Maronese Carlo Alberto (Orcid ID: 0000-0002-9449-849X)
Ramoni Stefano (Orcid ID: 0000-0002-4473-0721)
Giacalone Serena (Orcid ID: 0000-0003-0464-3356)
gaspari valeria (Orcid ID: 0000-0001-9712-7910)
Rapparini Luca (Orcid ID: 0000-0002-4029-941X)
Robuffo Silvia (Orcid ID: 0000-0001-9361-5423)
Carugno Andrea (Orcid ID: 0000-0002-8231-2205)
Parietti Michele (Orcid ID: 0000-0003-4673-4635)
Ribero Simone (Orcid ID: 0000-0002-0098-1406)
QUAGLINO Pietro (Orcid ID: 0000-0003-4185-9586)
PIRACCINI Bianca Maria (Orcid ID: 0000-0001-6537-9689)
Marzano Angelo Valerio (Orcid ID: 0000-0002-8160-4169)

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Title: Monkeypox: an Italian, multicenter study of 104 cases

Article type: Research letter

Carlo Alberto Maronese, MD[1,2], Stefano Ramoni, MD, PhD[1], Gianluca Avallone, MD[1,2,3], Serena Giacalone, MD[1,2], Eleonora Quattri, MD[1,2], Valeria Gaspari, MD[4], Luca Rapparini, MD[4,5], Silvia Robuffo, MD[4,5], Sergio Delmonte, MD[3], Martina Merli, MD[3], Marco Tutone, MD[6], Giulia Facci, MD[6], Andrea Carugno, MD[7,8], Michele Parietti, MD[7], Alessandra Latini, MD[9], Eugenia Giuliani, MRes[10], Paolo Sena, MD[7], Simone Ribero, MD, PhD[3], Pietro Quaglino, MD[3], Bianca Maria Piraccini, MD, PhD[4,5], Angelo Valerio Marzano, MD[1,2]

1. Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
2. Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy.
3. Dermatology Clinic, Department of Medical Sciences, University of Turin, Turin, Italy.
4. Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
5. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
6. Ce.Mu.S.S., Department of Prevention - ASL Città di Torino, Turin, Italy.
7. Dermatology Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy.
8. Ph.D. Program in Molecular and Translational Medicine (DIMET), University of Milan-Bicocca, Milan, Italy.
9. STI/HIV Unit, San Gallicano Dermatological Institute IRCCS, Rome, Italy.
10. Scientific Direction, San Gallicano Dermatological Institute IRCCS, Rome, Italy.

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Running head: Monkeypox: an Italian multicenter study

Corresponding Author: Prof. Angelo Valerio Marzano. Dermatology Unit - Via Pace, 9, 20122 Milan, Italy. Tel. +39 0255034717; fax: +39 0255035236; e-mail: angelo.marzano@unimi.it

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Dear Editor,

Monkeypox (mpox) has become a sexually transmitted infection (STI) of international concern, spreading disproportionately among men that have sex with men (MSM). More than eighty thousand cases have been reported during the 2022 outbreak, with a subsequent marked decline.[1,2] Factors associated with disease severity, however, are still incompletely understood.[3]

A multicenter, retrospective study was conducted i) to characterize the epidemiological and clinical features of patients with polymerase chain reaction (PCR)-proven mpox seen from June 1st, 2022 to October 31st, 2022 across five dermatology referral centers in Italy and ii) to assess differences in presentation and lesional extent based on factors hypothesized to influence mpox clinical expressivity, including HIV status[4], oropharyngeal swab positivity on PCR[5] and previous anti-smallpox vaccination.[6]

Comparisons of clinical features between groups were performed using chi-square/Fisher's exact tests for categorical variables, as appropriate. Associations were then retested after excluding features influenced by sexual history (such as lesion localization and related symptomatology) and patients with concurrent STIs. P values lower than 0.05, two-sided, were considered statistically significant. Correction for multiple testing was conducted by means of the Benjamini–Hochberg procedure (false discovery rate set at 0.1) (IBM SPSS Statistics, 28.0. Armonk, NY: IBM Corp).

Epidemiologic, clinical and laboratory data of 104 mpox patients were collected (**Table 1**).

Of the latter, 103 (99%) were males and 29 (27.9%) admitted to travelling abroad in the month preceding the diagnosis. Of note, about a fifth of reported cases (of whom only four were unilesional) was initially misdiagnosed, underscoring the challenges in correctly identifying mpox even in specialized STI clinics. History of and concurrent sexually transmitted infections (STI) were documented in 61 (58.7%) and 22 (21.2%) cases, respectively. HIV positivity was detected in 28 (26.9%) cases, with CD4 counts ranging from 225 to 1307 cells/mm^3.

On initial analyses, HIV positivity was associated with lack of fever (p=0.004), maculopapular rash (p=0.006), airway obstruction (p=0.001), rectal secretions (p=0.043) as well as perianal (p=0.031) involvement.

Oropharyngeal swab positivity was associated with fever (p=0.010), lip involvement (p=0.015), dysuria (p=0.018), sore throat (p=0.048), penile oedema (p=0.018) and lack of maculopapular rash (p=0.033).

Previous anti-smallpox vaccination was associated with lack of fever (p=0.004), this being the only association retaining statistical significance after excluding concomitant STIs and correction for multiple testing (**Table 2**).

Clinical and epidemiological features proved consistent with those reported in the main series published during the 2022 outbreak.[3]

Evidence on the role of HIV status in determining mpox clinical expressivity is conflicting. Indeed, well-controlled HIV does not appear to result in a markedly aggravated clinical picture[3,7-10] but may be associated with greater dissemination of lesions.[4] In the present study no clear association emerged between HIV status and lesional extent or disease severity, casting doubt on the influence of HIV status on mpox course. While it is known that clinically meaningful immunosuppression predisposes to poor outcomes[1,8], further research is required to ascertain the impact, if any, of more nuanced immune disturbances.

Interestingly, oropharyngeal swab positivity was associated with fever on initial analyses, possibly reflecting viral dissemination at a systemic level.[9,10] This is in keeping with the current concept of disease progression, whereby lesions initially form at the site of inoculation, may be followed by the development of systemic symptoms and subsequently disseminate.[3,10]

On the other hand, vaccine status appeared to exert some degree of protection against systemic involvement.

The main limitation of this study is related to its retrospective nature and its lack of HIV+ cases with substantial immune compromise.

In conclusion, this study confirms the clinical and epidemiological features of mpox in Italian patients, while supporting a possible protective role of past anti-smallpox vaccination.

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TABLES

Table 1. Demographics, epidemiologic and laboratory features of the 104 monkeypox patients included in the study.

Patients' characteristics		
Sex, n (%)	Male	103 (99)
	Female	1 (1)
Median age at onset, years (IQR)		37 (29.3-43.8)
Ethnicity, n (%)	White	92/104 (88.5)
	Hispanic	5/104 (5.0)
	Asian	2/104 (1.9)
	Black	1/104 (1.0)
	Other	4/104 (3.8)
Sexual orientation, n (%)	has sex with men	94/102 (92.1)
	has sex with women	13/102 (12.7)
	has sex with transexual individuals	2/102 (2.0)
Anti-smallpox vaccination, n (%)		13/99 (13.1)
Travelled in the month preceding the diagnosis, n (%)		29/104 (27.9)[#]
Travel destination, n (%)	Spain	13/104 (12.5)
	Italy	7/104 (6.7)
	France	5/104 (4.8)
	Portugal	1/104 (1.0)
	Greece	1/104 (1.0)
	Switzerland	1/104 (1.0)
	Tunisia	1/104 (1.0)
	The Netherlands	1/104 (1.0)
	Taiwan	1/104 (1.0)
	Brazil	1/104 (1.0)
	Cuba	1/104 (1.0)
HIV+, n (%)		28/104 (26.9)
Last CD4+ T cell count, median (IQR)		752 (551-982)*
HIV- subjects in PrEP, n (%)		18/76 (23.7)
History of STI, n (%)		61/104 (58.7)
	gonorrhoea	35/104 (33.7)
	chlamydia	29/104 (27.9)
	syphilis	41/104 (39.4)
	genital warts	12/104 (11.5)
	herpes	8/104 (7.7)
	LGV	5/104 (4.8)
	MC	2/104 (1.9)
History of STI in the year preceding the diagnosis, n (%)		42/104 (40.4)
	gonorrhoea	21/104 (20.2)
	chlamydia	16/104 (15.4)
	syphilis	28/104 (26.9)
	genital warts	9/104 (8.7)
	herpes	4/104 (3.8)
	LGV	2/104 (1.9)
	MC	2/104 (1.9)
N. of partners in the month preceding the diagnosis, median (IQR)		4 (2-7)
N. of partners in the year preceding the diagnosis, median (IQR)		30 (10-41)
The patient is a sex worker, n (%)		2/80 (2.5)
Sex with a sex worker, n (%)		17/99 (17.2)
Sex during festivals or mass events in the month preceding the diagnosis, n (%)		16/67 (23.9)
Sex on site venue in the month preceding the diagnosis, n (%)		20/66 (30.3)
Chemsex in the month preceding the diagnosis, n (%)		7/65 (10.8)
Use of social networks to find sex partners in the month preceding the diagnosis, n (%)		27/64 (42.2)
Initially misdiagnosed, n (%)		21/104 (20.2)
	as primary or secondary syphilis	11/104 (10.6)
	as herpes genitalis	8/104 (7.7)
	as rectal prolapse	1/104 (1.0)
	as bacterial abscess	1/104 (1.0)
Concomitant STI, n (%)		22/104 (21.2)
	gonorrhoea	10/104 (9.6)
	rectal	5/104 (4.8)
	pharyngeal	9/104 (8.7)
	chlamydia	4/104 (3.8)
	rectal	4/104 (3.8)
	syphilis	7/104 (6.7)
	herpes	5/69 (7.2)
Positivity of oropharyngeal swab on PCR, n (%)		54/84 (64.3)

[#] three patients travelled in Spain and Greece (1), Spain and Italy (2), Switzerland and France (1); * full range: 225-1307; LGV=lymphogranuloma venereum; MC=molluscum contagiosum; PrEP=pre-exposure prophylaxis.

Table 2. Clinical features of reported monkeypox patients, compared by smallpox vaccination and HIV status as well as oropharyngeal swab positivity on PCR.

Clinical features	n (%)	Vaccinated for smallpox		p-value	HIV status		p-value	Oropharyngeal swab on PCR		p-value
		yes (n=13)	no (n=86)		yes (n=28)	no (n=76)		yes (n=54)	no (n=30)	
Fever	55/104 (52.9)	2	50	**0.004**§	8	47	**0.004**	38	12	**0.010**
Headache	23/104 (22.1)	3	20	0.989	6	17	1	10	9	0.280
Sore throat	11/104 (10.6)	1	10	0.674	3	8	0.978	10	1	**0.048**
Myalgias	33/104 (31.7)	5	28	0.755	10	23	0.639	14	7	1
Arthralgias	14/104 (13.5)	0	14	0.116	2	12	0.252	8	5	1
Fatigue	37/104 (35.6)	4	32	0.653	8	29	0.489	16	9	1
Rectal pain	18/104 (17.3)	1	16	0.331	7	11	0.246	11	3	0.222
Rectal secretions	9/104 (8.7)	0	9	0.221	5	4	**0.043**	4	3	0.680
Dysuria	6/104 (5.8)	1	4	0.641	1	5	0.560	0	3	**0.018**
n. of lesions (IQR)	16.8 (5-21.8)*	16 (5.5-35.5)	9 (5-21.25)	0.232#	13 (4-25)	8.5 (5-16)	0.413#	7.5 (5-15)	7 (1-13.5)	0.396#
lesions all in the same phase	39/99 (39.4)	4	35	0.495	8	34	0.178	27	14	0.770
unilesional cases	10/104 (9.6)	1	9	0.757	3	7	0.818	5	5	0.319
more than 10 lesions	52/104 (50.0)	7	42	0.774	18	34	0.121	22	12	1
more than 25 lesions	21/104 (20.2)	5	16	0.142	8	13	0.270	8	3	0.531
generalized**	22/104 (21.1)	1	21	0.176	6	16	1	14	5	0.420
penis, shaft	52/104 (50.0)	7	44	1	13	39	0.825	26	14	1
penis, glans	23/104 (22.1)	3	19	0.937	4	19	0.243	9	7	0.564
pubis	41/104 (39.4)	8	32	0.131	13	28	0.498	16	15	0.098
scrotum	16/104 (15.4)	1	15	0.373	6	10	0.360	9	4	0.686
anus	15/104 (14.4)	1	13	0.474	4	11	0.981	9	4	0.686
rectum	7/104 (6.7)	1	6	0.925	2	5	0.919	3	2	0.837
perianal region	31/104 (29.8)	4	26	0.969	13	18	**0.031**	14	6	0.603
abdomen	20/104 (19.2)	0	20	0.052	2	18	0.058	10	5	1
chest	19/104 (18.3)	4	15	0.255	10	9	0.090	8	6	0.555
dorsum	17/104 (16.3)	3	13	0.467	3	14	0.346	8	5	1
neck	9/104 (8.7)	1	8	0.851	3	6	0.650	3	4	0.217
upper limbs	18/104 (17.3)	0	17	0.078	2	16	0.096	11	4	0.420
palms of hands	12/104 (11.5)	0	11	0.171	3	9	0.873	6	3	0.875
lower limbs	20/104 (19.2)	1	16	0.331	6	14	0.781	13	4	0.240
plants of feet	2/104 (1.9)	0	2	0.579	1	1	0.458	0	2	0.055
head	23/104 (22.1)	3	18	0.860	9	14	0.182	15	4	0.129
lips/perioral region	16/104 (15.4)	2	13	0.980	3	13	0.423	13	1	**0.015**
oral mucosa	12/104 (11.5)	2	9	0.599	3	9	0.873	6	4	0.763
pharyngeal	3/104 (2.9)	0	2	0.579	1	2	0.799	3	0	0.189
conjunctival	1/104 (1.0)	0	1	0.696	0	1	0.542	1	0	0.453
perilesional erythema	68/99 (68.7)	10	55	0.359	18	50	1	32	16	0.650
lesions larger than 1 cm	16/99 (16.2)	2	13	0.980	4	12	0.850	8	8	0.185
lesions larger than 2 cm	6/99 (6.1)	1	5	0.791	2	5	0.560	4	2	0.899
confluent lesions	36/99 (36.4)	5	28	0.755	11	25	0.643	17	9	0.888
abscess-like lesions	2/99 (2.0)	0	2	0.579	1	1	0.458	2	0	0.286
maculopapular rash	5/104 (4.8)	0	5	1	4	1	**0.006**	1	4	0.033
lymphadenopathy	71/104 (68.3)	7	60	0.340	19	52	1	33	20	0.645
cervical	15/104 (14.4)	2	12	0.890	4	11	0.981	11	2	0.096
axillary	3/104 (2.9)	1	2	0.293	1	2	0.799	1	2	0.255
inguinal	61/104 (58.7)	5	53	0.138	16	45	1	25	19	0.173
oedema	21/104 (20.2)	4	17	0.366	5	16	0.791	11	3	0.222
penile oedema	12/104 (11.5)	3	9	0.194	2	10	0.394	9	0	**0.018**
airway obstruction	4/104 (3.8)	0	4	0.427	4	0	**0.001**	1	3	0.093
bacterial superinfection	6/104 (5.8)	0	6	0.326	1	5	0.560	4	2	0.899
neurologic complications	1/104 (1.0)	0	1	0.696	1	0	0.098	0	0	/
hospitalization	7/104 (6.7)	1	6	0.925	3	4	0.352	3	0	0.189
proctitis	4/7	1	3		2	2		1	0	
hyperpyrexia	1/7	0	1		1	0		1	0	
penile oedema with dysuria	1/7	0	1		0	1		0	0	
massive cervical lymphadenopathy leading to airway compression	1/7	0	1		0	1		1	0	

* full range: 0-65; ** defined as the simultaneous involvement of four or more body sites; # Mann-Whitney U test; § statistical significance retained after excluding those that had other concomitant sexually transmitted infections at the time of diagnosis and correcting for multiple comparisons (considering only features not influenced by sexual history, i.e., fever, arthralgia, myalgias, fatigue, headache, lymphadenopathy, unilesional, more than 25 lesions, generalized, lesions larger than 1 cm, perilesional erythema, maculopapular erythema, maculopapular rash, hospitalization). IQR=interquartile range; PCR=polymerase chain reaction.