PREDICTORS OF MPOX DURATION AND SEVERITY IN THE ITALIAN MULTICENTER MPOX ICONA COHORT

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Mpox behaves like a virulent pathogen with a direct association between viral load in the upper respiratory tract and disease severity

BACKGROUND

The mpox 2022 outbreak was characterized by novel clinical presentation and new routes of transmission. We explored potential predictors of mpox severity and duration and described kinetics of inflammatory markers during disease and mpox virus (MPXV) persistence in relevant biological fluids after healing.

METHODS

Italian multicenter study in the network of Icona cohort, including adults with a laboratory-confirmed mpox diagnosis between May 2022 and September 2023. Severe mpox cases were defined as hospitalized or proctitis, pharyngotonsillitis, ocular lesion, or >20 skin lesions; recovery as the resolution of all mucocutaneous lesions. Biological fluids (blood, urine, saliva, oropharyngeal and rectal swabs) were collected during the disease and also after healing.

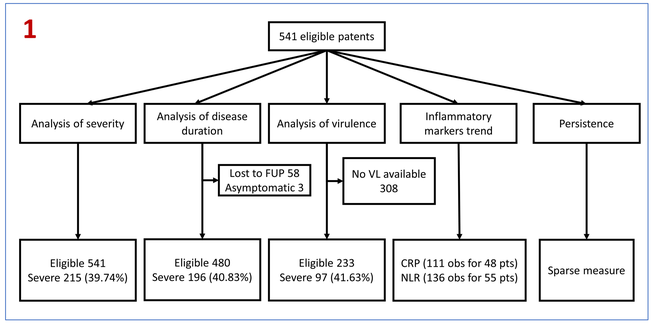
The primary outcome was the identification of predictors of disease severity and its association with viral load in biological fluids.

Secondary outcomes were the identification of disease duration, the description of the kinetics of inflammatory markers during disease and the viral persistence in biological fluids after clinical recovery.

Logistic and linear regression models were used for the assessment of predictors of mpox severity and duration, respectively. Assessment of early MPXV viral load (VL) as a predictor of severity was done by Kruskal Wallis test and mixed-effect logistic regression model including random intercept on clinical center.

For a subgroup of patients hospitalized with severe mpox infection, the temporal kinetics of inflammatory markers [including C Reactive Protein (CPR) and neutrophil-to-lymphocytes ratio (NLR)] were assessed by linear mixed model for a small sample according to Kenward and Roger model. MPXV DNA detection and viral load in samples obtained from convalescents (from clinical recovery to 46 days after) were described. Patients' enrollment and inclusion in the different analyses are reported in Figure 1.

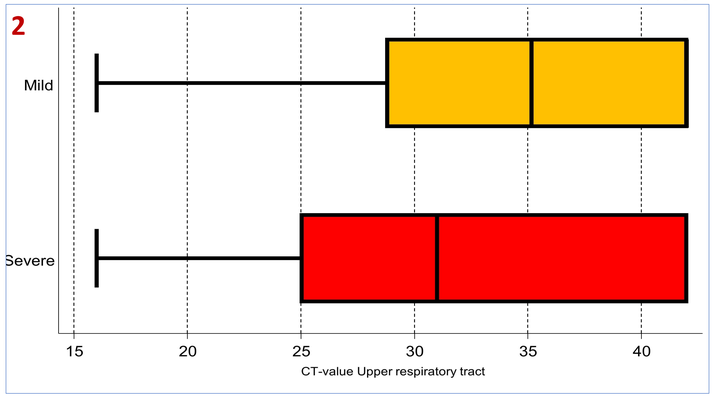
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RESULTS

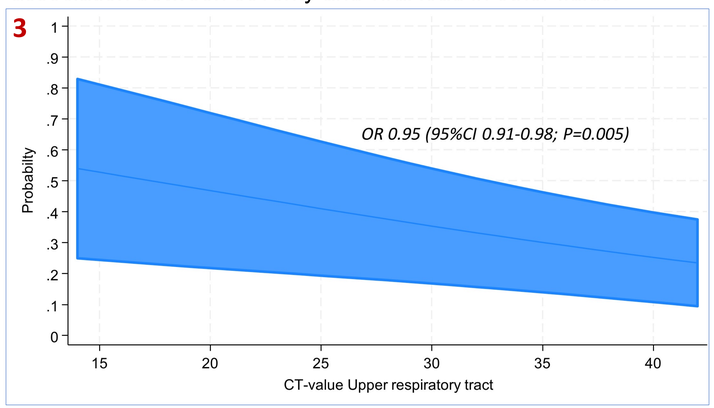
541 were enrolled in the study, including 4 (0.74%) females, with a median age of 38 years (IQR 33-44). Among the 235 PLWH (43.44%), 22 (4.07%) had a CD4 count lower than 350 cells/μL. Severe mpox was reported in 215 patients (39.74%). No patient died. After adjusting for potential confounders, we found that ***severe mpox was more likely among Caucasians*** (OR 1.82; 95%CI 1.14-2.90, p=0.012) and ***patients at onset with fever*** (1.95; 1.27-2.99, p=0.002), ***lymphadenopathy*** (2.30; 95%CI 1.52-3.48, p<0.001), ***sore throat*** (2.14; 1.27-3.59, p=0.004), and ***peri-anal lesions*** (2.91; 1.93-4.37, p<0.001). There was a significant difference (p=0.003) between the median Ct-value in the upper respiratory tract collected in the first week from the onset for patients presenting either with mild (35.15 IQR 28.77-42.01) or severe infection (31.00 IQR 25.00-42.01) (Fig 2).

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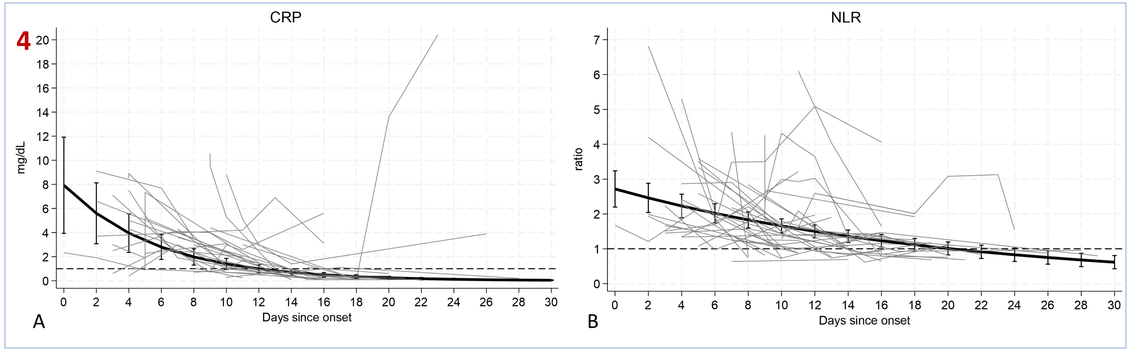


The risk of developing a severe disease decreased by about 5% per Ct (OR 0.95 95% 0.91-0.98; p=0.005) (Fig. C). We found no association between severity and viral load in other fluids.

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The ***mean disease duration was 23.1 days*** (95% CI 21.9-24.3). After adjustment for potential confounders, we found that ***more prolonged disease was experienced by patients presenting with lymphadenopathy*** (+2.47 days; 95%CI 0.11-4.83, p=0.041), ***sore throat*** (+3.12; 0.05-6.20, p=0.046), ***proctitis*** (+4.78; 1.95-7.61, p=0.001) and ***extended rash*** (+3.42; 0.55-6.28, p=0.020). ***PLWH with a CD4 count lower than 350 cells/μL also experienced a more prolonged disease*** (vs PLWoH: +12.51; 6.79-18.22, p<0.001).

Analysis of ***CRP and NLR*** temporal kinetics showed a robust log-linear association with time, ***significantly above the upper standard limit during the first week since symptoms onset and eventually normalizing over the second and third weeks for both markers*** (Fig 4A-4B). Only one subject had a sudden increase in CRP during the third week of mpox infection. This event was associated with a secondary bacterial infection of the skin.

The persistence of MPXV-DNA was assessed in a convenient sample of subjects who returned to clinical centers after complete recovery. Upper respiratory tract specimens were available for 160 patients; 24 (15%) of them were positive (Ct range 26.00 – 40.70; collection time range since resolution 0-27 days). Seminal fluid specimens were available for 60 patients; 14 (23.33%) were positive (31.66 – 40.57; 0-46 days). Specimens of anorectal area (including stools and rectal swabs) in 72 patients; of them, 10 (13.89%) were positive (Ct range 29.93 – 38.31; 0-32 days). Urine specimens in 86 patients; five (5.81%) were positive, all collected on the same day of disease resolution (Ct range 31.00 – 36.13).

CONCLUSIONS

In the case of proctitis, pharyngotonsillitis, lymphadenopathy, and disseminated skin lesions, mpox may last longer, as well as in PLWH with a low CD4 count. The Caucasian race and presentation with fever, pharyngotonsillitis, lymphadenopathy, and peri-anal lesions could predict a severe evolution of the disease. Although mpox virus shows no tendency to produce specific organ damage, it behaves like a virulent pathogen with a direct association between viral load in the upper respiratory tract and disease severity and with viral shedding that may persist after clinical recovery in several anatomical sites, albeit with uncertain persistent infectivity.

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FIGURE LEGEND: 1. Flowchart for patient enrollment and inclusion in the different analyses; **2.** Kruskal Wallis test for comparison of median CT values for MPXV in the upper respiratory tract during the first week of infection; **3.**Mixed logistic regression model to assess the association of disease severity of viral load in upper respiratory tract; **4.** Decay model according to Kenward and Roger mixed effect model. Black solid lines represent estimates and relative 95% CI. Black dashed lines represent normal upper values. Model parameters are reported both as natural log (additive association) and exponential (multiplicative association). The constant value represents the estimate at the time of symptom onset, and the slope represents an estimate of the decay coefficient over time.