and 2.8% (n = 13) of the sample, respectively (Table 1).

Table 1. Reported occupations of patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024.

Occupation	Count (n = 465*)	Percent (%)
Primary and secondary students	162	34.8
Merchants and sellers	65	14.0
Casual sex partners	22	4.7
Drivers	19	4.1
Military and police	16	3.4
Health care professionals	4	0.9
University students	13	2.8
Mechanics	11	2.4
Other	153	32.9

* Among those for whom data is available.

3.2. Clinical Manifestations

Throughout the illness, generalized rash was the predominant clinical manifestation, occurring in 84.4% (n = 717) of the patients. Genital lesions (penile and vulvovaginal) were documented in 59.5% (n = 506) of the patients, and fever (temperature > 38.5°C) was present in 53.5% (n = 455). Additional clinical features included fatigue/asthenia in 34.5% (n = 293) of patients, local or regional

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lymphadenopathy in 32.7% (n = 278), headache in 31.1% (n = 264), and pharyngitis (sore throat) in 28.9% (n = 246). Conjunctivitis was documented in 5.5% (n = 47) of patients.

During illness, age-stratified analyses showed that genital lesions were most frequent in the 20–29 years age group (n = 209), with penile and vulvovaginal lesions in 50.2% (105/209) and 46.4% (97/209) of patients, respectively. The 5–15 years age group (n = 213) had the highest proportion of oral lesions (39.9%, 85/213). Fever exhibited a bimodal distribution, affecting the 5–15 years (90.1%, 192/213) and 20–29 years (82.3%, 172/209) age groups. Among the patients aged 20–29 years, lymphadenopathy manifested as local (54.1%, 113/209) or generalized (32.5%, 68/209) patterns. In contrast, patients aged ≥ 50 years (n = 42) had a low frequency of lymphadenopathy (local: 14.3%, 6/42; generalized: 9.5%, 4/42). The frequency of conjunctivitis was highest among children aged 0–5 years (21.6%, 25/116), followed by those aged 5–15 years (7.0%, 15/214).

3.3. Clinical Complications and Comorbidities

Complications occurred in 3.1% of the patients (n = 26) (Table 2). Secondary complications included vaginitis (1.1%, n = 9), genital ulceration (0.5%, n = 4), complicated pyelonephritis with vaginitis (0.1%, n = 1), and Fournier gangrene (0.1%, n = 1). Although lymphadenopathy is commonly observed as a characteristic clinical feature of mpox, it was analyzed as a presenting symptom rather than a complication.

Table 2. Complications recorded among patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024.

Primary Complication	Count	Percent (%)
No complications	820	96.5
Any complication	26	3.1
Vaginitis	9	1.1
Ulceration in the genital area	4	0.5
Conjunctivitis	2	0.2
Necrotic lesions in the scrotum/penis	2	0.2
Other specific complications (e.g., cellulitis, human immunodeficiency virus-related ocular lesions, genital necrosis, complicated pyelonephritis with vaginitis, Fournier gangrene)	≤ 1 each	< 0.2 each
Secondary complication		
No secondary complications	807	94.9
Any secondary complication	43	5.1
Specific cases (e.g., complicated pyelonephritis, Fournier gangrene)	≤ 1 each	< 0.2 each

Vaginitis was the most common complication at a rate of 1.1% overall (n = 9; 2.3% among 388 females; 9.1% among women aged ≥ 16 years). No deaths were reported in this study. Comorbidities were infrequent and included diabetes (0.35%, n = 3), renal insufficiency (0.24%, n = 2), hypertension (0.08%, n = 1), and malignancy (0.08%, n = 1).

A history of either prior or concurrent sexually transmitted infections was reported in 7.9% (n = 67) of patients. Most participants were HIV-negative (92.4%, n = 785), whereas 3.3% (n = 28) were HIV-positive, and 3.9% (n = 33) had an unknown status (not tested or data not available). Among those who tested positive for HIV, 46.4% (n = 13) were aware of their HIV-positive status, whereas 53.6% (n = 15) were newly diagnosed through testing during the clinical assessment for mpox. HIV-positive cases mainly were found among the age groups of 20–29 years and 30–39 years (n = 9 each),

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followed by 40–49 years (n = 5) and 16–19 years (n = 4) (Table 3). CD4 counts and HIV viral load data were not available for all HIV-positive cases.

Table 3. Demographic and clinical characteristics and comorbidities among patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024.

Category	Subcategory	Count	Percent (%)
Comorbidity	STI history (No)	710	58.1
	STI history (Yes)	67	5.49
	Hypertension (No)	871	68.6
	Hypertension (Yes)	1	0.08
	Diabetes (No)	814	66.7
	Diabetes (Yes)	3	0.25
	Cancer (No)	844	69.1
	Cancer (Yes)	1	0.08
	Kidney failure (No)	843	69.0
	Kidney failure (Yes)	2	0.16
	Others (No)	204	16.67
	Others (Yes)	2	0.16
	Erythematous-squamous dermatosis	1	0.08
	Pyelonephritis complicated by vaginitis	1	0.08
Lesions	Anorectal	181	14.8
	Penile	306	36.0
	Vaginal	200	23.5
	Oral	250	29.4
	Generalized rash	717	84.4
HIV status	Negative	785	92.4
	Unknown	33	3.9
	Positive	28	3.3
Age (HIV-positive cases)	16–19 years	4	
	20–29 years	9	
	30–39 years	9	
	40–49 years	5	
	50+ years	1	

Stratified analyses across age and HIV status with interaction testing confirmed consistent associations despite varying effect magnitudes in the key subgroups. HIV, human immunodeficiency virus; STI, sexually transmitted infection.

3.4. Risk Factors for Mpox Complications

In the balanced dataset, Firth's penalized multivariate logistic regression identified conjunctivitis as the most significant predictor of complications (OR, 27.30; 95% CI, 7.67–122.23; $p < 0.001$). Other notable predictors included pharyngitis (sore throat) (OR, 12.63; 95% CI, 5.78–30.21; $p < 0.001$) and genital edema (OR, 5.66; 95% CI, 1.55–23.28; $p = 0.008$). Conversely, generalized rash lesions (OR, 0.10; 95% CI, 0.04–0.24; $p < 0.001$) and oral lesions (OR, 0.20; 95% CI, 0.07–0.55; $p = 0.001$) were minimally associated with the occurrence of complications (Table 4). Low odds were associated with

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back pain (OR, 0.05; 95% CI, 0.01–0.43; $p = 0.006$), chills/sweats (OR, 0.03; 95% CI, 0.0002–0.30; $p < 0.001$), and local lymphadenopathy (OR, 0.24; 95% CI, 0.08–0.62; $p = 0.003$). These findings were also supported by the unbalanced dataset, particularly the strong associations with conjunctivitis (OR, 45.44; 95% CI, 5.98–464.05; $p < 0.001$) and vaginal lesions (OR, 8.88; 95% CI, 2.45–39.30; $p < 0.001$) (Table 4).

Table 4. Risk factors associated with mpox complications: Firth's penalized multivariate logistic regression analysis of laboratory-confirmed cases in Bujumbura, Burundi, July-October 2024.

Variables	**Balanced Dataset**		**Unbalanced Dataset**	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sore throat	12.63 (5.78–30.21)	< 0.001*	4.32 (1.15–19.61)	0.030
Conjunctivitis	27.30 (7.67–122.23)	< 0.001*	45.44 (5.98–464.05)	< 0.001*
Asthenia/fatigue	0.33 (0.10–0.93)	0.036	1.81 (0.35–9.58)	0.477
Muscle pain	2.86 (1.07–8.00)	0.037	1.06 (0.23–4.73)	0.940
Back pain	0.05 (0.01–0.43)	0.006*	0.21 (0.01–2.01)	0.185
Chills/sweats	0.03 (0.00–0.30)	< 0.001*	0.27 (0.00–3.23)	0.344
Local lymphadenopathy	0.24 (0.08–0.62)	0.003*	0.13 (0.01–1.06)	0.058
Genital edema	5.66 (1.55–23.28)	0.008*	3.67 (0.58–22.69)	0.162
Generalized lesions	0.10 (0.04–0.24)	< 0.001*	0.36 (0.05–1.69)	0.203
Oral lesions	0.20 (0.07–0.55)	0.001*	0.44 (0.07–2.01)	0.304
Vaginal lesions	3.44 (1.68–7.14)	< 0.001*	8.88 (2.45–39.30)	< 0.001*

OR, odds ratio; CI, confidence interval. *Statistically significant after Benjamini–Hochberg correction (false discovery rate = 0.05). Only the variables with significant associations in at least one dataset are shown. Model fit: Hosmer–Lemeshow test $P = 0.82$; Area under the curve = 0.83.

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3.5. Disease Severity

Of the 850 laboratory-confirmed mpox cases followed prospectively, 566 (66.6%) remained mild throughout their clinical course (≤ 5 skin lesions), 180 (21.2%) progressed to moderate disease (6–100 lesions or mild complications), and 104 (12.2%) progressed to severe disease (≥ 100 lesions or serious complications such as secondary bacterial infections, encephalitis, pneumonia, genital necrosis, or ocular involvement requiring intensive clinical management).

4. Discussion

The results of our prospective cohort study of patients with laboratory-confirmed mpox who were hospitalized in Bujumbura, Burundi, highlight the necessity of a tailored, risk-based approach for treating patients with mpox. Our findings revealed critical clinical features of mpox, such as a high occurrence of generalized rash lesions (84.4%), fever (53.5%), lymphadenopathy (32.7%), and slight male predominance (54.4%). The overall proportion of patients who experienced complications was lower (3.1%) than that in previous reports, and no deaths were noted during the study period.

Conjunctivitis and sore throat were significant predictors of complications, with ORs of 27.30 (95% CI, 7.67–122.23) and 12.63 (95% CI, 5.78–30.21), respectively. We observed an inverse association between local lymphadenopathy, widespread rash, and oral lesions. Our data imply that a skin-dominated disease could result in a favorable prognosis, likely because of its early recognition and rapid treatment. Additionally, some systemic signs, such as conjunctivitis and sore throat, were important indicators of severe disease status, necessitating continuous monitoring of the affected individuals.

Unlike the male predominance (96.4%) in the global outbreak [14], particularly among men who have sex with men [15], our African cohort demonstrated balanced transmission patterns (54.4% males) [16, 17]. The prevalence of fever (53.7%) and widespread rash (84.4%) in a study by Yon et al. [18] was similar to that in our cohort and comparable to both global data for clade II MPXV (62.3% and 85.7%, respectively) and historical clade I MPXV data from DRC-endemic regions (fever, 72.4%; rash, 89.3%) [14]. This finding was prior to the 2023 emergence of strain Ib, which is characterized by low case fatality compared to the historical clade I disease.

In this analysis, conjunctivitis and sore throat were significant predictors of complications, indicating a substantial prognostic value. The correlation between conjunctivitis and subsequent disease severity aligns with the findings of a previous study by Chattopadhyay et al. [19], who identified ocular symptoms as indicators of severity. These findings highlight the need for vigilant assessment and monitoring of conjunctivitis and/or sore throat early in the course of the illness [20]. Our findings regarding the inverse associations of specific symptoms are in line with the broad understanding that early detection and treatment play a crucial role in minimizing the disease burden [21].

These mucosal manifestations (conjunctivitis and sore throat) may indicate enhanced viral tropism in ocular and mucosal tissues, suggesting an increase in both the viral burden and the systemic inflammatory response. The predictive value of sore throat for the development of severe disease supports the observations of De la Herrán-Arita et al. [22]; however, our study extends this significance, indicating a stronger association than previously documented.

Similarly, the negative correlation of local lymphadenopathy contrasts with the findings of Álvarez-Moreno et al. [23], which showed neutral associations. This discrepancy may stem from differences in immune responses, suggesting that localized lymphadenopathy may reflect efficient viral containment. The age-related vulnerability observed in our study aligns with the findings of Cho et al. regarding the severity of mpox in older populations [24].

The strong association of conjunctivitis with severe disease emphasizes the potential significance of noncutaneous manifestations as indicators of systemic progression [19, 25]. Analyses of the time to treatment demonstrated that the protective associations persisted even after adjusting for delays in seeking care, thus strengthening the hypothesis of a biological mechanism. Variance inflation

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factors and correlation analyses validated the independence of the predictors, and stepwise variable selection mitigated potential issues of collinearity. Evidence suggests that HIV infection without immune suppression is not a direct risk factor but instead correlates through shared behavioral and immunological factors [22].

The lower frequency of complications in our study than in the U.S. data by Eustaquio et al. may reflect differences in clinical surveillance systems, case definitions, reporting mechanisms, and viral strains or biological host factors, such as the frequency of advanced HIV disease in the cohorts affected [26]. The presence of skin lesions without concurrent mucosal or systemic symptoms was associated with few complications, supporting the observation of Ogoina et al. that isolated cutaneous involvement may not indicate a severe disease course [25].

4.1. Study Limitations

Several methodological constraints must be considered when interpreting our findings. It was challenging to establish a temporal relationship between initial symptoms and disease progression, as patients presented with varying stages of illness (median time from symptom onset to hospitalization, 5.2 days; IQR, 3–8 days). Although our study provides valuable insights from multiple centers in Burundi, the findings should be interpreted within the context of our setting's specific health care infrastructure and patient population. The wide CIs observed for conjunctivitis as a prognostic indicator suggest that this clinical feature should be evaluated, along with other presenting symptoms and patient characteristics. Further assessment of this potential early warning sign in different clinical contexts would enhance our understanding of its prognostic value while maintaining vigilance for severe disease progression. Variations in treatment protocols across study centers may have influenced our risk factor analysis. In contrast, the limited duration of the study precluded the assessment of seasonal patterns in disease presentation and transmission dynamics.

Burundi's mandatory hospitalization policy for laboratory-confirmed mpox cases has both strengths and limitations. Although this approach enabled comprehensive clinical documentation, it potentially introduced selection bias by deterring individuals from seeking diagnoses. Although we achieved high retention rates, with 99.6% of patients completing their hospital stay, facilitated by the provision of free health care and nutritional support, this differs notably from settings such as the DRC, where socioeconomic constraints frequently lead to premature discharge.

Our E-value analysis (E = 3.2) indicated that substantial unmeasured confounding is necessary to nullify the observed associations. However, the dynamic nature of mpox manifestations complicates our analysis. Despite implementing standardized daily assessment forms, capturing the complex evolution of skin lesions and their relationship with systemic complications requires sophisticated temporal analysis. Future prospective studies incorporating detailed temporal data collection methods across diverse health care settings are required.

4.2. Clinical Implications

These findings highlight the need to prioritize monitoring conjunctivitis and sore throat as possible key predictors of severe mpox and to stratify risk by age and sex, particularly for older adults and women. The early detection of cutaneous symptoms and risk-based care pathways can optimize outcomes in resource-limited settings. The inverse association between local lymphadenopathy and complications suggests that it may represent a typical immune response rather than a marker of disease severity. Future studies should explore the immunological significance of lymphadenopathy patterns in mpox disease across different geographic regions. Developing standardized and locally adapted risk tools and investigating host and viral factors may enable personalized care. Research on immunocompromised populations, particularly those with advanced HIV, is essential to refine targeted treatments and understand severe mpox outcomes. With two-thirds of mpox cases meeting the criteria for mild disease in Burundi, in the absence of warning signs such as those found here, implementing structured home-based care strategies could optimize health care resources while maintaining effective disease surveillance and control.

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5. Conclusions

This study provides a comprehensive analysis of mpox clinical manifestations and associated risk factors in Burundi and offers novel insights into the clinical progression of the disease. Conjunctivitis and sore throat are key predictors of severe disease, with conjunctivitis showing an exceptionally high prognostic value. These findings highlight the importance of mucosal symptoms and findings as red flags in clinical assessment. In contrast, generalized rash and lymphadenopathy limited to the local distribution in the body were associated with low severity. They may signify robust immune responses rather than signs of an advanced disease stage. Older age was identified as a risk factor, emphasizing the need for targeted monitoring and intervention in older patients who are at an increased risk of severe outcomes.

These findings have important clinical implications, especially in resource-limited settings, where the recognition of easily observable markers, such as conjunctivitis, sore throat, and skin lesions, can guide risk stratification and optimize patient management. This study provides a foundation for the development of evidence-based management protocols that emphasize risk-stratified care pathways and structured home-based strategies.

In conclusion, the inclusion of clinical markers in patient assessment protocols may aid the distribution of resources, enhancement of outcomes, and development of public health initiatives, particularly in endemic and resource-constrained areas. These results indicate a significant advancement in the global improvement of mpox management caused by clade Ib MPXV.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1. Reported occupations of patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024; Table S2. Complications recorded among patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024; Table S3. Demographic and clinical characteristics and comorbidities among patients with laboratory-confirmed mpox, Bujumbura, Burundi, July-October 2024; Table S4. Risk factors associated with mpox complications: Firth's penalized multivariate logistic regression analysis of laboratory-confirmed cases in Bujumbura, Burundi, July-October 2024.

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by the WHO headquarters mpox technical team in collaboration with partners. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Data Availability Statement: All relevant data generated during this study are included in the manuscript and its Supplementary Materials.

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Abbreviations

The following abbreviations are used in this manuscript:

AIDS	Acquired Immunodeficiency Syndrome
CD4	Cluster of Differentiation 4
CI	Confidence Interval
DNA	Deoxyribonucleic Acid
DRC	Democratic Republic of the Congo
E E-value	(statistical measure)
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
LASSO	Least Absolute Shrinkage and Selection Operator
MPXV	Orthopoxvirus monkeypox
OR	Odds Ratio
P	Probability value
PCR	Polymerase Chain Reaction
RNA	Ribonucleic Acid
SD	Standard Deviation
STI	Sexually Transmitted Infection
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
U.S.	United States
UCL	University College London
USAID	United States Agency for International Development
WHO	World Health Organization

References

1. Beer E M, Rao V B. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis 2019; 13: e0007791. https://doi.org/10.1371/journal.pntd.0007791
2. Švecová D. Update on Monkeypox Virus Infection. J Med Healthcare 2024;6:1-3. https://doi.org/10.47363/jmhc/2024(6)274

 doi:10.20944/preprints202502.2195.v1

3. Ogoina D, Izibewule J H, Ogunleye A, Ederiane E, Anebonam U, Neni A, et al. The 2017 human monkeypox outbreak in Nigeria —Report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. PLoS One 2019; 14: e0214229. https://doi.org/10.1371/journal.pone.0214229
4. Sarker R, Roknuzzaman ASM, Shahriar M, Bhuiyan MA, Islam MR. The WHO has ended public health emergency of international concern for mpox: assessment of upside and downside of this decision. Int J Surg. 2023;109(10):3238-3239. https://doi.org/10.1097/JS9.0000000000000545
5. Torales J, Barrios I, Ventriglio A. The Mpox outbreak is a public health emergency of international concern: Implications for mental health and global preparedness. Int J Soc Psychiatry. 2024 Jan. https://doi.org/10.1177/0020764024128071 [Online ahead of print]
6. Africa Centers for Disease Control and Prevention. Africa CDC declares Mpox a public health emergency of continental security, mobilizing resources across the continent [Internet]. 2024 [cited 2024 Nov 26]. Available from: https://africacdc.org/news-item/africa-cdc-declares-mpox-a-public-health-emergency-of-continental-security-mobilizing-resources-across-the-continent/
7. Vakaniaki EH, Kacita C, Kinganda-Lusamaki E, O'Toole Á, Wawina-Bokalanga T, Mukadi-Bamuleka D, et al. Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo. Nature Med. 2024;30(10):2791-2795. https://doi.org/10.1038/s41591-024-03130-3
8. Ogoina D, Iroezindu M, James H I, Oladokun R, Yinka-Ogunleye A, Wakama P, et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis 2020; 71: e210-e214. https://doi.org/10.1093/cid/ciaa143
9. Adler H, Gould S, Hine P, Snell L B, Wong W, Houlihan C F, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis 2022; 22: 1153-1162. https://doi.org/10.1016/S1473-3099(22)00228-6
10. Thornhill J P, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison L B, et al. Monkeypox virus infection in humans across 16 countries - April-June 2022. N Engl J Med 2022; 387: 679-691. https://doi.org/10.1056/NEJMoa2207323
11. Zucker J, McLean J, Huang S, DeLaurentis C, Gunaratne S, Stoeckle K, et al. Development and pilot of an mpox severity scoring system. J Infect Dis 2024; 229: S229-S233. https://doi.org/10.1093/infdis/jiad492
12. Li Y, Zhao H, Wilkins K, Hughes C, Damon I K. Real-time PCR assays for the specific detection of monkeypox virus West African and Congo Basin strain DNA. J Virol Methods 2010; 169: 223-227. https://doi.org/10.1016/j.jviromet.2010.07.012
13. Schuele L, Masirika L M, Udahemuka J C, Siangoli F B, Mbiribindi J B, Ndishimye P, et al. Real-time PCR assay to detect the novel Clade Ib monkeypox virus, September 2023 to May 2024. Euro Surveill 2024; 29: 2400486. https://doi.org/10.2807/1560-7917.ES.2024.29.32.2400486
14. World Health Organization. Multi-country outbreak of mpox, External situation report#31 - 22 December 2023. Geneva: WHO; 2023.
15. Seyed Alinaghi S, Afsahi AM, Afzalian A, Shahidi R, Tamehri Zadeh SS, Varshochi S, et al. Monkeypox: a systematic review of epidemiology, pathogenesis, manifestations, and outcomes. Russ J Infect Immun. 2023. https://doi.org/10.15789/2220-7619-mas-15632
16. Okoli G N, Van Caeseele P, Askin N, Abou-Setta A M. Comparative evaluation of the clinical presentation and epidemiology of the 2022 and previous mpox outbreaks: a rapid review and meta-analysis. Infect Dis (Lond) 2023; 55: 490-508. https://doi.org/10.1080/23744235.2023.2214609
17. Li P, Li J, Ayada I, Avan A, Zheng Q, Peppelenbosch M P, et al. Clinical features, antiviral treatment and patient outcomes: a systematic review and comparative analysis of the previous and the 2022 mpox outbreaks. J Infect Dis 2023; 228: 391-401. https://doi.org/10.1093/infdis/jiad034
18. Yon H, Shin H, Shin J I, Shin J U, Shin Y H, Lee J, et al. Clinical manifestations of human mpox infection: a systematic review and meta-analysis. Rev Med Virol 2023; 33: e2446. https://doi.org/10.1002/rmv.2446
19. Chattopadhyay S, Manwal M, Gupta R, Kukreja V, Mehta S. Integrative CNN-RF Frameworks for Stratified Human Monkeypox Virus of Severity Assessment. In: Proceedings of the International Conference on Emerging Technologies (INCET); 2024. https://doi.org/10.1109/incet61516.2024.10593194

 doi:10.20944/preprints202502.2195.v1

20. Núñez-Cortés R, Calatayud J, López-Gil J F, Koyanagi A, Casaña J, López-Bueno R. Risk profile and mode of transmission of mpox: a rapid review and individual patient data meta-analysis of case studies. Rev Med Virol 2023; 33: e2410. https://doi.org/10.1002/rmv.2410
21. Prasad S, Galván Casas C, Strahan A G, Fuller L C, Peebles K, Carugno A, et al. A dermatologic assessment of 101 mpox (monkeypox) cases from 13 countries during the 2022 outbreak: skin lesion morphology, clinical course, and scarring. J Am Acad Dermatol 2023; 88: 1066-1073. https://doi.org/10.1016/j.jaad.2022.12.035
22. De la Herrán-Arita AK, González-Galindo C, Inzunza-Leyva GK, Valdez-Flores MA, Norzagaray-Valenzuela CD, Camacho-Zamora A, et al. Clinical Predictors of Monkeypox Diagnosis: A Case-Control Study in a Nonendemic Region during the 2022 Outbreak. Microorganisms. 2023;11(9):2287. https://doi.org/10.3390/microorganisms11092287
23. Álvarez-Moreno CA, Alzate-Ángel JC, De La Hoz-Siegler IH, Bareño A, Mantilla M, Sussman O, et al. Clinical and epidemiological characteristics of mpox: A descriptive cases series in Colombia. Travel Med Infect Dis. 2023;53:102594. https://doi.org/10.1016/j.tmaid.2023.102594
24. Cho W, Park S, Kim HJ, Lee M, Choi YS, Yeo SG, et al. Clinical characteristics and outcomes of patients with mpox during the 2022 mpox outbreak compared with those before the outbreak: A systematic review and meta-analysis. Rev Med Virol. 2024;34(1):e2508. https://doi.org/10.1002/rmv.2508
25. Ogoina D, Dalhat MM, Denue BA, Okowa M, Chika-Igwenyi NM, Yusuff HA, et al. Clinical characteristics and predictors of human mpox outcome during the 2022 outbreak in Nigeria: a cohort study. Lancet Infect Dis 2023; 23: 1418-1428. https://doi.org/10.1016/S1473-3099(23)00427-9
26. Eustaquio PC, Salmon-Trejo LAT, McGuire LC, Ellington SR. Epidemiologic and Clinical Features of Mpox in Adults Aged >50 Years - United States, May 2022-May 2023. MMWR Morb Mortal Wkly Rep. 2023;72(33):893-896. https://doi.org/10.15585/mmwr.mm7233a3