Gastrointestinal Manifestations of Monkeypox Infection: A systematic review and meta-analysis

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Abstract

Background: Since early May 2022, outbreaks of Monkeypox (Mpox) cases have emerged and become a global concern. Studies exploring the gastrointestinal (GI) and/or liver manifestations of Mpox are still very limited. This systematic review and meta-analysis is the first to summarize the GI manifestations reported by Mpox patients. **Methods**: We searched for Mpox studies published until October 21, 2022, in MEDLINE, EMBASE, SCOPUS, and organization websites. Mpox studies were observational studies that reported at least one of either GI and/or liver manifestations. Meta-analysis was done to obtain the pooled prevalence of GI manifestations in Mpox patients. The quality of included studies was assessed using the NIH Quality Assessment Tool. **Results**: Overall, 31 studies that reported GI and/or liver manifestations in Mpox patients were included. The five most commonly reported GI manifestations by studies were abdominal pain, anorexia, diarrhea, nausea and/or vomiting, and proctitis. There is a lack of reporting for liver manifestations. The most prevalent GI manifestations in Mpox patients were anorexia (47%; 95%CI 41-53%), followed by nausea and/or vomiting (12%; 95%CI 11-13%), proctitis (11%; 95%CI 11-12%), abdominal pain (9%; 95%CI 8-10%), and diarrhea (5%; 95%CI 4-6%). **Conclusion**: Anorexia was the most frequently reported GI manifestation in Mpox patients, followed by nausea and/or vomiting, proctitis, abdominal pain, and diarrhea. The presentation of proctitis during the ongoing Mpox outbreak highly suggests a potential for Mpox diagnosis.

Introduction

Human Monkeypox, now referred to by the WHO as Mpox, is caused by the Monkeypox Virus (MPV) [1]. The MPV was first isolated in 1958 in a laboratory facility in Denmark, which later became endemic in Central and West Africa [2]. Interestingly, amidst the COVID-19 pandemic, Mpox reemerged as a global concern starting in May 2022, as an increasing number of active cases and mortalities in non-endemic countries were reported in different parts of the world. Mpox produced similar presentations, although considered much milder, to the lethal smallpox virus, predominantly presenting as skin rash and with a mortality rate ranging from 1-10%. Notable complications of Mpox included secondary bacterial infections, respiratory distress, bronchopneumonia, encephalitis, corneal infection with ensuing loss of vision, as well as gastrointestinal involvement, such as vomiting and diarrhea with dehydration [3]. To date, gastrointestinal manifestation in Mpox patients remains poorly understood and characterized, as there is an evident lack of literature. This systematic review aims to summarize available evidence regarding the prevalence of gastrointestinal manifestations in Mpox patients from available reports and studies.

Methods

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines was used as a guide for the writing of this review (**Table S1**). We created a protocol for this systematic review, which was

registered to the International Prospective Register of Systematic Reviews (PROSPERO CRD42022369584).

Search Strategy

Electronic databases such as MEDLINE (Ovid Interface), EMBASE (Ovid Interface), and SCOPUS were searched to obtain peer-reviewed studies indexed from database conception to October 21, 2022. Additional relevant studies published on Monkeypox with data on Gastrointestinal and/or Liver Manifestations were searched through hand-searching in the New England Journal of Medicine (NEJM), the Lancet series, JAMA, BMJ, Gastroenterology, Gut, American Journal of Gastroenterology, and the US Centers for Disease Control and Prevention. Additionally, reference lists of included studies were screened for potentially eligible studies. Only articles published in English were included in this systematic review. The entire search strategy was created with the help of a librarian, including keywords such as "Monkeypox," "Gastrointestinal," and "Liver," and was adjusted based on the specific electronic databases (**Table S2**).

Eligibility Criteria

We included studies reporting any gastrointestinal and/or liver manifestations in Mpox patients with at least 10 cases and reporting at least a minimum of one gastrointestinal and/or liver symptom. Any observational studies (cohort, case-control, cross-sectional, or case series) were included, regardless of prospective or retrospective nature. Preprints were excluded from this review to minimize the risk of incorrect or missed data reporting.

Study Selection and Data Extraction

At least two reviewers performed the study selection, data extraction, and quality assessment processes (IP, NGA, or KT). Initially, studies extracted were compiled and imported to Covidence for further processing. Duplicate studies were excluded, and unique studies were screened for relevancy according to its title and abstracts. Then, studies were reviewed for inclusion based on the full text and any additional supplementary files. For studies that have met the inclusion criteria, the following data were extracted using an extraction form:**(1)** author and its publication date, **(2)** study design,**(3)** location of study, **(4)** baseline characteristics: sample size, age, sex, history of smallpox vaccine, specimen detection, race/ethnicity, HIV status, sexual orientation, any GI and liver comorbidities, and any antiviral treatment used, **(5)** outcome of interest: proportion of GI and/liver manifestations in Mpox patients. In a case of a disagreement between two reviewers, a third reviewer arbitrated the dispute by performing an independent review of the study.

Quality Assessment

The quality of included observational studies (cohort and/or cross-sectional studies; case series) was evaluated using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case Series. Any disagreement between the two reviewers was resolved by an independent review by a third reviewer.

Data Synthesis

Data were summarized narratively and presented in tabular format. A meta-analysis was done with the meta package in the R program (Vienna, Austria). A forest plot was used to visualize the proportion of gastrointestinal manifestations in each study and the overall pooled prevalence estimates. The fixed effect model will be used to derive the pooled prevalence estimates, assuming that all effect estimates in each study estimate the same underlying effect and avoiding giving greater weighting to studies with smaller sample sizes. The heterogeneity was measured using the I^2. Subgroup analyses were done to compare studies based on the study location (African vs. non-African studies) and age groups (Adult only, Mixed, Pediatrics only). Test for subgroup differences was performed, and a p-value for interaction of <0.1 indicates a statistically significant difference between subgroups. The publication bias was qualitatively assessed by visualizing the studies with a funnel plot and quantitatively using an Egger's test. A p-value of less than 0.05 suggests the presence of publication bias.

Results

Study Selection and Study Characteristics

From the three electronic databases, 2985 studies were identified, and after the removal of duplicates, screening based on title and abstract, and full-texts, 16 studies were eligible for inclusion. Additionally, 18 relevant studies were identified through hand-searching from organization websites and citation searching, of which 15 were included in this systematic review. A total of 31 studies with 9189 Mpox patients were included in this systematic review and subsequent meta-analysis (**Figure 1, Table S3**). Of the included studies, two studies were multinational [4, 5], nine studies were from Spain [6-14], followed by seven studies from the United States of America [15-21], four from Congo [22-25], three from France [26-28] and Nigeria [29-31], and one each from Israel [32], Sudan [33], and the United Kingdom [34] (**Table 1**). The studies were comprised of 18 case series [5, 6, 9, 11, 12, 14, 15, 17-19, 21, 23, 25, 28, 29, 31, 32, 34], eight cross-sectional [4, 7, 8, 16, 20, 22, 30, 33], and five cohort studies [10, 13, 24, 26, 27]. Additionally, studies were done on adult patients, pediatrics, and a mix of the two. The most common method of detection for MPV was through PCR, while other methods of detection include Antibody Test/Serology, Electron Microscopy, ELISA, Genomic Sequencing, Immunohistochemistry, and Viral Culture, among others.

Quality Assessment of Included Studies

A total of 13 studies were assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, while 18 were evaluated using the NIH Quality Assessment Tool for Case Series (**Table S4-S5**). Overall, 14 studies were rated good [5, 10-12, 14, 16, 17, 19, 24, 26, 28, 29, 32, 34], ten studies were rated fair [9, 13, 15, 18, 21-23, 25, 27, 31], and the remaining seven were rated as poor [4, 6-8, 20, 30, 33].

Gastrointestinal and Liver Manifestations in Monkeypox Patients

All studies included in this systematic review reported at least one GI manifestation; however, there were only two studies that reported liver manifestations in Mpox patients and so were not included in the meta-analysis [16, 24]. The five most reported GI manifestations were: (1) Nausea and/or Vomiting (17 studies); (2) Proctitis (15 studies); (3) Diarrhea (11 studies); (4) Abdominal Pain (9 studies); (5) Anorexia (3 studies). The other GI and/or liver manifestations reported were summarized in **Table S6** . The overall pooled prevalence for abdominal pain, anorexia, diarrhea, nausea and/or vomiting, and proctitis were 9% (95%CI 8-10%), 47% (95%CI 41-53%), 5% (95%CI 4-6%), 12% (95%CI 11-13%), and 11% (95%CI 11-12%), respectively (**Figure 2**). All manifestations but diarrhea (I^2=27%) were heterogeneous among studies, with I^2 ranging from 78%-93%. The Funnel Plot analysis showed asymmetry suggesting a potential risk for publication bias; however, Egger's test indicated that quantitatively there was no risk of publication bias (p=0.35).

Subgroup analysis was done to explore whether there were differences in the overall prevalence based on study location and age group (**Table S7**). A higher prevalence of abdominal pain was reported in African studies (24%; 95%CI 19-30%) vs. Non-African studies (8%; 95% 7-9%) (p-interaction<0.0001). Additionally, nausea and/or vomiting were more frequently reported in African studies (16%; 95%CI 15-18%) compared to Non-African studies (9%; 95%CI 8-10%) (p-interaction<0.0001). However, no difference in the overall prevalence of diarrhea was found between the two groups (p-interaction=0.10). Additionally, in comparison to the mixed population, studies that included only adult patients reported significantly decreased prevalence of abdominal pain (8%; 95% 7-9% vs. 22%; 95%CI 18-28%), anorexia (10%; 95%CI 2-31% vs. 50%; 95%CI 44-57%), diarrhea (3%; 95%CI 2-5% vs. 6%; 95%CI 5-8%) and nausea and/or vomiting (9%; 95%CI 8-10% vs. 17%; 95%CI 15-19%) (p-interaction<0.10).

Discussion

This systematic review is the first to explore the GI manifestations of Mpox patients. Previous studies, especially those that arose from the 2022 outbreak, mainly described general symptoms, lacking GI manifestations which are less prominent in Mpox cases. Overall, five GI presentations in Mpox patients commonly reported across studies were abdominal pain, anorexia, diarrhea, nausea and/or vomiting, and proctitis. All but one manifestation (diarrhea) was found to be heterogeneous, with an I^2 value above 75%. The excep-

tion is diarrhea, which was consistently low across studies (I^2=27%). We reported that the most frequently occurring GI symptom was anorexia (47%), despite only being reported by three studies. This was followed by nausea and/or vomiting (12%), proctitis (11%), abdominal pain (9%), and diarrhea (5%).

Interestingly, our subgroup analysis showed that non-African studies and studies including only adults generally had lower GI symptoms. This suggests that more GI symptoms were potentially driven by pediatric patients and those infected by the African strain of MPV. A possible explanation for this difference is the genetic clade of the virus that contributed to the more recent outbreak (in 2022). A phylogenetic analysis of the MPV which caused the 2022 outbreak shared a common ancestry with the West Africa clade [35]. Due to genomic mutations and the absence of an immune-modulating factor, the West African clade is less virulent than the other major clade of MPV, such as the Central Africa/Congo Basin clade [36]. Previous outbreaks could have involved the Congo Basin clade of the MPV, thus explaining the higher prevalence of GI symptoms, especially abdominal pain, manifesting as higher virulence. Furthermore, the higher prevalence of GI symptoms in children could be explained by the general tendency of higher virulence of Mpox in children, which was observed in previous outbreaks. The possible biological explanation for this finding rests in the difference in the innate and adaptive immune responses of children compared to adults[37].

The common GI manifestations were generally reported by studies published during different outbreaks throughout the decades since the discovery of Mpox, except for proctitis. Only studies published in 2022 and those reported patients during the 2022 Mpox outbreak reported proctitis as one of the GI symptoms. The emergence of proctitis as a novel presentation of Mpox in this outbreak had been noted by previous case reports such as those by Yakubovsky *et al.* and Gedela*et al.* [32, 38]. A possible explanation suggested that proctitis is caused by the direct inoculation of the MPV to the anorectal mucosa during receptive anal sex [32]. Direct inoculation is an established pathophysiology in proctitis in cases of sexually transmitted infections, including HSV-2, chlamydia, syphilis, and gonorrhea [39]. The sudden increase in the prevalence of proctitis among Mpox cases during the 2022 outbreak suggested that this presentation could be used as a sign precluding the diagnosis of Mpox [40, 41]. The use of proctitis as an entry point to considering Mpox diagnosis became increasingly important since the reporting of cases such as those confirmed Mpox patients who presented without any typical cutaneous lesion but were found to have proctitis as a primary disease manifestation [32].

Despite only being reported by three studies, anorexia, or lack of appetite, was the most frequently reported GI manifestation in Mpox (47%). Pittman et al. reported that all Mpox patients with anorexia presented with the symptom during the first three days after admission, with most patients (98.1%) recovering from it [24]. Abdominal pain, and nausea and/or vomiting, although encountered less frequently, could potentially alter the appetite of Mpox patients. Moreover, oropharyngeal lesions such as ulcers and pharyngitis, commonly encountered in Mpox patients, can lead to dysphagia and reduced oral intake [42]. Anorexia, in conjunction with other gastrointestinal symptoms, could lead to more severe complications, such as dehydration. However, there is a lack of understanding in available literature as to whether anorexia or other GI manifestations of Mpox signify a more severe disease or poorer patient outcomes.

To our knowledge, this meta-analysis is the first to consolidate available data from studies that report GI and/or liver manifestations of Mpox patients. However, this meta-analysis has several limitations. First, some of the studies included in the analysis were found to be of low quality, primarily due to the nature of the study design, such as cross-sectional or retrospective studies. Second, due to the paucity of data available, liver manifestations of Mpox infection were underreported and could not analyze further. This could be due to the lack of Mpox patients who presents with liver manifestations, suggesting that further studies capture any hepatic manifestations encountered by Mpox patients. Lastly, significant heterogeneity was observed in most GI manifestations, possibly due to the different characteristics of subjects at baseline.

Conclusion

In conclusion, we reported that among the GI manifestations presented by Mpox patients, anorexia was the most reported symptom, followed by nausea and/or vomiting, proctitis, abdominal pain, and diarrhea.

Studies have suggested that the presentation of proctitis could warrant a high suspicion of Mpox, especially during the ongoing Mpox outbreak. Further studies should be conducted to determine whether Mpox patients who presented with GI and/or liver manifestations had more severe disease and/or worse prognosis, such as but not limited to a longer length of hospital stay. Additionally, studies should better report any liver manifestations encountered in Mpox patients, which are severely lacking.

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Conflict of Interest

All authors do not have a conflict of interest to report.

Authors' Contributions

DMS : study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript.

EL : study concept and design; acquisition of data; drafting of the manuscript

IP : acquisition of data; drafting of the manuscript

NGA : acquisition of data; drafting of the manuscript

KT : acquisition of data; drafting of the manuscript

MS : study concept and design; acquisition of data; drafting of the manuscript; critical revision of the manuscript

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