Original Article

Preventability and manageability of adverse drug reactions in COVID-19 with mucormycosis: An observational study

Sajal Dhingra[1,2#], Raj Hanjong[1,2#], Khushboo Bisht[2], Puneet Dhamija[2], Minakshi Dhar[3]

[1]Veer Madho Singh Bhandari, Uttarakhand Technical University, Dehradun, Uttarakhand, India, [2]Department of Pharmacology, Regional Adverse Drug Reaction Monitoring Center, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India, [3]Department of Internal Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
[#]Sajal Dhingra and Raj Hanjong have contributed equally to this work.

Abstract

Background: In the intricate landscape of healthcare amid the COVID-19 pandemic, the emergence of mucormycosis as a severe complication posed a significant challenge to primary healthcare. This study delved into the complexities of adverse drug reactions (ADRs) in COVID-19 patients with mucormycosis undergoing treatment with conventional amphotericin B. **Methods:** Ethically approved and meticulously conducted, the study scrutinized 154 ADRs in depth, shedding light on their classification, outcomes, and interventions in COVID patients with mucormycosis. A descriptive analysis was carried out to report the findings of this study. **Results:** The findings revealed that a substantial proportion (85.6%) of these ADRs were manageable, emphasizing the need for vigilant monitoring and timely interventions. Notably, gender disparities surfaced, indicating potential gender-specific responses to amphotericin B. Causality assessments based on the WHO-UMC scale classified the majority of ADRs as certain, providing a robust foundation for understanding the intricate relationships between amphotericin B and the observed adverse events. **Conclusion:** This research not only categorizes ADRs as preventable and manageable but also offers practical insights into their nature and the diverse strategies employed for their management. The study's outcomes underline the importance of personalized healthcare approaches that can be adopted by primary care physicians for effective patient care.

Keywords: Adverse drug reactions, COVID-19, mucormycosis, preventability

Introduction

The co-occurrence of mucormycosis in COVID-19 patients has been a topic of significant concern in the medical community.[1-3] Previous literature highlighted the challenges associated with adverse drug reactions (ADRs) in this patient population.[4] Understanding the preventable and manageable aspects of these ADRs is paramount for primary healthcare providers, given the intricate nature of treating both severe viral infections and aggressive fungal diseases simultaneously.[5] Prior research underscored the need to study monitoring and intervention strategies for mitigating amphotericin B-related adverse events. In addition, gender-specific responses and susceptibilities to antifungal treatments have been a subject of interest, hinting at potential differences in ADR profiles between male and female patients.[6] These studies, while insightful, have often highlighted the complexity of managing multiple medical

Address for correspondence: Dr. Khushboo Bisht, Department of Clinical Pharmacology, All India Institute of Medical Sciences, Rishikesh - 249 203, Uttarakhand, India.
E-mail: khushboobisht12@gmail.com

Received: 15-10-2023 **Revised:** 17-02-2024
Accepted: 08-03-2024 **Published:** 11-09-2024

Access this article online
Quick Response Code:
Website: http://journals.lww.com/JFMPC
DOI: 10.4103/jfmpc.jfmpc_1691_23

How to cite this article: Dhingra S, Hanjong R, Bisht K, Dhamija P, Dhar M. Preventability and manageability of adverse drug reactions in COVID-19 with mucormycosis: An observational study. J Family Med Prim Care 2024;13:3672-8.

conditions concurrently, urging further exploration into tailored treatment protocols and interventions. As the healthcare system grapples with the optimization of patient care amid challenges, this study provides nuanced insights into the preventable and manageable ADRs associated with amphotericin B in COVID-19 patients with mucormycosis.[7]

The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale is a widely recognized and standardized tool used for the assessment of causality in ADRs.[8] This scale is developed by the WHO Collaborating Center for International Drug Monitoring in Uppsala, Sweden, and provides a systematic approach to evaluating the relationship between a drug and an adverse event reported by a patient. The WHO-UMC scale classifies ADRs into five categories based on the likelihood of the drug being the cause of the adverse event as certain, probable, possible, unlikely, and unclassifiable. The WHO-UMC scale is a subjective assessment that can help primary care physicians confirm the causal relationship between drugs and adverse events in a standardized and reliable manner. Unlike the WHO-UMC scale, the Naranjo scale is an objective scale used to evaluate drug safety. By employing these scales, primary physicians can assess causality and contribute valuable data to global pharmacovigilance databases, ultimately enhancing patient safety and the overall understanding of drug-related adverse events.

Schumock and Thornton criteria, also known as the Preventability Assessment Drug-Related Problem Scale, and Hallas criteria are systematic tools used to assess the preventability of ADRs.[9,10] These criteria provide a structured approach to evaluate whether an ADR could have been avoided by modifying drug therapy, monitoring, or other interventions. The scale categorizes ADRs into different levels of preventability based on specific criteria, including Definitely Preventable – ADR could have been avoided if appropriate measures were taken; Possibly Preventable – There is a chance that the ADR could have been avoided; and Not Preventable – ADR could not have been avoided given the patient's circumstances and medical conditions.[11] The criteria for determining preventability include assessing if the ADR resulted from medication errors, non-compliance, or drug interactions that could have been foreseen and prevented. This study aimed to identify preventable and manageable adverse drug events during administration of amphotericin B in COVID mucormycosis. The findings of this study can be used by primary care physicians to monitor and manage ADRs while managing COVID-19 mucormycosis.

Materials and Methods

Study conduct

This study was approved by the ethics committee (AIIMS/IEC/21/559), following which participants were recruited by convenience sampling. One person was dedicated for 24 hours to collect reports of any ongoing ADRs due to amphotericin B. Another dedicated person in the mucor ward collected data from the medication charts of patients after obtaining informed consent. These data were used for analysis of concurrent drug interactions.

Study population

All the patients diagnosed and admitted in the inpatient department for mucormycosis following COVID-19 infection were enrolled in this study after obtaining written informed consent. Pattern of ADRs were assessed and a search for drug-drug interactions was performed for individual patient enrolled in the study [Figure S1]. All the DDIs were identified during the study period.

Study objectives

The primary objective of this study was to analyze preventable and manageable adverse drug events in COVID-19 patients with mucormycosis on amphotericin B. Secondary objectives were to assess the impact of corrective measures for adverse drug reactions; to identify drug interactions; and to record, monitor and report any adverse drug event during the study period.

Study tools

We used the WHO-UMC scale and the Naranjo scale for causality assessment, while the Schumock and Thornton scale was used to assess the preventability of drug-related problems.[11,12] This scale categorized ADRs into definitely preventable, possibly preventable, and not preventable. The Hartwig and Seigel Severity Assessment scale was used to identify severity of ADRs.[13] They were classified as mild, moderate, severe, life-threatening, and fatal.

Drug-drug interactions search strategy

Data collected from medication charts were assessed by the physician for any unreported adverse event(s). Drug interactions were identified using a Medscape tool – Drug Interaction Checker and Lexicomp software.

Statistical analysis

Study data were analyzed using descriptive statistics (frequency and numbers). Data are reported as mean ± SD or median with interquartile range depending on the distribution of data. Values are specified where indicated.

Results

Demographic profile

During the second wave of COVID-19, a total of 103 cases who developed mucormycosis were admitted at the study center. All of them received any one formulation of amphotericin B: conventional or liposomal. Although liposomal formulation has substantial advantages over conventional formulation, we observed an increased utilization of conventional formulation during the COVID-19 pandemic [Figure 1]. Only five females received liposomal formulation. On average, 6.6 ± 6.6 interactions were reported per medication chart, and a medication chart consisted of at least 13.1 ± 3.8 medications on average. Among concomitant

drugs, injectables such as pantoprazole, paracetamol, ondansetron, Lantus insulin, amoxicillin-clavulanate, ceftriaxone, metronidazole, and diclofenac were commonly used. Syrup potassium chloride was commonly used in mucormycosis patients who suffered hypokalemia while on treatment with amphotericin B.

Reported adverse drug reactions

A total of 35 preventable and 119 manageable ADRs were recorded in post-COVID mucormycosis patients. Of all the reported preventable ADRs, 62.9% were of chills, 31.4% were of fever with chills, and 5.7% were cases of hypokalemia. Chills were the most preventable ADR. Manageable ADRs (119) were more as compared to preventable ADRs. Of manageable ADRs, there were 55.5% hypokalemia, 27.7% hypocalcemia, 7.6% increased serum creatinine, 5% hypocalcemia, 2.5% chills, and 0.8% fever with chills and diarrhea [Table 1].

Of the patients enrolled in this study, 50 patients had a history of diabetes mellitus and 20 patients suffered from hypertension.

A total of recovered ADRs (N = 91), recovering (N = 58), and not recovered ADRs (N = 5) out of 154 adverse drug events were observed in patients on amphotericin B for treatment of post-COVID mucormycosis [Figure 2].

Table 1: Frequency of types of preventable and manageable adverse drug reactions encountered during the study

Adverse drug reaction	Count of Preventable ADRs	Count of Manageable ADRs
Increased serum Creatinine	0	9
Hypokalemia	2	66
Chills	22	3
Hypocalcemia	0	33
Hypomagnesemia	0	6
Fever with chills	11	1
Diarrhea	0	1
Total	35	119

Manageable and preventable adverse drug reactions

A total of 154 ADRs were observed in patients admitted to the mucor ward for treatment of mucormycosis following COVID-19 with conventional amphotericin B during June–October 2021. Out of 154 observed adverse drug events, 75 required intervention following emergent adverse reactions [Table 2]. These adverse drug events were categorized into preventable and manageable. After an analysis of the intervention for adverse events, observations were made and they were classified as in Figure 1 (b). Out of all the observed adverse events, 85.6% were manageable and 29.4% were preventable adverse drug events. Patients were distributed based on their gender. A total of 75 patients were on amphotericin B for treatment of post-COVID mucormycosis, out of which 27 were females and 48 were males [Figure 1 (a)].

Causality assessment by WHO-UMC classification and Naranjo Scale

We identified the possible cause of ADRs by using the WHO-UMC scale and assessed the severity of ADRs. A total of 154 ADRs were reported in patients, out of which a total number of 147 ADRs were identified as certain and seven as probable ADRs according to the WHO UMC scale. On the evaluation of causality by the Naranjo scale, it was observed that 79% (122) ADRs were probably related while 21% (32 ADRs) were possibly related to their respective drugs.

Severity of adverse drug reactions by Hartwig scale

The severity of the reactions was assessed using the Hartwig severity assessment scale, which classified ADRs majorly into mild, moderate, and severe. We observed 76 mild ADRs, followed by 43 severe ADRs and 35 moderate ADRs. There were no reported deaths due to amphotericin B-related ADRs.

Drug interactions by Medscape

Medscape – Drug Interaction Checker (DIC) tool and Lexicomp software were used for the identification of drug interactions. All drugs in the medication charts of these 103 patients were entered into respective software for analysis. Medscape's DIC categorizes

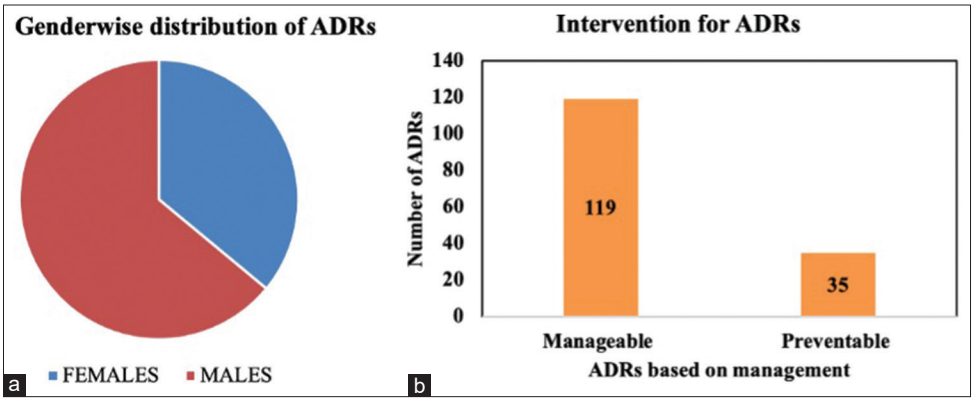

Figure 1: (a) Sex-wise distribution of ADRs; (b) ADRs classified based on intervention: A total of manageable adverse drug reactions (N = 119) and preventable adverse drug reactions (N = 35) out of 154 adverse drug events were observed in patients on amphotericin B for treatment of post-COVID mucormycosis

Table 2: Management of adverse drug reactions (ADRs)

Interventions used for managing ADRs	ADRs	Number of patients who received treatment
Conventional amphotericin B switched to liposomal amphotericin B	Increased serum creatinine	6
Injection or syrup potassium chloride	Hypokalemia	68
Injection chlorpheniramine maleate, injection hydrocortisone	Chills	28
Probiotics	Diarrhea	1
Hydration with normal saline	Increased serum creatinine	8
Held amphotericin B	Chills	3
Injection calcium gluconate	Hypocalcemia	23
Injection magnesium sulfate	Hypomagnesemia	3
Injection chlorpheniramine maleate, injection hydrocortisone, tablet paracetamol	Fever with chills	9
Total	154	149

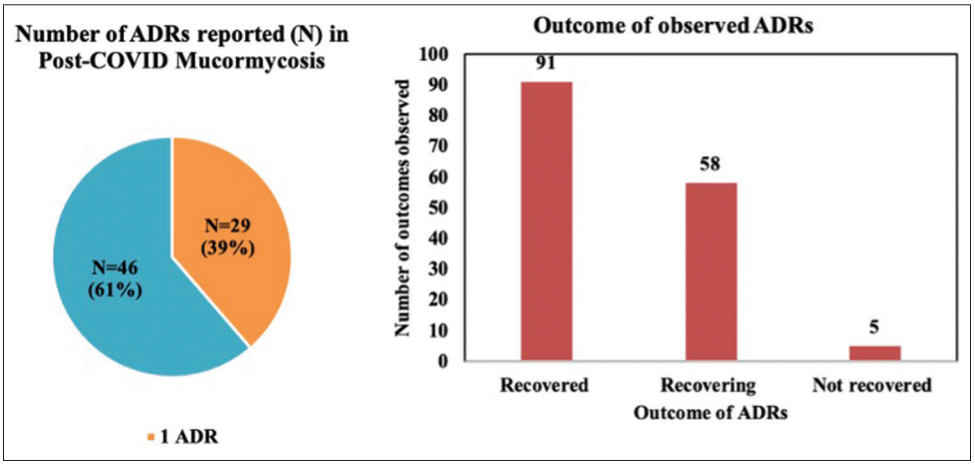

Figure 2: From left to right, number of adverse drug reactions (ADRs): one or more than one; and classification of adverse drug reactions (ADRs) based on outcomes

drug interactions into four categories: contraindicated, serious, monitor closely, and minor. Based on these categories, drug interactions were analyzed and their frequency was studied in the study population.

A total of 169 drug interactions were reported by DIC. A higher number of interactions were observed in males compared (69.2%) to females (30.8%). Patients who received conventional amphotericin B with concomitant drugs were higher in number (74%) compared to those on liposomal amphotericin (26%). The majority of analyzed interactions were categorized as minor (40.8%), followed by monitor closely (34.9%), serious (10.7%), and contraindicated (5.3%), around 8.3% of medication charts did not report any interaction. As per the DIC category, 155 (44.5%) interactions were categorized as minor, 38% as monitor closely, 11.6% as serious, and 5.8% as contraindicated.

Discussion

The study delved into the complex realm of ADRs in COVID-19 patients with mucormycosis undergoing treatment with conventional amphotericin B. The primary objective was to analyze preventable and manageable ADRs in this specific patient cohort. The research identified a total of 154 ADRs, offering valuable insights into their classification, outcomes, and interventions that would help primary physicians in identifying, managing, and reporting similar ADRs. Thus, in this study, a higher number of participants were enrolled compared to previous studies.[14] However, preventability and severity with their respective management strategy were not reported.

During the second wave outbreak of COVID mucormycosis, India had more than twice the global prevalence of the disease.[15] In our study, we shed light on distinct characteristics of ADRs associated with amphotericin B, which is widely available and used in primary care facilities. Notably, a significant proportion (85.61%) of these events were deemed manageable, emphasizing the need for careful monitoring and intervention strategies. A study reported less than 1% prevalence of ADRs with liposomal amphotericin B in management of mucormycosis, but none with conventional amphotericin B formulation.[16] Severity assessment revealed a spectrum of reactions, ranging from mild to severe, highlighting the diverse impact of amphotericin B on patients. In our opinion, the majority of amphotericin B ADRs were manageable as well as preventable. However, severe ADRs were higher compared to ADRs with moderate severity.

In addition, an important observation relevant to primary care physicians is that most of the patients had comorbidities such as diabetes (67%) and hypertension (27%), which mandate critical monitoring of ADRs when being managed with amphotericin B and steroids.[17] As expected, hypokalemia (<3 meq/L) was the most common ADR in amphotericin B users. A substantial portion of ADRs demonstrated positive outcomes, with 91 cases recovering, underscoring the importance of timely intervention and management. Causality assessment based on the WHO-UMC scale classified the majority of ADRs as certain, providing a strong basis for understanding the relationships between amphotericin B and the observed adverse events.

This study detailed the interventions employed for managing ADRs, showcasing the varied approaches taken by healthcare professionals.[4] Gender disparities were evident, with a higher number of male patients experiencing ADRs, suggesting potential gender-specific responses or susceptibilities to amphotericin B. Prevalence of diabetes was consistent in mucormycosis patients as reported in previous studies.[7,14,18] Thus, diabetes continues to be a risk factor for mucormycosis.[15]

The findings carry significant clinical implications, emphasizing the need for personalized approaches in managing COVID-19 patients with mucormycosis even at the primary care level. The identification of specific ADRs and their interventions provides a practical framework for healthcare providers, aiding in the development of tailored treatment protocols.[19,20] However, the study's limitations, such as its observational nature and the limited timeframe, warrant further research. Yet in a resource constraint setting and owing to drug shortage problems, it is wise to continue vigilance on known products to assure quality control and continued signal evaluation.[21,22] Future studies could explore the underlying mechanisms of gender-based differences in ADRs and delve into the long-term outcomes of patients post intervention, enhancing our understanding of this critical healthcare challenge. In addition, the widespread adoption of clinical pharmacologists and clinical pharmacists in the system at all levels of healthcare would enhance safe medication practices.[23]

While the study acknowledges its limitations, including its observational nature and limited timeframe, it points toward significant implications for future research. Acknowledging the study's limitations, further research avenues should explore the underlying mechanisms of gender-based differences in ADRs and delve into the long-term outcomes of patients post intervention, thereby enhancing our comprehension of this critical healthcare challenge. Devising simple management techniques to encounter preventable and manageable ADRs could make use of conventional amphotericin B formulations more affordable in times of need.

Conclusion

In conclusion, this study significantly contributes to the understanding of preventable and manageable ADRs linked with amphotericin B in COVID-19 patients with mucormycosis. By meticulously delineating specific ADRs, their outcomes, and the interventions applied, this research enriches the field of pharmacovigilance. These insights underscore the need for personalized approaches in managing patients with this specific medical profile when encountered by primary care physicians, paving the way for m ore precise and effective patient care strategies.

Ethical statement

This study was approved by the ethical committee of the institute (AIIMS/IEC/21/559) following which participants were recruited in the study by convenience sampling.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Dangi N, Mehendiratta H, Sharma S. Mucormycosis: A serious catastrophe involving COVID-19 patients. Coronaviruses 2023;4. doi: 10.2174/2666796704666230801092541.
2. Zakaria OM, Alkuwaity DW. View of mucormycosis during the era of COVID-19 infection: A cross-sectional study. J Family Med Prim Care 2023;12:2608.
3. Andreescu M, Moldovan C, Lespezeanu DA, Mocanu AI, Schipor MA, Mocanu H. COVID-19-associated rhinocerebral mucormycosis, an incidental finding or a matter of concern – mixed-method systematic review. Infect Drug Resist 2024;17:387–402.
4. Mahesh S, Srivastava S, Sakshi, Tripathi R. The impact of SARS-CoV-2 on the sudden onset of mucormycosis in the Indian subcontinent-A review. J Family Med Prim Care 2022;11:4246.
5. Jose D, Nair KS, Alagesan M, Pappachan JM. The safety and effectiveness of antifungal medications in the management of mucormycosis during the COVID-19 pandemic. Curr Drug Saf 2023;19:3–7.
6. Shimoda C, Yanagishima N, Sakurai A, Tamura S. Mating reaction in Saccharomyces cerevisiae. IX. Regulation of sexual cell agglutinability of a type cells by a sex factor produced by alpha type cells. Arch Microbiol 1976;108:27–33.
7. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, *et al.* The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. Clin Microbiol Infect 2019;25:26–34.
8. Deb T, Garg R, Kaur M, Beniwal A, Gupta V. ADR profile of the covishield vaccine among healthcare workers in a tertiary care teaching hospital in India. Curr Drug Saf 2022;17:344–9.
9. Robinson EG, Hedna K, Hakkarainen KM, Gyllensten H. Healthcare costs of adverse drug reactions and potentially inappropriate prescribing in older adults: A population-based study. BMJ Open 2022;12:e062589.
10. Mahadevappa M, Meher C, Pushpa N, Kulkarni P, Poornima K, Desai N. Study of pattern & distribution of adverse drug

reactions in acute coronary syndrome patients in a tertiary care hospital. Indian J Med Res 2022;156:111–21.

11. Sharma S, Swamy S, Bhambhani A, Nadig P. Adverse drug reactions attributed to fondaparinux and unfractionated heparin in cardiovascular care unit: An observational prospective pilot study in a tertiary care Hospital. J Pharm Bioallied Sci 2018;10:90–5.
12. Shukla A, Jhaj R, Misra S, Ahmed S, Nanda M, Chaudhary D. Agreement between WHO-UMC causality scale and the Naranjo algorithm for causality assessment of adverse drug reactions. J Family Med Prim Care 2021;10:3303.
13. Shaikh S, Raut A, Jambhale P, Iyer S, Shah J. Incidence and severity of adverse drug reactions in medical intensive care unit. Curr Drug Saf 2023. doi: 10.2174/1574886318666230816090606.
14. Chatterjee S, Bhattacharjee M, Hazra A, Mukhopadhyay P, Ray B, Chatterjee S, *et al.* Pharmacovigilance study of amphotericin B for mucormycosis in post-COVID and non-COVID patients at a tertiary care hospital in Eastern India. Indian J Pharmacol 2022;54:417–22.
15. Balushi A Al, Ajmi A Al, Sinani Q Al, Menon V, Berieki Z Al, Shezawi A Al, *et al.* COVID-19-associated mucormycosis: An opportunistic fungal infection. A case series and review. Int J Infect Dis 2022;121:203.
16. Sachdeva K, Saji TA. Adverse drug reaction of antifungals in the management of black fungus: A tertiary care centre experience. Indian J Otolaryngol Head Neck Surg 2022;74(Suppl 2):3111–7.
17. Kumar R, Misra AK, Dutta S, Gupta A, Kumar B, Charan J. A systematic review of mucormycosis cases in COVID-19: Is it an unholy trilogy of COVID-19, diabetes mellitus, and corticosteroids? J Family Med Prim Care 2022;11:2573.
18. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, *et al.* A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Med Mycol 2019;57:395–402.
19. Garbino J, Markham L, Matulionyte R, Rives V, Lew D. Should we continue using amphotericin B deoxycholate for the treatment of fungal infections? Adverse events and clinical outcomes. Scand J Infect Dis 2006;38:110–3.
20. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, *et al.* Comparison of 2 doses of liposomal amphotericin b and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: A randomized, double-blind clinical trial of efficacy and safety. Clin Infect Dis 2010;51:225–32.
21. Ferner RE, Aronson JK, Heneghan C. Crisis in the supply of medicines. BMJ 2019;367:l5841.
22. Aronson JK, Heneghan C, Ferner RE. Drug shortages. Part 1. Definitions and harms. Br J Clin Pharmacol 2023;89:2950–6.
23. Urbańczyk K, Guntschnig S, Antoniadis V, Falamic S, Kovacevic T, Kurczewska-Michalak M, *et al.* Recommendations for wider adoption of clinical pharmacy in Central and Eastern Europe in order to optimise pharmacotherapy and improve patient outcomes. Front Pharmacol 2023;14:1244151.

Supplementary Material

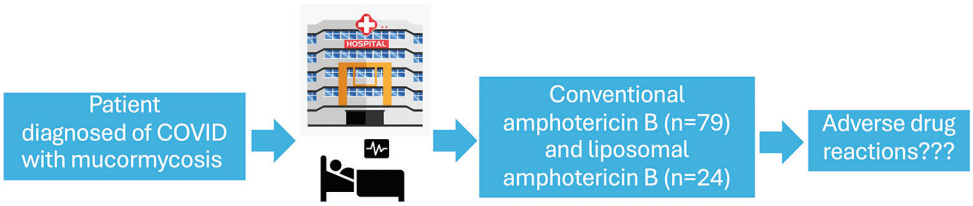

Figure S1: Graphical abstract of the study - recruitment of participants, catergorization and study outcomes assessment