International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Characteristics and Differences in Mpox Patients with and without HIV Infection: A Retrospective Cross-Sectional Study in Chengdu, China

Bennan Zhao[1,*], Qingxiao Liu[2,*], Qing Du[3], Jun Kang[1], Rong Tang[4], Yalan Tu[5], Dafeng Liu[1]

[1]The First Ward of Internal Medicine, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China; [2]Department of Neurology, Hospital of Chengdu University of TCM, Chengdu, People's Republic of China; [3]The Second Ward of ICU, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China; [4]Department of Integrated Chinese and Western Medicine, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China; [5]Scientific Research and Teaching Department, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dafeng Liu, The First Ward of Internal Medicine, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China, Tel +86 1 309 449 4836, Email ldf312@126.com; Yalan Tu, Scientific Research and Teaching Department, Public Health Clinical Center of Chengdu, Chengdu, People's Republic of China, Tel +86 1 501 326 6454, Email tyl950330@163.com

Purpose: To date, there are few reports about mpox case series in China, and scarce information is available about the in-vivo kinetics of T-cell responses in the early stage of mpox infection. This study aims to investigate the clinical difference among mpox patients with and without human immunodeficiency virus (HIV) infection.

Patients and Methods: A total of 56 patients diagnosed with mpox by Chengdu Center for Disease Control and Prevention (CDC) and hospitalized in Public Health Clinical Center of Chengdu were retrospectively included and divided into an HIV-infected group (n=23) and a non-HIV-infected group (n=33). Clinical characteristics and serum chemistry findings of mpox patients were collected in order to analyze the differences between the HIV-infected group and the non-HIV-infected group.

Results: Multiple laboratory abnormalities, including elevated C-reactive protein (69.1%), hypocalcemia (50.9%), elevated CD3+CD8+T counts (47.0%) and inverted ratio of CD3+CD4+T to CD3+CD8+T (64.7%) were common in mpox cases. There were statistically significant differences (all $P < 0.05$) in age, serum calcium levels, CD3+CD4+T counts, the ratio of CD3+CD4+T to CD3+CD8+T, proportion with >10 rashes, incidence of proctitis anus and time from rash growth to rash scab shedding between HIV-infected group and non-HIV-infected group. In the early stage of mpox infection, the median of CD3+CD8+T counts in the non-HIV-infected group was significantly higher than that in healthy donors ($P<0.001$), and the median of CD3+CD4+T/CD3+CD8+T ratio was significantly lower ($P<0.001$). The median of CD3+CD4+T counts in mpox patients co-infected with HIV significantly decreased compared to the pre-infection level ($p =0.033$).

Conclusion: Our study indicates that mpox co-infected with HIV patients have longer lasting rash lesions and a higher incidence of proctitis anus. T-cell responses may be different between HIV-infected and non-HIV-infected individuals in the early stage of mpox infection.

Keywords: mpox, HIV, clinical characteristics, complication, T-cell response

Introduction

Mpox (formerly known as monkeypox) is a zoonotic viral disease caused by monkeypox virus (MPXV). The illness is similar to smallpox; it can cause a painful rash and fever, but mpox is characterized by enlarged lymph nodes and a low case fatality rate.[1] Mpox rash usually transforms through a macular, papular, and vesicular phase and disappears after crusting in approximately 3 weeks,[2] most mpox patients fully recover.[3] Testing skin lesion material by polymerase-chain reaction (PCR) is the most commonly used method for laboratory confirmation of mpox. Before 2022, mpox mainly related to Central and West Africa, with few mpox cases occurring outside of Africa, starting in 2003 in the USA. In May 2022, a multi-country outbreak of mpox broke out in non-endemic countries.[4] As October 2023, the current

Received: 22 December 2023
Accepted: 27 March 2024
Published: 8 April 2024

outbreak has come with 91,788 confirmed mpox cases in 116 countries worldwide.[5] Mpox outbreak is mostly affecting young and middle-aged men who have sex with men (MSM) who participate in high-risk sexual behaviors,[5–8] which is typically the case among human immunodeficiency virus (HIV) infected individuals. It is still unclear whether MPXV can spread through semen or vaginal fluids, but studies have reported that, during this mpox epidemic, the prevalence of HIV and other sexually transmitted diseases has also increased.[9] Unfortunately, there is no evidence that a condom may protect from mpox,[10] although it might help protect from other sexually transmitted diseases.

According to the data released by World Health Organization (WHO), approximately 50% of mpox patients in this global epidemic are co-infected with HIV,[5] which shows that people with HIV may be more vulnerable to mpox, because their immune systems are weakened. It is reasonable to assume that the clinical presentation of mpox individuals co-infected with HIV is different due to underlying immunosuppression. Since June 2023, Chinese Center for Disease Control and Prevention (CDC) has released the surveillance result of mpox epidemic in Chinese mainland every month,[11] the number of mpox has increased rapidly in the short term. The world has just experienced a pandemic of Corona Virus Disease 2019 (COVID-19), and none of us want another infectious disease to have such a pandemic. Therefore, it is obviously necessary to continue to pay attention to the epidemic of mpox. There have been many reports on the epidemiological investigation and clinical characteristics of mpox patients, but the change trend of T lymphocyte in mpox patients, and the characteristics of mpox patients co-infected with HIV are unclear and worthy of study. This study aims to investigate the clinical difference among mpox patients with and without HIV infection in China and to report the in-vivo kinetics of T-cell responses in the early stage of mpox infection.

Materials and Methods

Study Population

A retrospective cross-sectional study was used in this study. Fifty-six patients with a laboratory-confirmed MPXV positivity diagnosed by Chengdu CDC and hospitalized in Public Health Clinical Center of Chengdu from July 1 to August 8 2023 were included, they were with no age or gender restrictions. All patients were hospitalized 3–15 days after symptoms onset.

T lymphocyte subset results of 30 healthy donors were collected in this study in order to compare and analyze the in-vivo kinetics change of T-cell responses in the early monkeypox infection. Healthy donors were physically examined in a population aged 20–46 years in Public Health Clinical Center of Chengdu in 2022 without mpox or HIV.

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Public Health and Clinical Center of Chengdu (No.: YJ-K2023-61-01). All of them voluntarily signed informed consent and agreed to undergo further follow-up.

Diagnostic, Prognosis and Discharge Criteria

Diagnosis criteria of mpox were based on "Guidelines for Diagnosis and Treatment of Monkeypox (2022 Edition)"[12] and "Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention".[13]

Prognosis and discharge criteria of mpox patients were normal body temperature for more than 3 consecutive days, the shedding of rash scabs, and significant improvement in clinical symptoms.[12]

Grouping Standards

Of 56 patients with mpox, 23 and 33 cases were further divided into the HIV-infected group and the non-HIV-infected group, respectively.

Measurement of MPXV

The throat and acne swab specimen of patients were taken and sent to the laboratory of the district CDC in which the hospital located in, or to the Chengdu CDC. Specific real-time PCR assay was used to detect MPXV nucleic acid in those two types of specimen, and those exhibiting with at least one positive result were diagnosed with mpox.

Detection Methods and Analysis Methods of T Lymphocytes

EDTA anticoagulated peripheral blood (2 mL) samples were collected from patients with mpox and controls and tested by Beckman Coulter flow cytometry within 6 hours of being obtained. Briefly, CD3+/CD4+/CD8+ T-cell counts (cells/μL) were measured by multiple-color flow cytometry with human monoclonal anti-CD3-fluorescein isothiocyanate (FITC), anti-CD4-PE and anti-CD8-allophycocyanin (APC) according to the manufacturer's instructions. A total of 1200 CD3 cells were recorded per tube, and flow cytometry data were analyzed using the Beckman application software CyExpert for DxFLEX. The samples of patients with mpox were collected at admission.

Treatments of Mpox

Mpox is treated with supportive care according to the Chinese guideline[12] and our clinical experience. We took strengthening skin care, pain symptoms relief, combined with traditional Chinese medicine treatment means. At the stage of herpes, fusidic acid and penciclovir were applied externally, and local immersion with normal saline was performed. At the stage of herpes, Fusidic acid cream and penciclovir cream were applied externally, and local immersion with normal saline was performed. After the herpes burst, POvidone iodine was applied externally and alginate dressing was applied externally to promote healing. Patients with bacterial infection were treated with antibiotics, and patients with rectal proctitis were treated with hemorrhoid cream and Chinese herbal sitz bath.

To be brief, our traditional Chinese medicine has the function of clearing heat and detoxifying, promoting the absorption of blister fluid, promoting ulcer repair and relieving perianal pain.

Follow Up Time

All of mpox patients were followed up until who were discharged or died.

Data Collection

All data of 56 cases, including demographic information, clinical data such signs, symptoms, duration of illness, laboratory values (ie, hematologic and serum chemistry findings) and ultrasonic results, were collected to establish databases. Laboratory values of peripheral venous blood were collected from all patients on the day of hospitalization or the next day. Researchers strictly controlled the accuracy, completeness and authenticity of all data.

Statistical Analysis

Statistical and cartographic software, including SPSS 26.0 (SPSS, Chicago, IL, USA) and GraphPad Prism 8 (GraphPad, CA, USA), were used for statistical analyses and cartography production. Continuous variables of normal distribution were expressed as mean ± standard deviation, the comparison between any two groups used an independent-sample *t*-test. Continuous variables of skew distribution were expressed as the median and interquartile range between the 25th and 75th percentiles, the comparison between two groups used Wilcoxon signed-rank test or Mann–Whitney *U*-test. Categorical variables were expressed as frequencies with percentages, and comparisons of these data were performed using the chi-square test or Fisher's exact test. Pearson contingency coefficient test was used to analyze the correlation between the two categorical variables. $P<0.05$ was considered to define statistical significance.

Results

General Information and Epidemiological Characteristics

The cases were 56 individuals with mpox, all of whom were proactively sought medical treatment to the hospital displaying symptoms as rash with or without fever. They were all Chinese males, with a mean age of 31.5 years (range 19 to 51). Among the 56 patients, one person has resided in Deyang city, Sichuan Province, and went to Chengdu for medical treatment with the development of rash; three people were previously in other places before coming to work in Chengdu, and they had been in Chengdu within three months before falling ill; one person had been living in the United Kingdom for an extended period and fell ill while visiting Chengdu. The remaining 51 people have been working and living in Chengdu for a long time. Among the 51 local cases, one person had traveled to Thailand within 21 days before

falling ill, while the rest of the patients had not traveled abroad or had contact with foreigners or individuals with rashes within the 21 days prior to their illness. 94.6% (53/56) were MSM, 51 of whom admitted having sex with men within 21 days before the onset of illness (25 took protective measures by using condoms, 26 people did not take protective measures), and the specific sexual behavior and the detailed process are unknown. Medical workers did not conduct a more in-depth epidemiological investigation on the research subjects; it is unknown whether there is any contact relationship between the patients, however one patient proactively informed the doctor that his same-sex partner was being treated in isolation in our hospital due to mpox during the treatment process.

Among the patients, 25.0% (14/56) presented complications with syphilis, as indicated by positive results in both the Treponema pallidum particle agglutination (TPPA) assay and toluidine red unheated serum test (TRUST) assays. Additionally, 41.1% (23/56) of the patients were complicated with HIV-1 infection, there were no HIV-2 infected individuals in our case series.

Out of the 23 mpox patients co-infected with HIV, 21 were already people living with HIV (PLWH) before infected with MPXV and were consistently receiving antiretroviral therapy (ART) for a median duration of 85 months (range: 5–180 months); 2 individuals were newly diagnosed co-infected with HIV after mpox infection. Among the 21 patients who were PLWH currently adherent to ART, there are 9 individuals who are regularly monitored at the Infectious Diseases Department of the Public Health Clinical Center of Chengdu, and underwent annual assessments of high-precision HIV viral loads and peripheral venous blood T lymphocyte subpopulation assays. The results of their most recent tests before mpox infection are summarized in Table 1. The $CD4^+$T cell count of most patients was >400 cells/mL, and the HIV virus was undetectable under the high-precision examination. The HIV-RNA level of patient G was retested on the day of hospitalization for mpox, which showed fewer than 20 copies/mL, indicating the well-controlled HIV status of these 9 patients before they were infected with MPXV.

Clinical Characteristics

Rash Characteristics

All patients exhibited rash development, with 32.1% (18/56) of them not experiencing fever during the disease. Among the 38 patients who did have fever, its onset varied: in 9 cases, fever preceded the appearance of the rash; in 23 cases, it occurred after the rash emerged; and in 6 cases, both fever and rash appeared on the same day, making it difficult to distinguish their order. The median duration from symptom onset to hospitalization for both HIV-infected and non-HIV-infected patients was 7 days.

Regarding the anatomical sites where the rash initially appeared, the highest proportion of patients were the penis or scrotum (39.3%, 22/56), followed by the mons pubis (25.0%, 14/56), and perianal area (14.3%, 8/56). The limbs (71.4%, 40/56) were the most commonly affected area, followed by the genital region (57.1%, 32/56) (Table 2).

Table 1 The Most Recent Results of 9 Patients with HIV Before Mpox Infection

Patients	ART Course (m)	The Interval Between the Testing and Mpox Infection (d)	HIV Viral Load (Copies/mL)	$CD4^+$T Counts (Cells/μL)	$CD8^+$T Counts (Cells/μL)	$CD4^+$T/ $CD8^+$T ratio
A	85	166	TND	677	732	0.93
B	100	6	TND	405	546	0.74
C	60	179	TND	1245	1075	1.16
D	132	82	TND	602	646	0.93
E	48	146	TND	550	768	0.72
F	96	19	TND	263	512	0.51
G	7	108	3.28E+01	519	506	1.03
H	60	19	TND	777	978	0.82
I	48	266	TND	438	491	0.89

Note: TND - HIV viral load was categorised as undetectable.
Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy.

Table 2 Characteristics and Anatomical Location of Lesions in Patients with Mpox Infection

Characteristics	No. (%) of Patients (n=56)
Sites of typical lesions	
Mons pubis	22(39.3)
Penis and/or oschea	32(57.1)
Perianal region and/or buttock	23(41.1)
Head and/or face	26(46.4)
Neck	15(26.8)
Human limbs	40(71.4)
Chest and/or back	28(50.0)
Belly and/or loin	15(26.8)
No. of sites	
1	8(14.3)
2	4(7.1)
3	16(28.6)
4	13(23.2)
≥5	15(26.8)
No. of lesions	
≤5	8(14.3)
6–10	20(35.7)
>10	28(50.0)

Notably, the number of rashes observed in patients in this study series was smaller compared to foreign case reports, in which the scattered distribution and the number of rashes below 10 were more prevalent characteristics (Table 2).

Laboratory Test and Ultrasonic Results

Venous blood samples were collected from all mpox patients immediately after admission and sent to the laboratory for testing, but not all patients have every serum chemistry result due to their financial hardship. Mpox patients exhibited a range of abnormal laboratory test findings, with elevated CRP (69.1%, 38/55), hypocalcemia (50.9%, 28/55), increased CD3+CD8+T counts (47.0%, 24/51), and $CD3+CD4^{+}/CD3+CD8^{+}$ ratio inversion (64.7%, 33/51) (Tables 3 and 4). In terms of liver function and cardiac enzyme, elevated ALT and LDH levels were the primary abnormality manifestations, with incidence rates of 28.3% (15/53) and 31.5% (17/54), respectively (Table 3). There was no report about mpox patients with hypocalcemia, we analyzed the correlation between calcium levels and other laboratory parameters, Pearson contingency coefficient test showed a negative association of calcium levels with CRP levels in the HIV-infected group ($r=-0.540$, $P<0.001$), (Figure 1).

Among mpox patients, abnormal ultrasound findings primarily manifested as superficial lymphadenopathy, with all patients displaying inguinal lymphadenopathy. Spleen enlargement was observed in 32.1% (18/56) of the cases (Table 5).

Complications and Prognosis

Complications associated with mpox include acute tonsillitis, skin infections, anorectitis, urethritis and bacterial pneumonia. Among them, skin infections and anorectitis exhibited the highest incidence rates, both were 32.1% (18/56) (Table 6). Six patients with anorectitis also presented with perianal abscesses, and four patients with acute tonsillitis developed suppurative tonsillitis.

There were no severe cases or fatalities among the patients. Of them, 55 individuals were discharged upon meeting the discharge criteria. Another HIV-infected patient was admitted to the hospital on July 26th presenting with body rash and perianal discomfort over the course of two weeks. Simultaneous to mpox diagnosis, this patient was newly diagnosed with HIV infection. The high-precision HIV viral load was measured to be 1.10E+06 copies/mL, with a CD3+CD4+T count 60 cells/μL. The patient exhibited extensive pustular rashes, with lesions ranging from 2–3cm in diameter distributed across the

Table 3 Comparison of Abnormal Laboratory Findings Between the HIV-Infected Group and the Non-HIV-Infected Group

Abnormal Laboratory Parameter	Most Severe Abnormal Finding	HIV-Infected Group		Non-HIV-Infected Group		x^2	P^a
		No. Evaluated	No. (%) of Patients with Abnormal Laboratory Findings	No. Evaluated	No. (%) of Patients with Abnormal Laboratory Findings		
Elevated WBC count	13.45×10^9/L	22	4(18.2)	33	5(15.2)	–	1.000
Low WBC count	3.47×10^9/L	22	0(0)	33	1(3.0)	–	1.000
Elevated LYM count	6.00×10^9/L	22	4(18.2)	33	9(27.3)	0.604	0.437
Low LYM count	0.65×10^9/L	22	3(13.6)	33	2(6.1)	–	0.379
Elevated NEUP	84.6%	22	5(22.7)	33	1(3.0)	–	0.033
Low PLT count	52×10^9/L	22	2(9.1)	33	1(3.0)	–	0.557
Elevated CRP level	110.03 mg/L	22	16(72.7)	33	22(66.7)	0.227	0.634
Elevated ALT level	100 U/L	22	7(31.8)	31	8(25.8)	0.229	0.632
Elevated AST level	58 U/L	22	1(4.5)	31	4(12.9)	–	0.389
Low ALB level	32.4 g/L	22	2(9.1)	31	0(0)	–	0.168
Elevated LDH level	418 U/L	22	4(18.2)	32	13(40.6)	3.044	0.081
Elevated HBDH level	258 U/L	22	4(18.2)	32	5(15.6)	–	1.000
Elevated CK level	288 U/L	22	0(0)	32	1(3.1)	–	1.000
Elevated CK-MB level	43 U/L	22	5(22.7)	32	1(3.1)	–	0.036
Low Calcium level	2.00 mmol/L	22	14(63.6)	33	14(42.4)	2.377	0.123
Elevated CD4+T count	1272 cells/ul	21	0(0)	30	2(6.7)	–	0.506
Low CD4+T count	60 cells/ul	21	11(52.4)	30	2(6.7)	13.592	<0.001
Elevated CD8+T count	2056 cells/ul	21	11(52.4)	30	13(43.3)	0.406	0.524
Low CD8+T count	196 cells/ul	21	1(4.8)	30	0(0)	–	0.412
CD4+T/CD8+T ratio<1.0	0.07	21	17(80.9)	30	16(53.3)	4.126	0.042

Notes: No x^2 value when using Fisher's exact test. [a]Comparison of no. (%) of patients with abnormal laboratory findings of the HIV-infected group vs the non-HIV-infected group.
Abbreviations: LYM, lymphocytes; NEUP, neutrophil percentage; PLT, platelet; CRP, c-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase isoenzyme.

Table 4 Comparison of Laboratory Findings Between the HIV-Infected Group and the Non-HIV-Infected Group

Laboratory Parameter	Nomal Adult Range	HIV-Infected Group		Non-HIV-Infected Group		Z^a	P^a
		No. Evaluated	Median value (P_{25}, P_{75})	No. Evaluated	Median value (P_{25}, P_{75})		
WBC count, 10^9/L	3.50–9.50	22	6.49(5.83, 8.86)	33	7.02(5.84, 9.09)	−0.412	0.680
LYM count, 10^9/L	1.10–3.20	22	2.26(1.21, 2.93)	33	2.51(1.80, 3.26)	−0.117	0.264
NEUP, %	40–75	22	58.90(46.32, 71.40)	33	56.70(46.80, 63.35)	−1.014	0.311
PLT count, 10^9/L	125–350	22	194.50(158.00, 223.75)	33	216.00(166.50, 268.50)	−0.825	0.410
CRP level, mg/L	0–10	22	16.49(8.67, 41.50)	33	16.73(7.78, 28.50)	−0.722	0.471
ALT level, U/L	0–37	22	27.00(20.50, 39.25)	31	28.00(24.00, 38.00)	−0.163	0.871
AST level, U/L	0–37	22	22.50(18.75, 28.50)	31	23.00(21.00, 27.00)	−0.362	0.718
ALB level, g/L	35–55	22	39.95(36.58, 43.38)	31	41.40(39.90, 43.80)	−1.508	0.132
LDH level, U/L	109–245	22	202.00(184.75, 233.00)	32	238.50(198.25, 267.00)	−1.541	0.123
HBDH level, U/L	72–182	22	129.50(116.75, 151.25)	32	142.00(127.75, 172.75)	−1.418	0.156
CK level, U/L	25–196	22	63.00(42.75, 86.75)	32	75.00(53.25, 106.75)	−1.224	0.221
CK-MB level, U/L	0–24	22	16.00(13.75, 22.75)	32	15.50(11.00, 19.00)	−1.263	0.207
Calcium level, mmol/L	2.20–2.55	22	2.14(2.05, 2.24)	33	2.21(2.14, 2.26)	−1.858	0.063
CD4+T count, cells/ul	414–1123	21	351.00(253.00, 541.00)	30	688.50(574.25, 872.00)	−4.306	<0.001
CD8+T count,cells/ul	238–874	21	881.00(473.00, 1278.50)	30	820.50(525.75, 1357.50)	−0.249	0.804

Notes: Results of laboratory tests were available on the day of admission. [a]Comparison of median values between the HIV-infected group and the non-HIV-infected group.
Abbreviations: LYM, lymphocytes; NEUP, neutrophil percentage; PLT, platelet; CRP, c-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase isoenzyme.

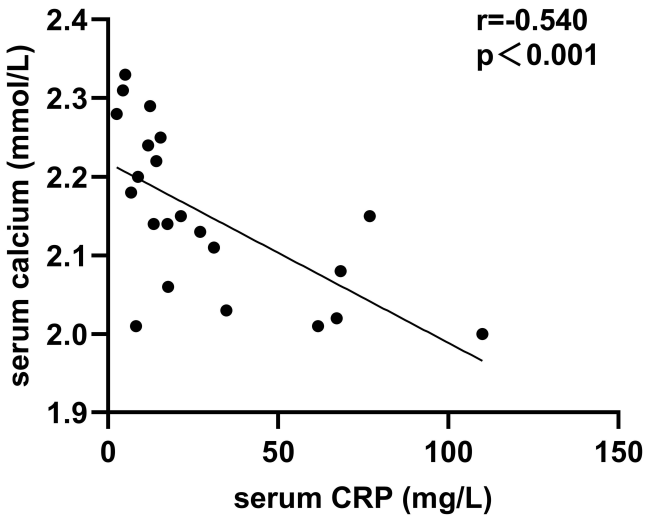

Figure 1 Correlation between serum c-reactive protein (CRP) and calcium in the HIV-infected group.

body, notably concentrated on the forehead and face. During his hospitalization, complications arose, including urinary tract infection, pneumonia, procto-anal inflammation, and oral fungal infection. Due to financial constraints, the patient chose voluntary discharge after 19 days of hospitalization, with facial rash scabbing just commencing (Figure 2).

Differences of Clinical Characteristics Between the HIV-Infected Group and the Non-HIV-Infected Group

Patients with HIV infection were older than those without HIV infection (mean age of 34.6±5.4 years vs.29.4±5.2 years, *P*=0.001) (Table 7).

Table 5 Comparison of Incidence of Abnormal Ultrasound Findings Between the HIV-Infected Group and the Non-HIV-Infected Group (n=56)

Abnormal Ultrasonic Findings	HIV Infected Group (n=23)	Non-HIV-Infected Group (n=33)	x^2	*P*
Splenomegaly	9(39.1)	9(27.3)	0.874	0.350
Enlargement of Superficial lymph nodes				
Neck	22(95.7)	32(97.0)	–	1.000
Axilla	22(95.7)	28(84.8)	–	0.384
Groin	23(100.0)	33(100.0)		

Note: No x^2 value when using *Fisher's exact test.*

Table 6 Comparison of Complication Rate Between the HIV-Infected Group and the Non-HIV-Infected Group (n=56)

Complication	HIV-Infected Group (n=23)	Non-HIV-infected Group (n=33)	x^2	*P*
Acute tonsillitis	4(17.4)	3(9.1)	–	0.429
Skin infection	5(21.7)	13(39.4)	1.937	0.164
Proctitis anus	12(52.2)	6(18.2)	7.180	0.007
Urethritis	3(13.0)	1(3.0)	–	0.295
Pneumonia	5(21.7)	1(3.0)	–	0.071

Note: No x^2 value when using *Fisher's exact test.*

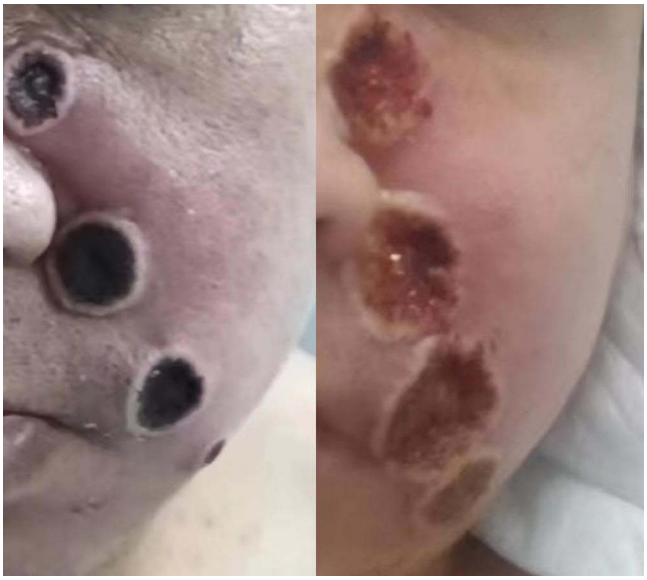

Figure 2 Photos of the facial rash of a mpox patient co-infected with advanced HIV infection, who opted for voluntary discharge from hospital. The left photo was captured upon admission, and the right photo was taken one day before discharge (on the 18th day of hospitalization and the 33rd day of rash grew).

The proportion of HIV-infected patients with >10 rashes was higher than that of non-HIV-infected patients (69.6% vs 36.4%, P=0.014), and the proportion of rashes-affected anatomical sites ≥5 was similar to non-HIV-infected patients (26.1% vs 27.3%, P=0.921) (Table 7).

Compared with non-HIV-infected patients, mpox patients co-infected with HIV demonstrated higher NEUP levels and CK-MB levels, lower CD3+CD4+T counts, and higher incidence of CD3+CD4+T/CD3+CD8+T ratio inversion (all P<0.05) (Tables 3 and 4).

Although there were no statistically significant differences in the incidence rates of splenomegaly, cervical lymphadenopathy, and axillary lymphadenopathy between HIV-infected and non-HIV infected individuals (all P>0.05) (Table 5). The incidence of anorectitis in HIV-infected patients was significantly higher than that in non-HIV infected patients (52.2% vs 18.2%, P<0.05) (Table 6); Furthermore, the incidence of acute tonsillitis, urethritis, and bacterial pneumonia was also higher than that in non-HIV infected patients, while the differences were not statistically significant (all P>0.05) (Table 6).

Table 7 Comparison of Clinical Features Between the HIV-Infected Group and the Non-HIV-Infected Group (n=56)

Variable	No. (%) or Mean ± Standard		x^2 or t Score	P
	HIV-Infected Group (n=23)	Non-HIV-Infected Group (n=33)		
Age (yr.)	34.6±5.4	29.4±5.2	−3.658	0.001
Fever	17(73.9)	21(63.6)	0.656	0.418
Rash				
No. of anatomical sites of typical lesions				
<5	17(73.9)	24(72.7)	0.010	0.921
≥5	6(26.1)	9(27.3)		
No. of rash lesions				
≤10	7(30.4)	21(63.6)	5.976	0.014
>10	16(69.6)	12(36.4)		

Furthermore, it is worth noting that the hospitalization duration and the time from rash growth to rash scab shedding were both longer for HIV-infected patients compared to non-HIV-infected patients (mean time of 10.4±4.3 days vs.8.4 ±2.4 days; 18.7±4.1 days vs.14.2±3.6 days, both $P<0.05$), as shown in Figure 3.

Differences in T Lymphocyte Subset Among the Healthy Donors, the HIV-Infected Group and the Non-HIV-Infected Group in the Early Stage of Mpox Infection

The median of CD3+CD4+T counts in the HIV-infected group was 351 cells/ul (range 60 to 833 cells/ul), the changes in T lymphocyte subset before and after mpox infection in 9 HIV-infected patients who underwent regular evaluations at our hospital and maintained effective HIV control are shown in Figure 4. The median of CD3+CD4+T counts after infection significantly decreased compared to the pre-infection levels (337 cells/ul vs.550 cells/ul, $P=0.033$), accompanied by slightly elevated CD3+CD8+T counts and decreased the ratio of CD3+CD4+T to CD3+CD8+T ($P>0.05$) (Figure 4).

Healthy donors were with an average age of 31.8±5.7 years old, which matched the non-HIV-infected patients ($P=0.147$). Mann–Whitney *U*-test showed that the median of CD3+CD8+T counts in the non-HIV-infected group was significantly higher than that in healthy donors (820.5 cells/ul vs.438.5 cells/ul), and the median of CD3+CD4+T/ CD3 +CD8+T ratio was significantly lower (0.85 vs.1.66). The median of CD3+CD4+T counts was little difference between the two groups (688.5 cells/ul vs.656.5 cells/ul) (Figure 5).

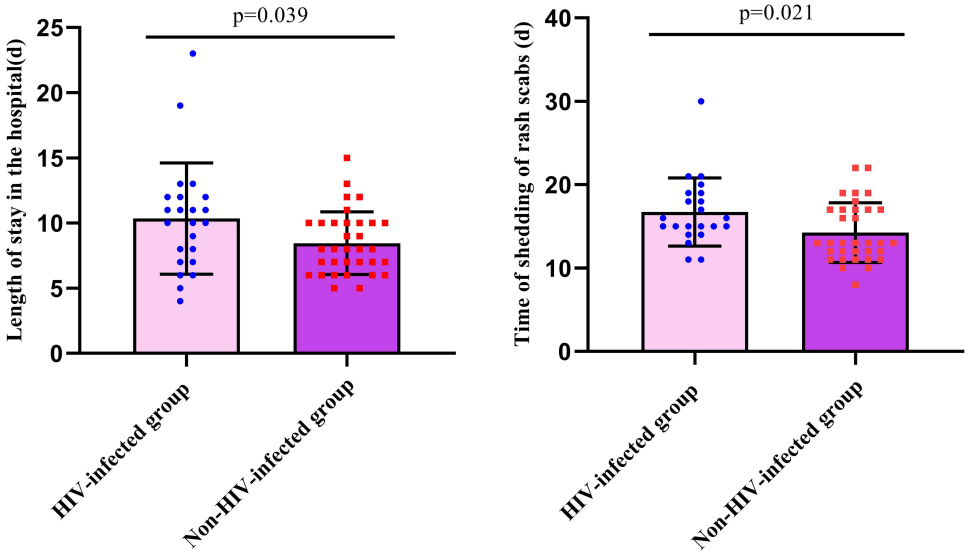

Figure 3 Comparison of the length of stay in hospital and the time of rash scabs shedding between the HIV-infected group and the non-HIV-infected group. Independent-sample *t*-test was used for comparisons between the two groups.

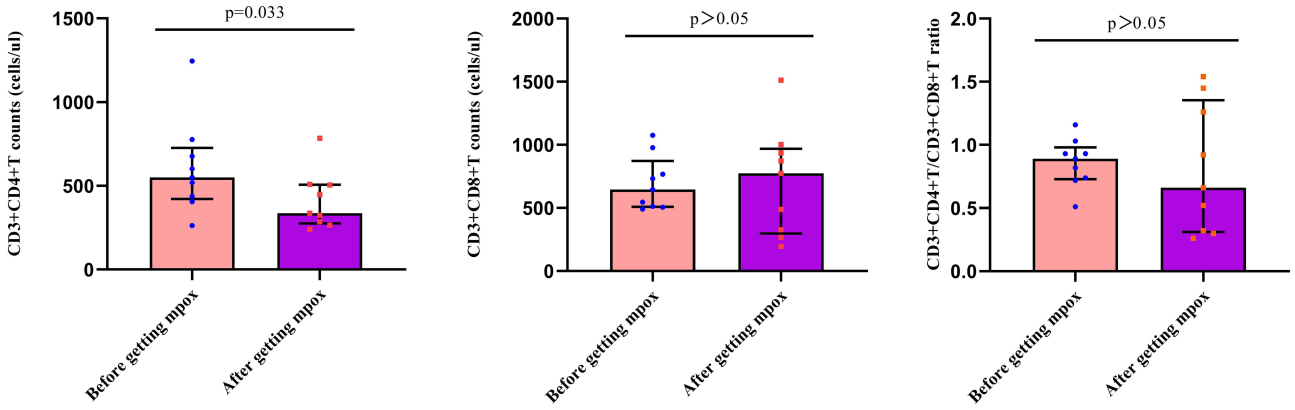

Figure 4 Comparison of T lymphocyte subset of HIV infection patients between before and after getting mpox ($n=9$). Wilcoxon signed-rank test was used for comparisons.

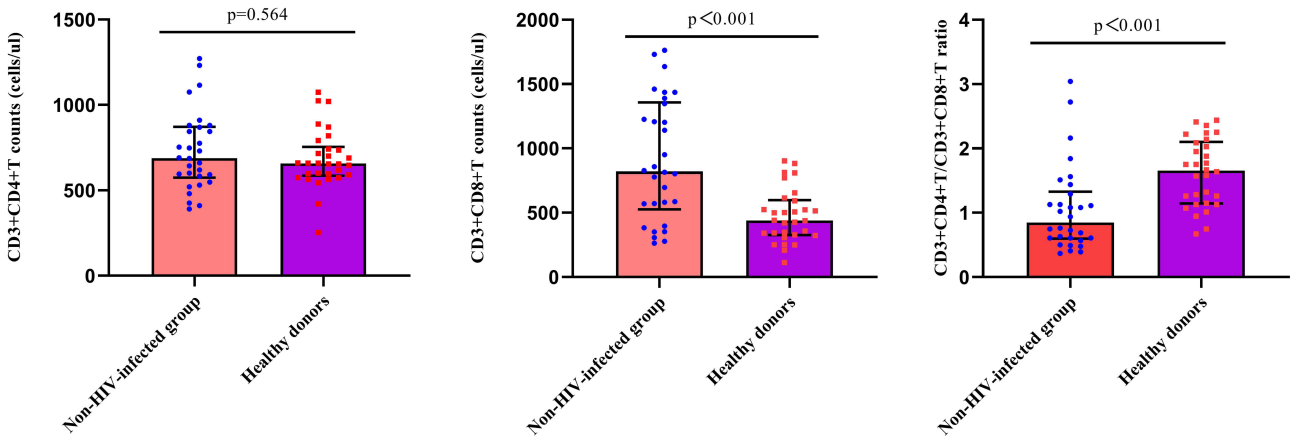

Figure 5 Comparison of T lymphocyte subset between the non-HIV-infected group and healthy donors. Mann–Whitney *U*-test was used for comparisons.

Discussion

There are three clades (clade I, clade IIa, and clade IIb) of MPXV existing in the world, clade I and clade IIa are both a zoonosis.[14] According to the report of WHO, this global outbreak by human transmission of mpox in 2022–2023 is caused by a strain known as clade IIb.[3] Although the genetic basis of clade IIb for differences in virulence and transmission has not been determined, the research result of an animal model in CAST/EiJ mice showed that the replication of clade IIb decreases significantly compared with the other two clades.[14] The evolution of clade IIb may be good for adapting to other species.[14] Chengdu CDC did not genotype the MPXV from mpox patients in our study, epidemiological investigation showed that the first mpox case in Chengdu has no relation with the previously reported mpox cases in Guangzhou or Beijing. There is reasonable to suppose that mpox has been concealed spreading in China for some time according to rapid increase in the number of mpox cases in a short period of time.

In this study, there were 23 cases with MPXV and HIV co-infection, accounting for 41.1% of the total hospitalized mpox patients in this cohort. 91.3% (21/23) of mpox patients co-infected with HIV were PLWH and consistently receiving ART at least 5 months. There were no severe cases or fatalities among the 56 patients, but we found that, mpox patients with HIV infection had higher proportion with ≥10 rashes (69.6% vs 36.4%), longer time from rash growth to rash scab shedding, and the incidence of anorectitis was also higher than that in non-HIV infection patients (all $P<0.05$). It is worth mentioning that the above clinical characteristics were more prominent in the patient with 60 CD4 T counts who had never been antiviral therapy in our study. Whether the clinical manifestations and severity of mpox differ in HIV infection individuals are still controversial. Previous studies have shown that most mpox patients exhibit skin vesicles with diameters less than 2 cm, primarily affecting the face and limbs.[15–18] In a study involving 40 Nigerian mpox patients, nine of whom had HIV infection (with at least seven presenting high HIV viral loads and low CD4 counts), it was observed that acquired immune deficiency syndrome (AIDS) patients with mpox were more likely to develop rashes ≥2 cm, genital ulcers, secondary bacterial skin infections, and experienced a longer duration of the disease.[18] Another study conducted in Nigeria, which included 118 mpox patients, showed a mpox mortality rate of 6% (7/118), and 4 of the deceased individuals were late-stage AIDS patients and had not received antiretroviral treatment.[15] However, in the mpox outbreak of 2022, many studies showed that mpox co-infected with HIV patients seem to have a good prognosis, and the clinical manifestations and severity of mpox were similar in well-controlled HIV-infected individuals and non-HIV infected individuals.[6,19–24] But a recent study reported by Mitjà et al[25] showed that, death was incrementally more likely among people in the lowest CD4 strata (CD4 <100 cells per mm^3 27% vs CD4 100–200 cells per mm^3 4% vs CD4 >200 cells per mm^3 0%) and among those with the highest viral loads (HIV viral load ≥log4 16% vs HIV viral load undetectable 1%) in this mpox pandemic. Therefore, it is reasonable to get a conclusion as mpox co-infected with HIV patients may face a more adverse prognosis, including more persistent rash lesions, increased complications, and even potential fatalities, and this clinical manifestation appears to be particularly pronounced in patients with uncontrolled advanced AIDS. We should have to pay attention to this situation.

Multiple laboratory abnormalities, including elevated C-reactive protein (69.1%), hypocalcemia (50.9%), elevated CD3+CD8+T counts (47.0%) and inverted ratio of CD3+CD4+T to CD3+CD8+T (64.7%) were common in our mpox case series. There are few reports on blood test results in mpox patients. A 2003 study conducted in the United States that included 34 mpox patients[17] showed that abnormal laboratory findings predominantly included elevated transaminase levels (50%), reduced blood urea nitrogen levels (61%), hypoalbuminemia (50%), leukocytosis (45%), and thrombocytopenia (35%). The incidence rates of the aforementioned abnormal laboratory results in our case series were generally lower than those reported by Huhn et al,[17] while the incidence rates of elevated CRP (69.1%) and hypocalcemia (50.9%) exceeded 50%. It is necessary to mention that, only two patients in our study had low albumin levels, calcium level did not need to be corrected for serum albumin. Previous studies have shown that hypocalcemia is a frequent biochemical finding in hospitalized COVID-19 patients, and the prevalence of hypocalcemia, reported ranging from 62.6% to 87.2%.[26–28] Some studies even showed a negative association of calcium levels with CRP levels in COVID-19 patients.[26,29,30] Interestingly, we found that calcium and CRP were negatively correlated in HIV-infected mpox patients. Higher CRP levels usually tend to predict more severe ill in infectious diseases, our research result indicates that it is valuable to examine serum calcium level in mpox patients with HIV/AIDS.

Our data showed that apart from the lower $CD4^+$ T cell count observed in HIV-infected patients, the laboratory parameters between the two groups did not exhibit much difference, and irrespective of HIV co-infection, mpox patients displayed a higher incidence of higher-than-normal CD3+CD8+ T counts in the early stages of infection. To date, scarce information is available about the in-vivo kinetics of T-cell responses in MPXV infection. The study by Agrati et al also showed that the percentage of CD8+T in mpox patients (not including those with HIV infection) was higher than that in healthy controls.[31] In addition, through meticulous categorization of CD4+T and CD8+T cell subtypes, Agrati et al observed rapid activation and expansion of both CD4+ and CD8+T cells shortly after the onset of symptoms in mpox patients, which demonstrated a robust poxvirus-specific Th1 cell response, indicating that regardless of whether HIV infection is combined, all patients show a rapid and potent T-cell response.[31] However, our study showed that T-cell responses maybe different for HIV-infected and non-HIV-infected individuals in the early stages of infection, which is mainly reflected in the significant decrease of CD4+T counts in HIV-infected people, but the change of CD4+T counts in non-HIV-infected people may not be significant.

A systematic review that included 53 studies with a total sample size of 6345 cases[32] showed that HIV infection is the most prevalent comorbidity among mpox patients (40.32%), followed by gonorrhea (10.26%) and syphilis (3.81%). Gonorrhea is a sexually transmitted disease caused by Neisseria gonorrhoeae, primarily characterized by purulent infections in the genitourinary system. Aside from affecting the urethra, male patients can also be affected in the pharynx, rectum, and palpebral conjunctiva. In our case series, there were also patients displayed purulent infections in these aforementioned sites. However, no gonococcal pathogenic examination was conducted, suggesting that the possibility that gonorrhea might have been overlooked in these cases.

Limitation of the Study

This study has certain limitations. Firstly, it is a single-center retrospective cross-sectional study, and its sample size, when compared to similar international studies, is relatively small, potentially limiting the generalizability of the results. Additionally, although the patients were all diagnosed and treated by a team of specialists from the Department of Infectious Diseases, Dermatology, Anorectal Surgery, Urology, Respiratory Medicine, and Traditional Chinese Medicine in our hospital, each specialty was represented by only 1 to 2 doctors, this could introduce observer bias or a lack of experience, potentially resulting in an incomplete assessment of complications. At last, due to the lack of sufficient healthy donors, it is impossible to match on sex between healthy donors and mpox case series in our study.

Conclusion

In summary, we found that mpox co-infected with HIV individuals have longer lasting rash lesions and more complications, which is more evident in patients with uncontrolled advanced AIDS. T-cell responses may be different between HIV-infected and non-HIV-infected individuals in the early stage of mpox infection. It is valuable to examine serum calcium level in mpox patients with HIV/AIDS.

Data Sharing Statement

The datasets used during this study are available from the author (Bennan Zhao, Email: 993896436@qq.com) on reasonable request.

Ethics Approval and Consent to Participate

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Public and Health Clinic Centre of Chengdu (ethics approval number: YJ-K2023-61-01). All patients gave written informed consent.

Acknowledgments

We thank Dr Yi Mao and Lei Bao (Public Health Clinic Center of Chengdu, Emergency department).

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.

Consent for Publication

All of the participants understand that the information will be published without their child's or ward's/their relative's (circle as appropriate) name attached but that full anonymity cannot be guaranteed. All of the participants understand that the text and any pictures published in the article will be freely available on the internet and may be seen by the general public. The pictures and text may also appear on other websites or in print and may be translated into other languages or used for commercial purposes. All of the participants were offered the opportunity to read the manuscript.

Funding

This research was supported by the Sichuan Province Health Commission (17PJ070), Chengdu Municipal Health Commission (2019079) and Sichuan and Chongqing jointly implemented key research and development projects in 2020 (cstc2020jscx-cylhX0001).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Saied AA, Metwally AA, Choudhary OP, Choudhary OP. Monkeypox: an extra burden on global health. *Int J Surg*. 2022;104:106745. doi:10.1016/j.ijsu.2022.106745
2. Abaza H, Agadi K, Anand A, Elsaid M. Clinical manifestations of monkeypox. *Adv Exp Med Biol*. 2023;1410:7–11. doi:10.1007/5584_2022_747
3. World Health Organization. Mpox (monkeypox). Available from: https://www.who.int/news-room/fact-sheets/detail/monkeypox. Accessed November 29, 2023.
4. Saied AA, Dhawan M, Metwally AA, et al. Disease history, pathogenesis, diagnostics, and therapeutics for human monkeypox disease: a comprehensive review. *Vaccines*. 2022;10(12):2091. doi:10.3390/vaccines10122091
5. World Health Organization. 2022-23 Mpox (Monkeypox) outbreak: global trends. Available from: https://worldhealthorg.shinyapps.io/mpx_global. Accessed November 29, 2023.
6. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries - April-June 2022. *N Engl J Med*. 2022;387(8):679–691. doi:10.1056/NEJMoa2207323.
7. Aljabali AA, Obeid MA, Nusair MB, Hmedat A, Tambuwala MM. Monkeypox virus: an emerging epidemic. *Microb Pathog*. 2022;173:Pt A.
8. Rossotti R, Calzavara D, Cernuschi M, et al. Detection of asymptomatic Mpox Carriers among High-Ri Men who have sex with men: a prospective analysis. *Pathogens*. 2023;12(6):798. doi:10.3390/pathogens12060798
9. León-Figueroa DA, Barboza JJ, Garcia-Vasquez EA, et al. Epidemiological situation of monkeypox transmission by possible sexual contact: a systematic review. *Trop Med Infect Dis*. 2022;7(10):267. doi:10.3390/tropicalmed7100267.
10. Mohapatra RK, Mishra S, Kandi V, et al. Emerging monkeypox cases amid the ongoing COVID-19 pandemic in the Indian subcontinent: a probable healthcare challenge for South East Asia. *Front Public Health*. 2022;10:1066425. doi:10.3389/fpubh.2022.1066425

11. Chinese Center for Disease Control and Prevention. Mpox epidemic in China. Available from: https://www.chinacdc.cn/jkzt/crb/zl/szkb_13037/gwjszl_13092. Accessed November 29, 2023.
12. National Health Commission of the People's Republic of China. Guideline for diagnosis and treatment of Monkeypox (2022 Edition), *Chin J Viral Dis*. 2022;12(04):255–256. Chinese. doi:10.16505/j.2095-0136.2022.0040
13. Petersen E, Kantele A, Koopmans M, et al. Human monkeypox: epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin North Am*. 2019;33(4):1027–1043. doi:10.1016/j.idc.2019.03.001.
14. Americo JL, Earl PL, Moss B. Virulence differences of mpox (monkeypox) virus clades I, IIa, and IIb.1 in a small animal model. *Proc Natl Acad Sci USA*. 2023;120(8):e2220415120. doi:10.1073/pnas.2220415120
15. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis*. 2019;19(8):872–879. doi:10.1016/S1473-3099(19)30294-4.
16. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis*. 1987;156(2):293–298. doi:10.1093/infdis/156.2.293
17. Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis*. 2005;41(12):1742–1751. doi:10.1086/498115
18. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human Monkeypox in Nigeria. *Clin Infect Dis*. 2020;71(8):e210–e214. doi:10.1093/cid/ciaa143
19. Perez Duque M, Ribeiro S, Martins JV, et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. *Euro Surveill*. 2022;27(22):2200424. doi:10.2807/1560-7917.ES.2022.27.22.2200424
20. Girometti N, Byrne R, Bracchi M, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis*. 2022;22(9):1321–1328. doi:10.1016/S1473-3099(22)00411-X
21. Mailhe M, Beaumont AL, Thy M, et al. Clinical characteristics of ambulatory and hospitalized patients with monkeypox virus infection: an observational cohort study. *Clin Microbiol Infect*. 2023;29(2):233–239. doi:10.1016/j.cmi.2022.08.012
22. Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet*. 2022;400(10353):661–669. doi:10.1016/S0140-6736(22)01436-2
23. Núñez I, García-Grimshaw M, Ceballos-Liceaga SE, et al. Epidemiological and clinical characteristics of patients with human monkeypox infection in Mexico: a nationwide observational study. *Lancet Reg Health Am*. 2023;17:100392. doi:10.1016/j.lana.2022.100392
24. Silva MST, Coutinho C, Torres TS, et al. Ambulatory and hospitalized patients with suspected and confirmed mpox: an observational cohort study from Brazil. *Lancet Reg Health Am*. 2022;17:100406. doi:10.1016/j.lana.2022.100406
25. Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet*. 2023;401(10380):939–949. doi:10.1016/S0140-6736(23)00273-8
26. Di Filippo L, Formenti AM, Rovere-Querini P, et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine*. 2020;68(3):475–478. doi:10.1007/s12020-020-02383-5
27. Bossoni S, Chiesa L, Giustina A. Severe hypocalcemia in a thyroidectomized woman with Covid-19 infection. *Endocrine*. 2020;68(2):253–254. doi:10.1007/s12020-020-02326-0
28. Di Filippo L, Doga M, Frara S, et al. Hypocalcemia in COVID-19: prevalence, clinical significance and therapeutic implications. *Rev Endocr Metab Disord*. 2022;23(2):299–308. doi:10.1007/s11154-021-09655-z
29. Liu J, Han P, Wu J, Gong J, Tian D. Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. *J Infect Public Health*. 2020;13(9):1224–1228. doi:10.1016/j.jiph.2020.05.029
30. Sun JK, Zhang WH, Zou L, et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. *Aging*. 2020;12(12):11287–11295. doi:10.18632/aging.103526
31. Agrati C, Cossarizza A, Mazzotta V, et al. Immunological signature in human cases of monkeypox infection in 2022 outbreak: an observational study. *Lancet Infect Dis*. 2023;23(3):320–330. doi:10.1016/S1473-3099(22)00662-4.
32. Ortiz-Saavedra B, Montes-Madariaga ES, Cabanillas-Ramirez C, et al. Epidemiologic Situation of HIV and monkeypox coinfection: a systematic review. *Vaccines*. 2023;11(2):246. doi:10.3390/vaccines11020246.