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Original Article

Novel drug targets for monkeypox: From viral to host proteins

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ABSTRACT

Background: The ongoing threat of the monkeypox virus (MPXV) underscores the need for new antiviral treatments, yet drug targets and candidate therapies are limited.

Methods: Calculating the centrality, conservation, and immunogenicity of MPXV proteins in the network to identify viral drug targets. Constructing the MIP-human protein interaction network and identifying key human proteins as potential drug targets through network topology analysis.

Results: We constructed a comprehensive protein–protein interaction (PPI) network between MPXV and humans, using data from the P-HIPSTer database. This network included 113 viral proteins and 2 607 MPXV-interacting human proteins (MIPs). We identified three MPXV proteins (OPG054, OPG084, and OPG190) as key targets for antiviral drugs, as well as 95 critical MIPs (most interacting MIPs, MMIPs) within the MPXV–human PPI network. Further analysis revealed 31 MMIPs as potential targets for broad-spectrum antiviral agents, supported by their involvement in other viral interactions. Functional enrichment of MIPs indicated their roles in infection and immune-related pathways.

Conclusions: In total, we identified 112 drugs targeting MPXV proteins and 371 drugs targeting MMIPs, with fostamatinib, trilostane, and raloxifene being able to inhibit both viral and host proteins. This work provides critical insights into MPXV–human interactions and supports the development of targeted antiviral therapies.

1. Introduction

Monkeypox, caused by monkeypox virus (MPXV), is a zoonotic disease with a 3% to 6% fatality rate in humans.[1] MPXV, a member of the *Orthopoxvirus* genus in the *Poxviridae* family, is a double-stranded DNA virus with a 190-kb genome.[2,3] Originally identified in Africa in May 2022, the virus then spread to over 112 countries, with 88,288 cases and 152 deaths reported by July 2023.[4] The first case in China occurred in September 2022.[5] MPXV poses a significant public health threat and the development of effective anti-MPXV drugs is an urgent challenge.[5,6]

The MPXV epidemic is characterized by human infections with symptoms resembling smallpox, including a fever, rash, and swollen lymph nodes.[7] As a zoonotic virus, MPXV is primarily transmitted to humans through direct contact with infected animals, their bodily fluids, or contaminated materials.[8,9] Human-to-human transmission can also occur through respiratory droplets, contact with lesions, or contaminated objects.[8,9] MPXV can be divided into two main clades: the central African clade (Clade I) and the west African clade (Clade II).[10] Clade I is associated with a higher case fatality rate (approximately 10%) and more severe clinical symptoms, while

Abbreviations: MPXV, monkeypox virus; PPIs, protein–protein interactions; MIPs, MPXV-interacting human proteins; MMIPs, most interacting MIPs; MAPs, MPXV infection-associated proteins; MHC, major histocompatibility complex; KEGG, kyoto encyclopedia of genes and genomes; GO, gene ontology.

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Clade II typically has a lower fatality rate (1%–3%).[8,10] The 2022 outbreak primarily involved the west African Clade IIb subclade.[8,10] The west African Clade IIb subclade of MPXV became a major public health concern after the 2022 global outbreak.[11,12] Notable for its ability to spread through sustained human-to-human transmission (unlike traditional zoonotic patterns), the spread of Clade IIb to non-endemic regions led to its classification as a Public Health Emergency of International Concern (PHEIC).[12,13] Reports of sexual transmission and its predominance in adults underline the importance of improved surveillance and targeted interventions to prevent further outbreaks.[12,13]

Antiviral drugs are crucial for preventing and controlling viral infections.[14,15] *In vitro* studies have identified mycophenolic acid and ribavirin as inhibitors of MPXV, whereas tecovirimat and brincidofovir have shown therapeutic effects against monkeypox.[6,16] Tecovirimat, approved in the European Union and the United States for treating orthopoxviruses, represents a key advancement from laboratory research to clinical use.[6] Computational methods have predicted other potential treatments, including fostamatinib, tamoxifen, amentoflavone, and pseudohypericin.[17,18] However, the efficacy of tecovirimat is limited, and many antiviral drugs are not yet commercially available, highlighting the need for further drug development for MPXV.[18]

Antiviral drug research is divided into two categories based on the drug target.[19] One category targets viral proteins, such as those targeting HIV and *Flavivirus* proteins, and the other focuses on developing antiviral drugs targeting host proteins.[20,21] For example, the human protein APOBEC3G, which interacts with HIV proteins, has become an effective therapeutic target.[22] Compared with drugs targeting viral proteins, those targeting host proteins have a broader range of targets because of the much larger number of host proteins than viral proteins.[23] Additionally, because host proteins evolve much slower than viral proteins, they may be less sensitive to mutation.[23] Furthermore, with the rapid development of high-throughput technology, a large number of protein–protein interactions (PPIs) between viruses and hosts have been accumulated.[24] Analyzing the PPIs can help identify host and viral proteins that play significant roles in viral infection, which can serve as potential targets for antiviral drugs.[24,25] For example, Han et al.[25] identified potential antiviral drugs by analyzing the PPI network between enterovirus 71 and humans. Such studies highlight the significance of virus–host PPI network analysis in developing drugs that target host proteins.[25,26]

More potential antiviral drugs and targets are needed to treat monkeypox. The current study established a PPI network between MPXV and humans, and through network analysis, identified MPXV and host proteins as potential drug targets. The MPXV proteins were selected as potential drug targets based on their centrality, conservation, and immunogenicity. Of the MPXV-interacting human proteins (MIPs) identified, 95 critical MIPs (termed the most interacting MIPs, MMIPs) were identified as potential drug targets within the MPXV–human PPI network. A network of interactions between MIPs and other viruses was established, and 31 MMIPs were identified as potential targets for broad-spectrum drugs. Finally, 112 drugs targeting 44 MPXV proteins and 371 drugs targeting 15 MMIPs were identified.

2. Materials and methods

2.1. Protein–protein interactions between MPXV and human proteins

The PPI data between viruses and humans were downloaded from the P-HIPSTer database (http://phipster.org/).[27] The database includes 1 001 viruses that infect humans and approximately 13 000 of their encoded proteins, covering 280 000 potential PPIs. The PPI data between MPXV and humans are detailed in Supplementary Table S1. The interaction data between human proteins were downloaded from the STRING database (https://www.string-db.org/),[28] with PPIs scoring above 700 being retained. A total of 6 206 MPXV genome sequences were downloaded from the NCBI GenBank database (https://www.ncbi.nlm.nih.gov/genbank/).[29] Incomplete and missing genome sequences were removed. The redundant genome sequences were eliminated at a 0.99 level using CD-HIT (https://sites.google.com/view/cd-hit).[30] The 66 complete and non-redundant MPXV genomes were retained (Supplementary Table S2). All MPXV proteins were downloaded from the RefSeq database (https://www.ncbi.nlm.nih.gov/refseq/),[31] and the drug data were obtained from the DrugBank 5.0 database (https://go.drugbank.com/).[32]

2.2. Human protein–protein interaction network

All of the human PPIs were downloaded from the STRING database,[28] and PPIs with a median confidence score greater than 0.7 were retained, while redundant PPIs were removed. A PPI network consisting of 505 968 non-redundant PPIs between 16 814 human proteins was obtained for further analysis. The human proteins in the PPI network between MPXV and humans were defined as MIPs. The 11 791 human proteins in the MIP–human PPI network were defined as MAPs (MPXV infection-associated proteins). Over 403 human proteins, which interact with MIPs, were defined as MMIPs.

2.3. Network topological properties analysis and visualization

To analyze the network topology properties of the PPI network, several key metrics were calculated, including the degree, betweenness centrality, and shortest path length.[33] The degree of a protein node was determined as the number of direct interactions with other proteins in the network, serving as an indicator of the protein's connectivity and potential functional significance.[33] Betweenness centrality was computed to identify proteins that act as crucial bridges within the network, representing nodes that have the highest influence over the flow of information between other nodes.[33] This was calculated as the number of shortest paths between pairs of proteins that pass through a given node, normalized by the total number of shortest paths in the network.[33] To assess the efficiency of communication between proteins, the average shortest path length between all pairs of proteins was calculated. This metric provides insight into the overall cohesiveness of the network, where shorter path lengths indicate more efficient communication between interacting proteins. The igraph package (version 1.2.2)[34] in R was used to analyze the topology of the PPI network. The degree and betweenness of proteins in the PPI network were calculated with the functions of *degree()* and *betweenness()*, respectively. The shortest path length between two proteins in the PPI network was calculated with the function of *shortest.paths()*. The network was visualized using Cytoscape (version 3.7.1).[35] The interaction network was visualized using the "yFiles Organic Layout" style in the "Layout" module of the Cytoscape software.

2.4. Functional enrichment analysis

The Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for the human proteins were conducted with the functions *enrichGO()* and *enrichKEGG()* in the package "clusterProfiler" (version 4.6.2).[36] All of the GO terms and KEGG pathways with adjusted p smaller than 0.01 were considered to be significantly enriched.

2.5. Prediction of candidate drugs targeting MPXV and human proteins

Candidate drugs were predicted with the help of DrugBank (version 5.1.2).[32] The protein sequence of each MPXV protein, and that of each MIP was queried against DrugBank for similar targets with the default parameters. The drugs targeting the best hit were considered to be candidate drugs for the query protein. The properties of drugs, such as the type and group of drug and ATC code, were also obtained from DrugBank.

2.6. Analysis of the conservativity and immunogenicity of MPXV proteins

The conservation of MPXV proteins was calculated by comparing the amino acid differences in the same proteins across different strain genomes. First, the MPXV open reading frames and encoded proteins were identified using GeneMarkS.[37] Second, the MPXV proteins were grouped using OrthoFinder (version 2.2.7)[38] with default parameters. The groups containing only one protein were removed, resulting in 223 protein groups. The mean difference in protein sequences within the same group was defined as the conservation value for that protein. A smaller conservation value indicates a more conserved viral protein. The immunogenicity of the MPXV proteins was indicated by predicting cytotoxic T lymphocyte (CTL) epitopes within protein sequences using the NetCTL (version 1.2) server.[39]

2.7. Statistical analysis

The "np" module in the Python "numpy" package was used to calculate centrality, sequence conservation, and median immunogenicity of the MPXV proteins.[40] Subsequently, R was employed to conduct statistical comparisons of all human protein (All), MIP, and MMIP network topological properties using the Wilcoxon rank sum test. Finally, density distribution plots were visualized using the "ggplot" function in R. All statistical analyses were conducted in R (version 4.0.3).[41]

3. Results

3.1. Protein–protein interaction network between MPXV and humans

The PPI network between MPXV and humans, including 8 950 PPIs, was obtained from the P-HIPSTer database. The network involved 113 MPXV proteins and 2 607 human proteins (Fig. 1A). Specifically, most MPXV proteins were found to interact with human proteins no more than 50 times. We identified 14, 15, 12, 9, 9, 5, 2, 4, 8, 5, and 30 MPXV proteins interacting with 5 or fewer, 5–10, 11–15, 16–20, 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, and over 51 human proteins, respectively (Fig. 1B). Among these, the OPG189 protein showed the most interactions, with 1 027, whereas the OPG117 protein showed the fewest interactions, with 2. Most human proteins, 1 323 in total, were found to interact with only one viral protein. The remaining human proteins interacted with multiple viral proteins as follows: 449 interacted with 2, 188 interacted with 3, 109 interacted with 4, 69 interacted with 5, 81 interacted with 6, 76 interacted with 7, 109 interacted with 8, 90 interacted with 9 and 31 interacted with 10 viral proteins. Interestingly, there

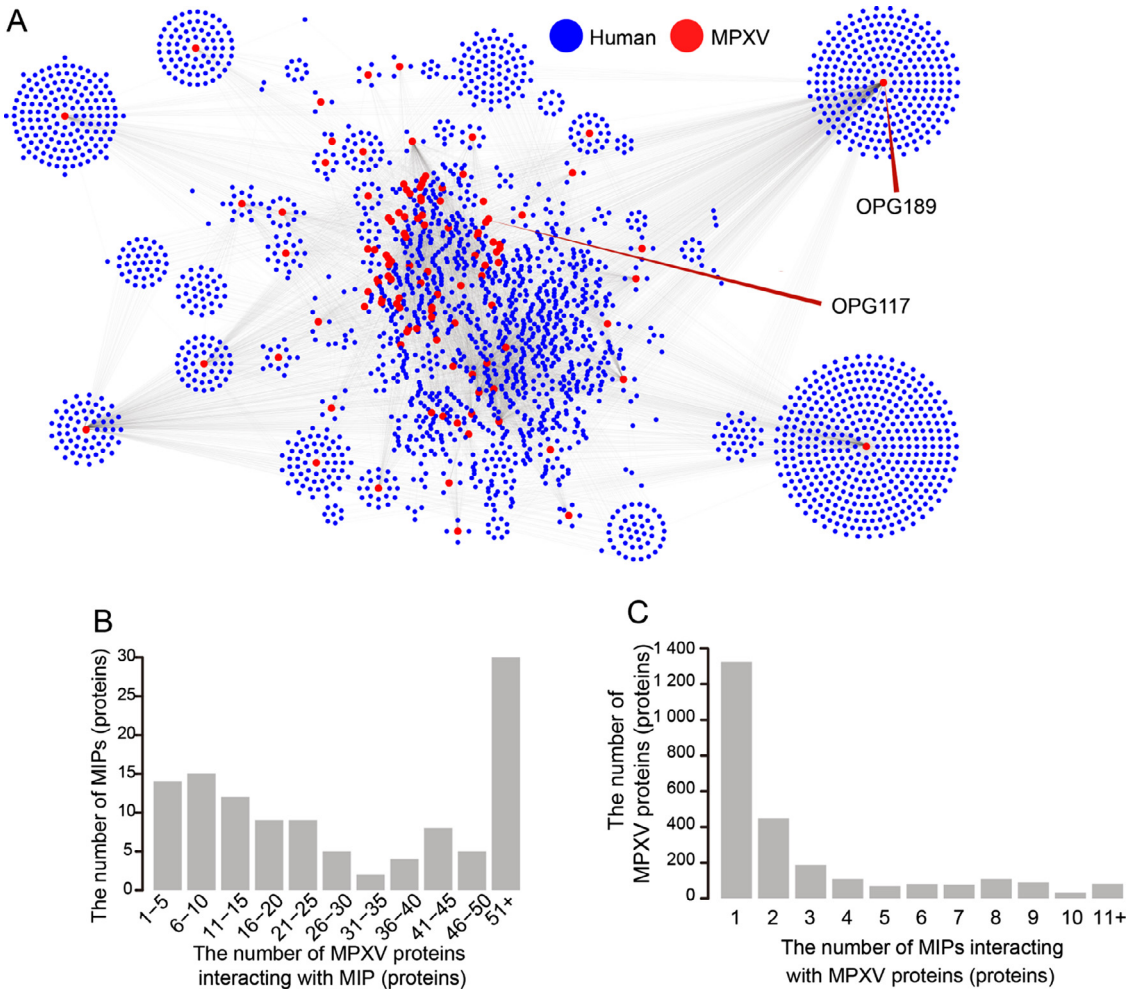

Fig. 1. Overview of PPIs between MPXV and humans. (A) The PPI network between MPXV and human proteins. (B) Number of MPXV-interacting human proteins (MIPs). (C) Number of MPXV proteins interacting with MIPs.
Abbreviation: PPIs, protein–protein interactions; MIPs, MPXV-interacting human proteins.

were 82 human proteins in the network that interacted with more than 10 viral proteins simultaneously (Fig. 1C).

3.2. Screening of MPXV proteins as drug targets

MPXV proteins were evaluated for centrality, sequence conservation, and immunogenicity to identify potential drug targets. Centrality, measured by the number of interactions with human proteins, suggests that proteins interacting with more human proteins are likely more critical during infection. Most viral proteins interacted with 5 to 100 human proteins, with a median of 23 (Fig. 2A). Because of the potential for drug resistance as a result of protein diversity, sequence conservation was also considered. Consequently, conserved sequences within viral proteins were identified as drug targets. The average amino acid difference between pairwise sequences of MPXV proteins was determined as the conservation value (see the Materials and Methods). As shown in Fig. 2B, most viral proteins in the PPI network between MPXV and humans were relatively conserved, with a median conservation value of 1.35. This result indicated a high degree of conservation among the viral proteins, suggesting that the average difference between pairwise sequences is likely to be only 1.35 amino acids.

Previous studies have indicated that viral proteins with high immunogenicity can serve as targets for antiviral drugs. The CTL epitopes of 113 MPXV proteins were predicted using the NetCTL 1.2 server. Most viral proteins possess CTL epitopes. Specifically, the median number of major histocompatibility complex (MHC) ligands across viral proteins was 10. The B21R protein exhibited the highest immunogenicity with 70 MHC ligands, whereas the OPG075 protein displayed the lowest immunogenicity with 0 MHC ligands (Fig. 2C). Finally, the proteins OPG054, OPG084, and OPG190 were screened as potential drug target proteins (abbreviated as vDTP), based on the median values of centrality, conservation, and immunogenicity of the MPXV proteins as thresholds.

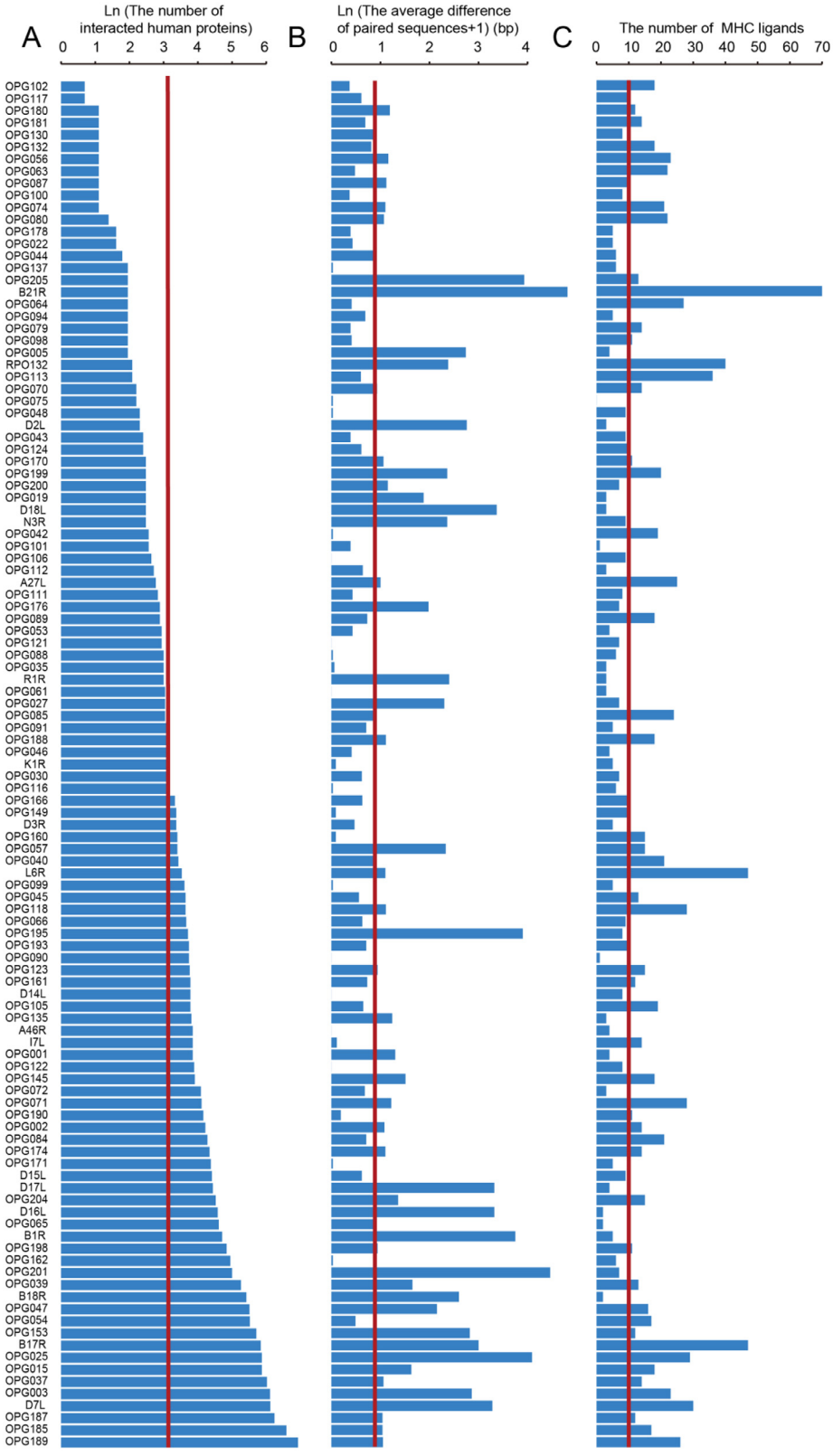

Fig. 2. Characteristics of MPXV proteins in the MPXV–human PPI network. (A) Number of human proteins interacting with MPXV proteins. (B) Conservation of MPXV proteins. The mean difference in protein sequences within the same group was defined as the conservation value for that protein. (C) Number of MHC ligands for MPXV proteins.
Abbreviations: MPXV, monkeypox virus; PPIs, protein–protein interactions; MHC, major histocompatibility complex.

3.3. Screening of human proteins as drug targets

To identify human proteins as drug targets, the role of MIPs in the human PPI network was examined using the STRING database. The network revealed 2 345 MIPs interacting with 11 791 human proteins (MAPs) (Fig. 3A). A sharp drop in MIPs (MMIPs) occurred when the number of interacting MAPs exceeded 403 (red arrow in Fig. 3B), suggesting that these MMIPs could play a critical role in viral infection and may serve as potential drug targets (Fig. S1).

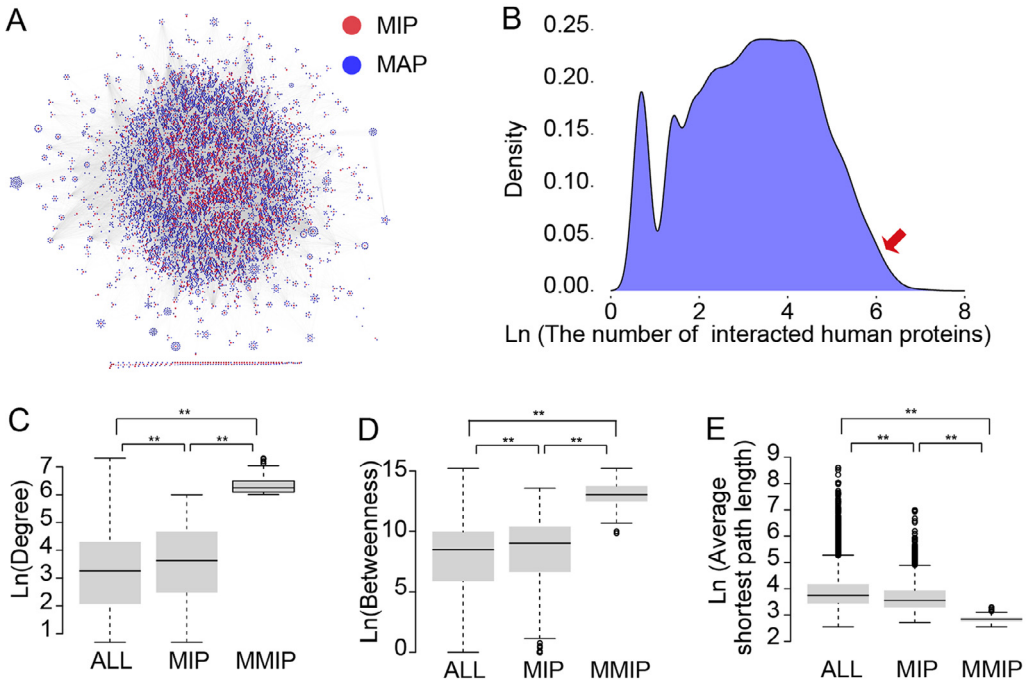

Fig. 3. The PPI network and topological analysis between MIPs and human proteins. (A) The PPI network between MIPs (in red) and MAPs (in blue). (B) Density plot of the number of interactions between MIPs and human proteins. (C) Distribution of connectivity for all human proteins, MIPs, and MMIPs. (D) Distribution of betweenness centrality. (E) Distribution of average shortest path length. $^{**}p < 0.01$.
Abbreviations: PPIs, protein–protein interactions; MIPs, MPXV-interacting human proteins; MMIPs, most interacting MIPs; MAPs, MPXV infection-associated proteins.

To investigate the centrality of MIPs and MMIPs, the degree, betweenness, and average shortest path length of each protein were calculated in the human PPI network. In this network, node degree represents the number of connections, betweenness is the count of shortest paths passing through a node, and the average shortest path length is the average distance between nodes. For all human proteins, the median values for degree, betweenness, and average shortest path length were 26, 4 892.73, and 3.75, respectively. Similarly, for MIPs, these values were 38, 8 194.20, and 3.55, respectively. For MMIPs, the values were 516, 459 942.98, and 2.84, respectively (Fig. 3C–E). Both MIPs and MMIPs exhibited significantly higher node degrees and betweenness, as well as a significantly lower average shortest path length, compared with all human proteins ($p < 0.001$). This suggests that MMIPs play a significant role in viral PPI networks, highlighting them as potential targets for anti-MPXV drug development.

3.4. Screening of human proteins as broad-spectrum drug targets

Broad-spectrum drug targets were identified by screening host proteins for interactions with various viruses within the PPI network. Using data from the P-HIPSTer database, interactions between MIPs and 29 viral families were analyzed (Fig. 4A). Most MIPs (94.86%) interacted with more than two viruses; however, as the number of interacting viruses increased, interactions with MPXV proteins decreased, especially beyond 50 viruses (Fig. 4B). A similar pattern was observed with viral families: as MIPs interacted with more families, MPXV interactions decreased, notably after 10 families (Fig. 4C). MMIPs interacting with over 50 viruses and 10 viral families were identified as potential broad-spectrum drug targets (Supplementary Table S3).

3.5. Functional analysis of MIPs

Building on the role of MIPs in human PPI networks, we analyzed their functions using functional enrichment (Fig. 5). For biological processes, four of the top 10 GO terms involved positive regulation, three were linked to phosphorylation, and two were linked to amino acid modification. For cellular components, MIPs were mainly involved in protein complexes, lamellipodia, and cell-matrix junctions. Seven of the top 10 molecular function terms related to kinase activity, with others relating to guanyl nucleotide binding, GTP binding, and cytokine receptor binding. KEGG pathway analysis highlighted MIP gene enrichment in infection pathways (e.g., “human cytomegalovirus” and “HIV-1”) and immune pathways, including chemokine signaling and natural killer (NK) cell-mediated cytotoxicity.

3.6. Prediction of antiviral drugs against MPXV infection

Potential drugs were predicted using the DrugBank database, targeting both MPXV and human proteins. A

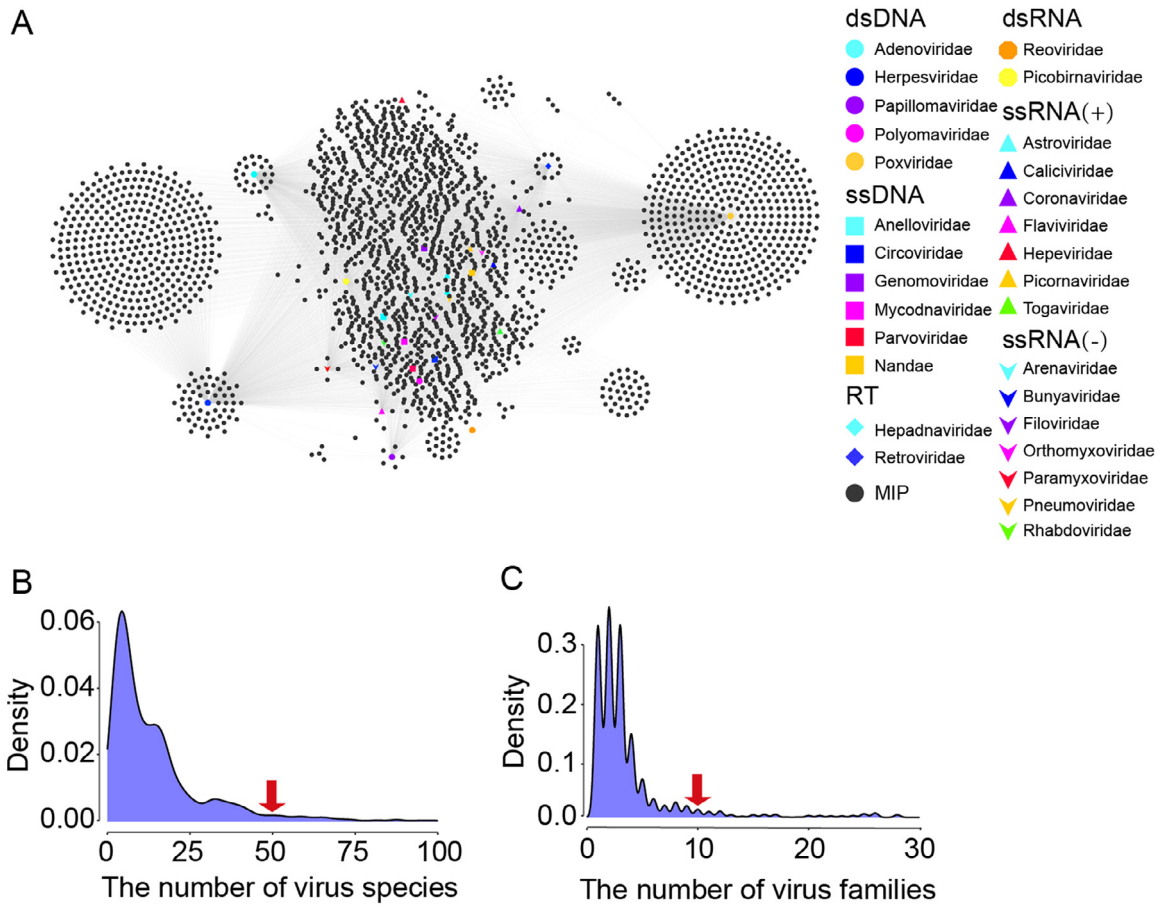

Fig. 4. Overview of the interactions between MIPs and other viruses. (A) The interaction network between MIPs and other viral families. (B) Density distribution plot of the number of interactions between MIPs and other viral species. (C) Density distribution plot of the number of interactions between MIPs and other viral families.
Abbreviations: MIPs, MPXV-interacting human proteins.

total of 112 drugs were identified that target 44 MPXV proteins (pink circles). The majority of these drugs were small molecules (ellipses), while a minority were proteins or peptides (rectangles) (Fig. 6). Interestingly, four drugs were found to target two vDTPs (see the results section of screening of MPXV proteins as drug targets), including OPG084 and OPG190. Specifically, OPG084 was targeted by guanosine triphosphate (DB04137), a small molecule drug in the experimental stage of development. OPG190 was targeted by three drugs: O2-sulfonate glucuronic acid (DB02264), N,O6-disulfonate glucosamine (DB03959), and suramin (DB04786). Unfortunately, none of these three drugs have been approved for marketing.

A total of 371 drugs (ellipses or squares) were predicted to target 15 MMIPs (red circles). Most of these drugs were small molecules (ellipses), while a minority was proteins or peptides (squares). Among the predicted drugs, 98 have already been approved for marketing, 34 are under investigation for potential clinical use, and 239 are in the experimental stage of development (Supplementary Table S4). Some MMIPs, such as the CKD2 and ESR1 proteins, were targeted by multiple drugs. The CKD2 protein, for example, was targeted by a staggering 137 drugs, most of which were small molecule inhibitors still in the experimental stage of development. Additionally, several drugs exhibited the ability to target multiple MMIPs. These included avocatinib (DB03496), PD-168393 (DB07662), and fostamatinib (DB12010), among others.

By analyzing the drug network targeting MMIPs and MPXV proteins in the MPXV–human PPI network, we identified five drugs with the potential to simultaneously target both viral and human proteins. These drugs included already approved drugs fostamatinib (DB12010), trilostane (DB01108), and raloxifene (DB00481), as well as the experimental drugs colforsin (DB02587) and phosphoaminophosphonic acid-adenylate ester (DB04395).

Fostamatinib (DB12010) exhibits the potential to target both viral proteins (e.g., OPG187, OPG189) and host protein kinases (e.g., SRC, EGFR). This drug is a novel oral spleen tyrosine kinase (SYK) inhibitor with a unique mechanism of action for the treatment of chronic immune thrombocytopenia (ITP) in adults who have not responded adequately to previous treatments.[32] As a prodrug, fostamatinib is converted in the gut to its active metabolite R406. R406 competitively inhibits ATP bind-

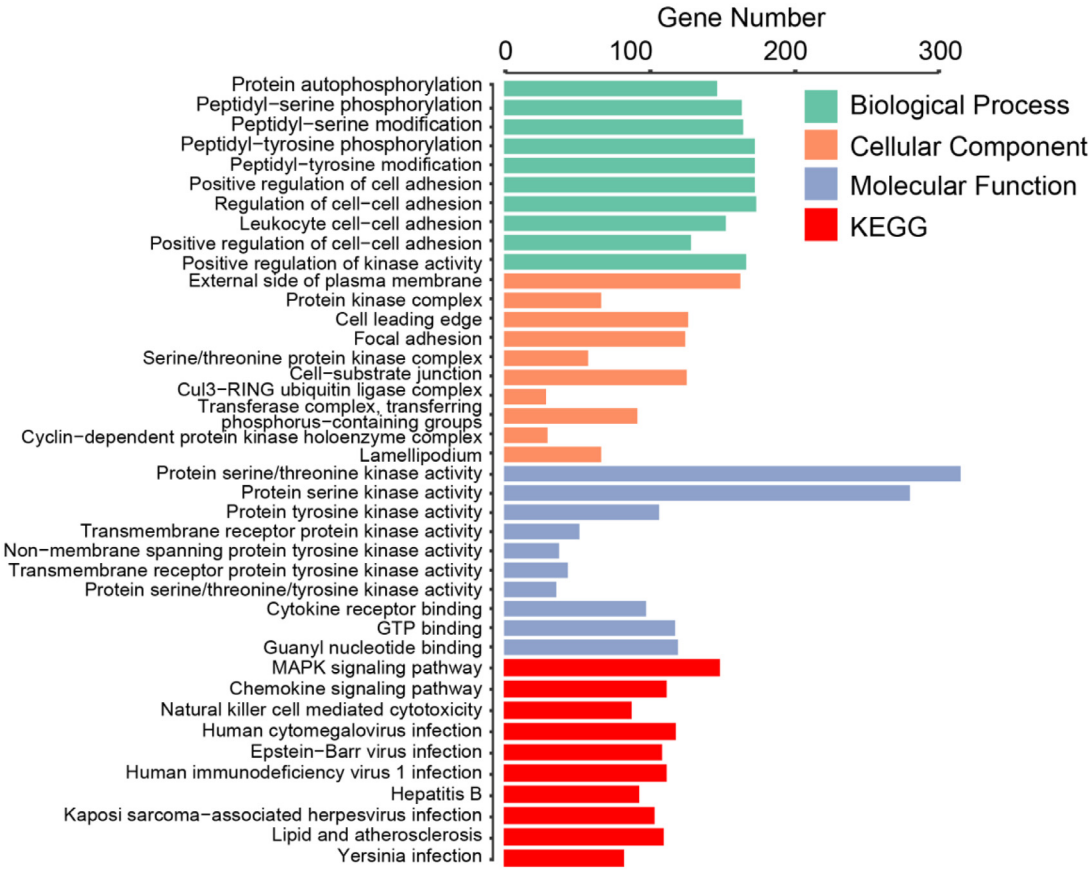

Fig. 5. Functional analysis of MIPs. The top 10 enriched terms in MIPs within the domains of biological processes, cellular components, molecular functions, and KEGG pathways.
Abbreviations: MIPs, MPXV-interacting human proteins; KEGG, Kyoto Encyclopedia of Genes and Genomes.

ing to SYK, with a inhibition constant of 30 nM and an the half maximal inhibitory concentration of 41 nM. By inhibiting SYK, fostamatinib reduces the destruction of platelets mediated by immune cells.[32]

Trilostane (DB01108) can target both the viral protein OPG174 and human estrogen receptor 1 (ESR1), a protein involved in various cellular processes. This drug is a small molecule used to treat Cushing's syndrome, a condition characterized by the overproduction of cortisol by the adrenal glands.[32] It acts as a competitive inhibitor of the enzyme 3-beta-hydroxysteroid dehydrogenase/delta 5,4 ketosteroid isomerase, blocking the synthesis of adrenal steroids and thereby reducing the overproduction of cortisol and other steroids.[32]

Raloxifene (DB00481) targets both the viral protein OPG205 and the human protein ESR1. This drug is a selective estrogen receptor modulator with the chemical formula $C_{28}H_{27}NO_4S$ and a molecular weight of 473.583.[32] It is known for its tissue-specific activity, acting as an estrogen agonist in bones and playing a role in lipid metabolism, while acting as an antagonist in breast and uterine tissues.[32] Raloxifene is used to prevent and treat osteoporosis in postmenopausal women and to reduce the risk of invasive breast cancer in high-risk postmenopausal women. Its mechanism of action involves stimulating osteoblasts (bone-building cells) and inhibiting osteoclasts (bone-resorbing cells), which helps increase bone mineral density and decrease bone resorption.[32]

4. Discussion

Although drugs are available that are highly effective against viruses, no specific treatments for monkeypox currently exist. Research on host-targeted drugs for MPXV is limited. Previous studies have identified mycophenolic acid and ribavirin as potential inhibitors of MPXV infection *in vitro*, but they remain uncommercialized. This study aimed to predict candidate drug targets and anti-MPXV drugs, potentially accelerating the development of effective therapies.

Our findings identified OPG054, OPG084, and OPG190 as key drug targets for MPXV based on their high centrality, sequence conservation, and immunogenicity. The interaction of these proteins with numerous human proteins highlights their importance in infection, while their sequence conservation suggests a lower risk of drug resistance. Their strong immunogenicity also makes them promising antiviral targets.[42] Different antiviral drug re-

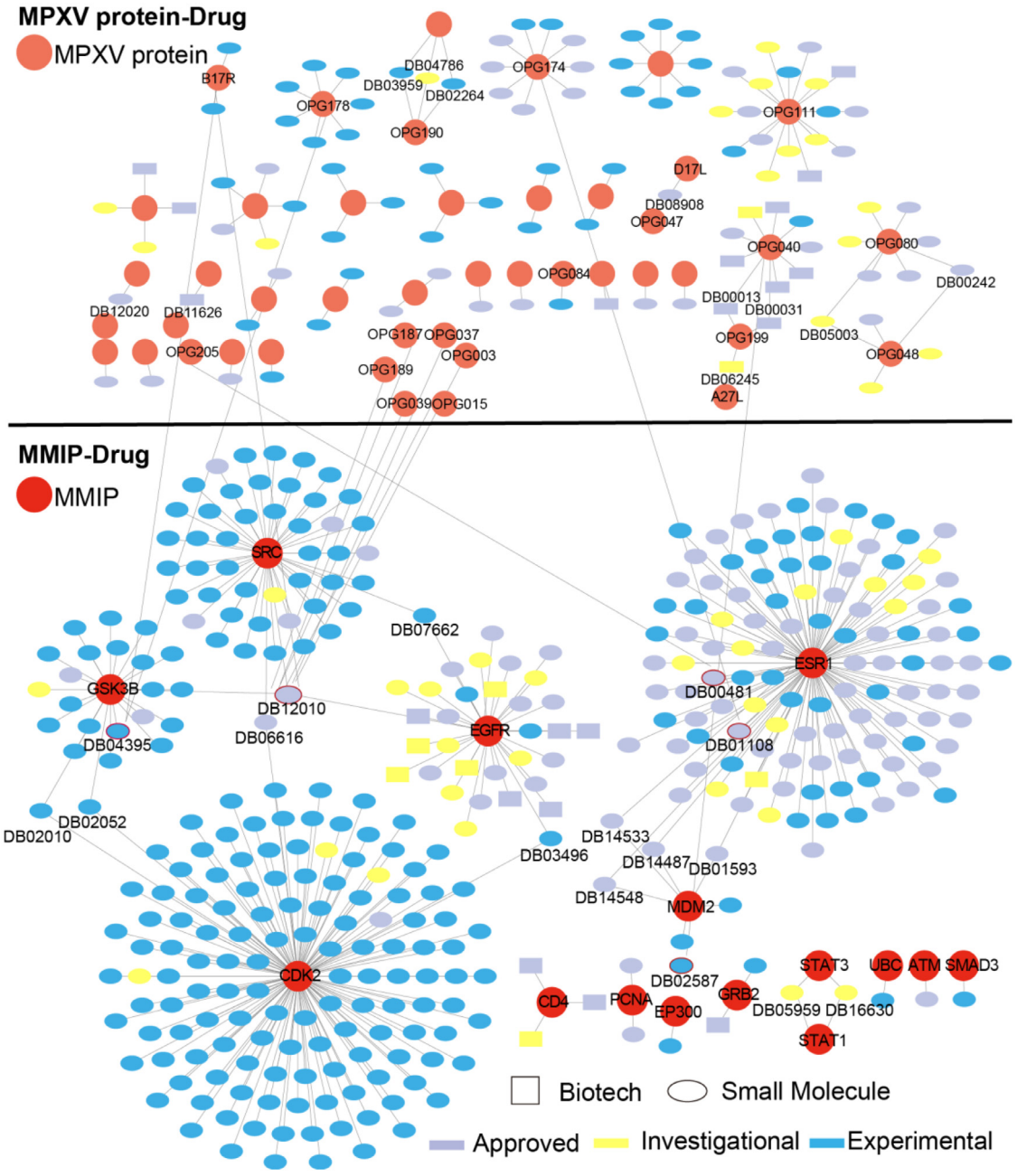

Fig. 6. Predicted drugs targeting MMIPs and MPXV proteins. Interactions above the black line indicate drug–MPXV protein interactions, whereas interactions below the black line indicate drug–MMIP interactions. MPXV proteins and MMIPs are represented as pink and red circles, respectively. Protein or peptide drugs and small molecule drugs are depicted as squares and ellipses, respectively. Drugs in the approved, investigational, and experimental stages are colored in gray, yellow, and light blue, respectively. Drugs that target both MPXV proteins and MMIPs are highlighted with red edges.
Abbreviations: MMIPs, most interacting MIPs; MPXV, monkeypox virus.

search strategies have their own advantages and limitations.[43] This study emphasizes virus-targeting, prioritizing highly conserved and immunogenic viral proteins to reduce resistance and improve efficacy. By integrating centrality, conservation, and immunogenicity, this study offers a comprehensive method for identifying effective drug targets. Compared with the network-based approach for drug repurposing against monkeypox reported by Tang et al.[44], this study expands the scope by not only focusing on virus-targeted proteins but also incorporating host proteins into the analysis.

This study identified MIP and MMIP as pivotal proteins within the human PPI network that interact with MPXV, making them potential drug targets. The significance of these findings lies in the possibility of developing antiviral strategies that target conserved host proteins, which could be effective against multiple viruses, including MPXV. MIP was notably enriched in two im-

mune system pathways: chemokine signaling and natural killer cell-mediated cytotoxicity. The functional roles of these proteins in immune responses and their centrality in the PPI network suggest that they may be key regulators of viral infection. This aligns with previous reports indicating that viruses often target central hubs in the human interactome.[45] By quantifying the centrality of these proteins, the research provides a foundation for developing broad-spectrum antiviral drugs. Future studies should delve into the functional roles of these identified proteins, experimentally validate their targets, and explore drug development strategies.

In this study, 478 potential anti-MPXV drugs were identified by network analysis. Three drugs in particular—fostamatinib (DB12010), trilostane (DB01108), and raloxifene (DB00481)—were predicted to simultaneously inhibit both viral and host proteins within the virus–host network. Among them, fostamatinib was previously predicted to be an anti-MPXV drug.[17, 44] Fostamatinib belongs to the protein kinase family.[32] It is involved in many important biological processes and has a variety of therapeutic effects, such as inhibiting the activity of multiple receptor tyrosine kinases.[32] This drug has also been found to inhibit the formation of neutrophil extracellular traps induced by plasma from COVID-19 patients, making it one of the potential candidate drugs that may reduce the immunopathological process of COVID-19.[46]

This study has two limitations. First, the PPI network between humans and MPXV is incomplete, with only 113 out of over 180 MPXV proteins included. Therefore, further research is required to establish a more complete PPI network between MPXV and humans. Despite the limitations of the current PPI network, some potential anti-MPXV drugs have been successfully predicted on the basis of available data. Second, the predicted drugs must undergo further experimental validation to confirm their efficacy. Some drugs, such as fostamatinib (DB12010), trilostane (DB01108), and raloxifene (DB00481), have been approved for marketing and are important for disrupting the virus–host network. These drugs can be prioritized for validation.

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CRediT authorship contribution statement

Zhaozhong Zhu: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Qin Sun:** Data curation. **Yunhai Xu:** Methodology, Investigation, Data curation. **Youya Niu:** Resources, Project administration, Funding acquisition. **Fei Yang:** Writing – review & editing, Writing – original draft. **Shuidong Feng:** Writing – review & editing, Supervision.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

All data used in the study are available in the P-HIPSTer database, which is accessible at http://phipster.org/.

Ethics statement

An ethical statement is not required as there were no human subjects involved in this study.

Informed consent

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.imj.2025.100165.

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