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ORIGINAL ARTICLE

Serum glucose-regulated protein 78 (GRP78) levels in COVID-19-associated mucormycosis: results of a case–control study

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Abstract

Background In experimental models, the expression of glucose-regulated protein 78 (GRP78) in endothelial cells played a role in the pathogenesis of mucormycosis. However, the role of GRP78 in COVID-19-associated mucormycosis (CAM) has not been studied. We hypothesized that serum GRP78 levels are elevated in subjects with CAM.

Objective To compare the serum GRP78 levels in subjects with CAM and COVID-19 controls without mucormycosis.

Design And Setting We performed a hospital-based, case–control study between 1 April 2021 and 31 May 2021.

Participants We enrolled 24 subjects each of CAM and COVID-19 subjects without mucormycosis. We also measured serum GRP78 levels in ten healthy controls.

Exposure The primary exposure studied was serum GRP78 concentration, estimated using a commercially available ELISA kit in stored serum samples.

Results We found the mean ± standard deviation (SD) serum GRP78 levels significantly higher ($p = 0.0001$) among the CAM (374.3 ± 127.3 pg/mL) than the COVID-19 (246.4 ± 67.0 pg/mL) controls. The proportion of subjects with an abnormal GRP78 level (> mean [184.8 pg/mL] plus two SD [23.2 pg/mL] of GRP78 from healthy participants) was 87.5% and 45.8% in the CAM group and COVID-19 controls, respectively. Serum GRP78 level was independently associated with CAM (odds ratio 1.011;

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95% confidence interval [1.002–1.019]) after adjusting for diabetes mellitus and hypoxemia during acute COVID-19.

Conclusion Serum GRP78 levels were significantly higher in CAM than in COVID-19 controls. Further studies are required to the role of GRP78 in the pathogenesis of CAM.

Keywords *Rhizopus* · Mucorales · Zygomycosis · Endothelium · SARS-CoV-2 · Heat shock protein · GRP

Introduction

Coronavirus disease 2019 (COVID-19) triggered an epidemic of mucormycosis worldwide, particularly in India [1]. Diabetes mellitus and glucocorticoid use were believed to be the significant risk factors for COVID-19-associated mucormycosis (CAM) [2]. A few small studies also suggested zinc supplementation as one cause of India's CAM outbreak [3–5]. However, CAM was also reported from countries where poorly controlled diabetes mellitus was not prevalent or zinc supplementation was not used [6, 7]. Hence, there must be several unexplored factors [2, 8].

Experimental studies conducted in the previous decade identified a novel host receptor (the 78 kilo-Dalton glucose-regulated protein 78 [GRP78]) on the endothelial cells that enabled invasion by *Rhizopus arrhizus* [9, 10] the most common etiologic agent causing mucormycosis [11]. Recently, GRP78 has also been shown to be a potential receptor for SARS-CoV-2, the causative agent of COVID-19 disease [12, 13]. The association of GRP78 (in serum and lung tissues) with COVID-19 has been supported by several observational studies conducted in the last two years [12, 14–17]. We hypothesized that the serum GRP78 levels are likely to be raised in subjects with CAM. Our primary objective was to estimate the serum GRP78 levels in subjects with CAM versus the COVID-19 controls.

Methods

Study design and setting: We conducted a retrospective, hospital-based, case–control study between 1st April and 31st May 2021. The Institute Ethics Committee approved the study protocol. We were granted a consent waiver, as we used anonymized patient data. A part of the patient data has been published previously [4, 18]. We report the study as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental file) [19].

Cases and controls: We enrolled consecutive subjects with CAM (cases) and COVID-19 subjects without mucormycosis (COVID-19-controls) from the emergency services of our hospital. We diagnosed COVID-19 using reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 in nasopharyngeal or oropharyngeal swabs. Mucormycosis was diagnosed in participants with compatible clinico-radiological features and confirmed microbiologically (smear showing aseptate hyphae or culture growth of Mucorales) or pathologically in tissue samples [1, 20].

We labeled subjects as CAM when the diagnosis of mucormycosis was concurrent or within eight weeks of COVID-19 diagnosis [4, 18]. The COVID-19 controls were hospitalized subjects with acute COVID-19 illness with no evidence of mucormycosis. We followed the controls for at least eight weeks after enrolment to ensure they had not developed mucormycosis.

Exposure assessment: The primary exposure of interest was serum GRP78 levels between cases and controls.

Study procedure: We retrieved the following information from our clinical records: (1) age, (2) sex, (3) the presence of diabetes mellitus or other risk factors for mucormycosis, (4) hypoxemia during acute COVID-19 (defined as oxygen saturation $< 94\%$ or the need for supplemental oxygen or respiratory support to maintain saturation $\geq 94\%$), (5) glucocorticoid therapy for COVID-19 illness, (6) the site of involvement by mucormycosis (rhino-orbital mucormycosis [ROM], pulmonary and others), and (7) laboratory parameters (complete blood count, renal functions, glycated hemoglobin, serum iron, and serum ferritin levels), if available.

Measurement of serum GRP78 levels: We used serum samples of subjects stored at -80 degrees Celsius. The blood samples were obtained within 48 h

of hospitalization for CAM (for cases) or the acute COVID-19 illness (for COVID-19 controls). We used the human GRP78 ELISA kit (Elabscience, E-EL-H5586; detection range [630–40000 pg/mL], sensitivity [380 pg/mL]) to estimate the GRP78 levels in serum samples as per the manufacturer's instructions. Briefly, we added the samples to the micro-ELISA plate wells pre-coated with an antibody specific to human GRP78. We conducted the experiment on blinded samples in duplicate and recorded the optical density (OD) at 450 nm (Epoch2 Microplate reader, BioTek Instruments, Inc., USA). We calculated the GRP78 values by comparing the mean OD of the samples with the standard curve using the linear equation ($y = 0.1218*x + 0.1538$), where x represents the mean OD of the samples, and y represents the serum GRP78 concentration in samples expressed as pg/mL.

We estimated the mean and standard deviation of serum GRP78 among healthy controls as its normal value is unknown. We selected ten (7/10 women; mean [range] age, 26 [21–28] years) healthy controls with no chronic illness, including diabetes mellitus or other risk factors for mucormycosis, history of smoking or substance abuse, or symptoms suggestive of COVID-19 illness at enrollment. None of the included healthy controls had a history of COVID-19 infection, except one who experienced mild COVID-19 illness nine months before estimating the GRP78 level.

A value of serum GRP78 greater than the sum of the mean and two SDs of healthy controls was labeled as positive GRP78. We also compared the proportion of subjects with positive GRP78 between CAM cases and COVID-19 controls. As an exploratory analysis, we compared the serum GRP78 levels of CAM patients who survived vs. non-survivors.

Statistical analysis: We used the commercially available statistical software package SPSS 22.0 (IBM SPSS Inc., Armonk NY, US). Data are presented as numbers with percentages or mean with standard deviation (SD). To adjust for confounders, we performed a binary logistic regression analysis to determine if serum GRP78 was independently associated with CAM after adjusting for diabetes mellitus and hypoxemia during COVID-19 illness. Further, we compared serum GRP78 in subjects with and without diabetes mellitus. The differences between categorical and continuous variables were compared using the chi-square test and the student t-test. We report the strength of association as an odds ratio (OR with 95% confidence interval [CI]). A p-value of < 0.05 was considered statistically significant.

Results

We enrolled 24 subjects each of CAM and COVID-19 without mucormycosis (Table 1). The mean (SD) age of the entire study population was 53.4 (13.1) years. More subjects with CAM had diabetes mellitus than the COVID-19 controls (70.8% vs. 37.5%, p = 0.04). Hypoxemia during acute COVID-19 was more frequent in the COVID-19 controls than in the CAM cases (95.8% vs. 62.5%, p = 0.01). Serum iron and ferritin levels were not significantly different between the two groups.

Primary objective: We found serum GRP78 concentration significantly higher among CAM cases (374.3 ± 127.3 pg/mL) than in the COVID-19 (246.4 ± 67.0 pg/mL) controls (Fig. 1, Table 2). The mean ± SD serum GRP78 level was also higher in subjects with COVID-19 (n = 48; including both cases and controls) than in the healthy individuals (310.4 ± 119.6 pg/mL vs. 184.8 ± 23.2 pg/mL; p = 0.002). The proportion of subjects with an abnormal GRP78 (i.e., > 231.2 pg/mL) was higher among CAM cases than the COVID-19 controls (87.5% vs. 45.8%, p = 0.01).

On binary logistic regression analysis, serum GRP78 was independently associated with CAM (OR [95% CI], 1.011 [1.002–1.019]) after adjusting for diabetes mellitus and hypoxemia during acute COVID-19 (Table 3).

The information on mortality was available for 19/24 CAM subjects and only 5/19 (26.3%) survived. The mean serum GRP78 level was not significantly different between survivors and non-survivors (425.9 pg/mL vs. 387.6 pg/mL; p = 0.59).

Discussion

We found significantly higher serum GRP78 levels among subjects with CAM than in COVID-19. GRP78, a member of the heat shock protein family, plays a vital role in the unfolded protein response [29–31]. GRP78 is expressed in the endoplasmic

Table 1 Clinical and laboratory features of COVID-19 controls and subjects with COVID-19-associated mucormycosis (CAM)

Parameters	COVID-19 controls (n = 24)	CAM cases (n = 24)	*p*-value
Age in years	58.0 ± 12.8	52.3 ± 14.3)	0.15
Male sex	17/24 (70.8)	18/24 (75)	0.75
Diabetes mellitus	9/24 (37.5)	19/24 (70.8)	0.008
Diabetic ketoacidosis	3/9 (33.3)	9/19 (47.4)	0.48
Hematological malignancy	1/24 (4.2)	0	1.00
Hypoxemia during COVID-19	23/24 (95.8)	15/24 (62.5)	0.01
Glucocorticoids for COVID-19	17/22 (77.3)	18/23 (78.3)	1.00
Site			-
Rhino-orbital mucormycosis	–	19/24 (79.2)	
Pulmonary mucormycosis	–	5/24 (20.8)	
Others[a]	–	–	
Hemoglobin, g/dL	11.7 ± 2.2	12.5 ± 2.7	0.28
Total leukocyte count, cells/mm^3	14885 ± 7045	16243 ± 7391	0.52
Platelet count, cells/mm^3	208 ± 100	245 ± 114	0.25
Urea, mg/dL	75.3 ± 70.4	67.8 ± 51.3	0.68
Serum creatinine, mg/dL	2.5 ± 3.6	1.5 ± 1.5	0.24
Glycated hemoglobin [b] %	7.9 ± 2.2	10.8 ± 3.5	0.07
Serum iron, µg/dL	60.2 ± 42.9	47.0 ± 41.8	0.31
Serum ferritin, ng/mL	1954 ± 1876	2102 ± 1789	0.78

The values are presented as mean ± standard deviation or number/total numbers (percentage)

[a]Includes one case each of renal and cutaneous mucormycosis

[b]Data on glycated hemoglobins available for 13/17 in the cases and 7/9 COVID-19 controls with diabetes mellitus

COVID-19 – coronavirus disease 2019; GRP78 – glucose related protein 78; ROM – rhino-orbital mucormycosis

reticulum of various tissues, including bronchial epithelial cells and endothelium. GRP78 has at least four domains to which several ligands, including viruses [21, 22], peptides (RoY) [23], and autoantibodies can bind [31]. Different ligands may cause different effects upon binding to GRP78 (e.g., promoting angiogenesis, inhibiting cell proliferation, or inducing apoptosis) [23, 24].

GRP78 is also a co-receptor facilitating the entry of SARS-CoV-2 [12, 13]. In a prospective case–control study, the serum GRP78 levels were significantly higher in subjects with COVID-19 infection (with or without pneumonia) than in healthy controls or pneumonia because of causes other than COVID-19 [16]. The serum GRP78 values were also higher in non-COVID-19 pneumonia versus the healthy controls; however, the greatest elevation was seen in the COVID-19 group [16]. GRP78 expression is a marker of cellular stress and has been observed in several conditions, including malignancies, infections (viral and bacterial), and metabolic disorders like obesity and diabetes [25]. While GRP78 may be elevated in several infectious and non-infectious conditions, a significantly higher level of GRP78 noted in our study and a previous study on COVID-19 subjects suggests an association with SARS-CoV-2 infection [16]. The higher levels in COVID-19 infection are likely because of a positive feedback loop existing between SARS-CoV-2 infection and GRP78 expression [26, 27]. Alternatively, our study's higher serum GRP78 concentration could have been because of diabetes mellitus (more frequently noted in the cases than in the controls) rather than COVID-19. However, the multivariate analysis and the subgroup analysis suggest GRP78 to be independently associated with CAM after adjusting for diabetes.

What do our study results imply? Diabetes mellitus and a high environmental burden of Mucorales were present in India even before the COVID-19 pandemic and probably explained the high background

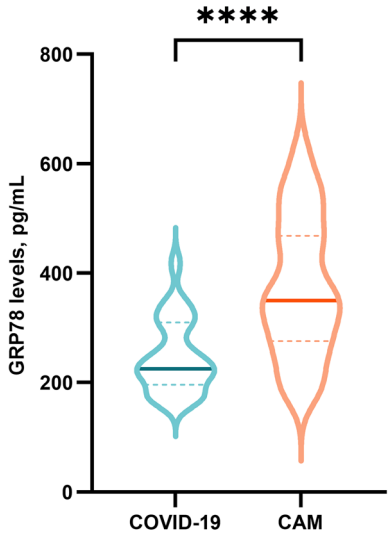

Fig. 1 Violin plot shows serum glucose-regulated protein 78 (GRP78) levels in COVID-19 controls and COVID-19-associated mucormycosis (CAM) cases. The solid central line in the plot represents the median value, while the dotted line below and above the median denotes the first and third quartiles, respectively. The concentration of GRP78 in the serum of CAM subjects was significantly (****) higher than COVID-19 controls

incidence of mucormycosis (70 times higher than reported elsewhere) [28, 32]. Following the COVID-19 pandemic, there was a definite rise in the cases of mucormycosis not only in India[1] but also in Germany[7] and several other countries[33] compared to the pre-pandemic period. Also, the proportion of patients with diabetes mellitus reported from other countries[7, 34] was much lower (7/30, 23.3%) in CAM than in our cohort. Intuitively, COVID-19 or its treatment should have contributed to the CAM outbreak. We have previously shown that inappropriate glucocorticoid use was associated with CAM [1]. We now provide indirect evidence implicating SARS-CoV-2 in the pathogenesis of CAM. Nearly all subjects with CAM had an elevated serum GRP78 concentration, significantly higher than COVID-19 controls.

Our study has a few limitations, the most important being the small sample size and monocentric design. We have not studied the expression of GRP78 in endothelial cells or lung tissue. Nevertheless, elevated serum GRP78 level could be a surrogate for increased expression at a cellular level and provides indirect evidence of their association with CAM. A high serum GRP78 was noted in a study of patients with renal carcinoma who had higher tissue expression of GRP78 [35]. However, more studies are required, particularly in diabetic subjects, to determine the correlation between tissue expression and circulating GRP78. While tissue expression of GRP78 in endothelial cells has been shown previously in an allogeneic transplant recipient with mucormycosis [36], there is no published data on serum GRP78 levels. We do not know the normal serum GRP78 level, its significance, and the probable factors (such as age, sex, ethnicity, the method used for estimating GRP78, sample storage, and several others) that could influence the levels. The elevated GRP78 in serum could also be because of other co-infection or unknown confounding factors in the CAM group. Thus, the current study is hypothesis-generating and needs further confirmation. Also, we did not include subjects with mucormycosis unrelated

Table 2 Serum GRP78 in the study groups

Parameters	COVID-19 controls (n = 24)		CAM cases (n = 24)		[a]*p*-value
	DM (n = 9)	No DM (n = 15)	DM (n = 19)	No DM (n = 5)	
Serum GRP78, pg/mL [b]	267.2 ± 72.8	234.0 ± 62.4	372.8 ± 122.5	380.1 ± 160.2	0.005
Positive GRP78 [b]	5/9 (55.5)	6/15 (40.0)	17/19 (89.5)	4/5 (80.0)	0.0001

The values are presented as mean ± standard deviation or number/total numbers (percentage)

COVID-19 – coronavirus disease 2019; CAM – COVID-19-associated mucormycosis; DM – diabetes mellitus; GRP78 – glucose related protein 78

[a]Between CAM cases and COVID-19 control groups

[b]The difference between those with and without diabetes mellitus was not statistically significant (p-values not shown)

The mean ± SD serum GRP78 in the healthy participants was 184.8 ± 23.2 pg/mL. We defined positive GRP78 as concentration > (mean + 2SD value of healthy controls) i.e., 231.2 pg/mL

Table 3 Binary logistic regression analysis demonstrating the factors associated with the mucormycosis in COVID-19 patients

Variables	COVID-19 controls (n = 24)	CAM cases (n = 24)	Odds ratio (95% confidence interval)	*p*-value
Diabetes mellitus	9/24 (37.5)	19/24 (70.8)	4.462 (0.950–20.96)	0.06
Hypoxemia during COVID-19	23/24 (95.8)	15/24 (62.5)	0.150 (0.012–1.856)	0.14
Serum GRP78, pg/mL	246.4 ± 67.0	374.3 ± 127.3	1.011 (1.002–1.019)	0.01

The values are presented as numbers/total number (percentage) or mean ± standard deviation

COVID-19 – coronavirus disease 2019; CAM – COVID-19-associated mucormycosis; GRP78 – glucose related protein 78

to COVID-19. Apart from COVID-19 and CAM, assaying GRP78 in diabetes mellitus (with and without mucormycosis) is likely to improve our understanding.

In conclusion, we found higher serum GRP78 levels in CAM than in COVID-19 and healthy controls. More extensive prospective studies are required, preferably in subjects of mucormycosis without diabetes mellitus, to confirm our findings.

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Data Availability Statement Data supporting the study results will be available on reasonable request from the corresponding author.

Declarations

Conflict of Interest VM- Conflicts of Interest- none, financial disclosures- none. MD- Conflicts of Interest- none, financial disclosures- none. AS- Conflicts of Interest- none, financial disclosures- none. DN- Conflicts of Interest- none, financial disclosures- none. MKH- Conflicts of Interest- none, financial disclosures- none. SMR- Conflicts of Interest- none, financial disclosures- none. ISS- Conflicts of Interest- none, financial disclosures- none. HC- Conflicts of Interest- none, financial disclosures- none. NP- Conflicts of Interest- none, financial disclosures- none. AC- Conflicts of Interest- none, financial disclosures- none. RA- Conflicts of Interest- none, financial disclosures- none

References

1. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis. India Emerg Infect Dis. 2021;27(9):2349–59. https://doi.org/10.3201/eid2709.210934.
2. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World. Mycopathologia. 2021;186(6):739–54. https://doi.org/10.1007/s11046-021-00584-8.
3. Kumar S, Acharya S, Jain S, Shukla S, Talwar D, Shah D, et al. Role of Zinc and Clinicopathological Factors for COVID-19-Associated Mucormycosis (CAM) in a Rural Hospital of Central India: A Case-Control Study. Cureus. 2022;14(2):e22528. https://doi.org/10.7759/cureus.22528.
4. Muthu V, Kumar M, Paul RA, Zohmangaihi D, Choudhary H, Rudramurthy SM, et al. Is there an association between zinc and COVID-19-associated mucormycosis? Results of an experimental and clinical study. Mycoses. 2021;64(10):1291–7. https://doi.org/10.1111/myc.13365.
5. Karoli R, Kulshreshtha MR, Gupta N, Singh M, Singh V, Shakya S. Clinical-epidemiological Profile of Coronavirus Disease 19 Associated Mucomycosis (CAM) and Relation with Zinc and Iron Levels. J Assoc Physicians India. 2022;70(2):11–2.
6. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe. 2022;In press:https://doi.org/10.1016/S2666-5247(21)00237-8.
7. Seidel D, Simon M, Sprute R, Lubnow M, Evert K, Speer C, et al. Results from a national survey on COVID-19-associated mucormycosis in Germany: 13 patients from six tertiary hospitals. Mycoses. 2022;65(1):103–9. https://doi.org/10.1111/myc.13379.
8. Gumashta J, Gumashta R. COVID19 associated mucormycosis: Is GRP78 a possible link? J Infect Public Health. 2021. https://doi.org/10.1016/j.jiph.2021.09.004.
9. Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest. 2014;124(1):237–50. https://doi.org/10.1172/JCI71349.

10. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2010;120(6):1914–24. https://doi.org/10.1172/JCI42164.
11. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020;26(7):944.e9-e15. https://doi.org/10.1016/j.cmi.2019.11.021.
12. Ibrahim IM, Elfiky AA, Elgohary AM. Recognition through GRP78 is enhanced in the UK, South African, and Brazilian variants of SARS-CoV-2; An in silico perspective. Biochem Biophys Res Commun. 2021;562:89–93. https://doi.org/10.1016/j.bbrc.2021.05.058.
13. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. COVID-19 spike-host cell receptor GRP78 binding site prediction. J Infect. 2020;80(5):554–62. https://doi.org/10.1016/j.jinf.2020.02.026.
14. Khan A, Mohammad A, Haq I, Nasar M, Ahmad W, Yousafi Q et al. Structural-Dynamics and Binding Analysis of RBD from SARS-CoV-2 Variants of Concern (VOCs) and GRP78 Receptor Revealed Basis for Higher Infectivity. Microorganisms. 2021;9(11). https://doi.org/10.3390/microorganisms9112331.
15. Köseler A, Sabirli R, Gören T, Türkçüer I, Kurt Ö. Endoplasmic Reticulum Stress Markers in SARS-COV-2 Infection and Pneumonia: Case-Control Study. In Vivo. 2020;34(3 Suppl):1645–50. https://doi.org/10.21873/invivo.11956.
16. Sabirli R, Koseler A, Goren T, Turkcuer I, Kurt O. High GRP78 levels in Covid-19 infection: A case-control study. Life Sci. 2021;265:118781. https://doi.org/10.1016/j.lfs.2020.118781.
17. Puzyrenko A, Jacobs ER, Sun Y, Felix JC, Sheinin Y, Ge L, et al. Pneumocytes are distinguished by highly elevated expression of the ER stress biomarker GRP78, a co-receptor for SARS-CoV-2, in COVID-19 autopsies. Cell Stress Chaperones. 2021;26(5):859–68. https://doi.org/10.1007/s12192-021-01230-4.
18. Kumar HM, Sharma P, Rudramurthy SM, Sehgal IS, Prasad KT, Pannu AK, et al. Serum iron indices in COVID-19-associated mucormycosis: A case-control study. Mycoses. 2022;65(1):120–7. https://doi.org/10.1111/myc.13391.
19. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500–24. https://doi.org/10.1016/j.ijsu.2014.07.014.
20. Muthu V, Agarwal R, Patel A, Kathirvel S, Abraham OC, Aggarwal AN, et al. Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: Delphi consensus statement from the Fungal Infection Study Forum and Academy of Pulmonary Sciences India. Lancet Infect Dis. 2022. https://doi.org/10.1016/S1473-3099(22)00124-4.
21. Triantafilou K, Fradelizi D, Wilson K, Triantafilou M. GRP78, a coreceptor for coxsackievirus A9, interacts with major histocompatibility complex class I molecules which mediate virus internalization. J Virol. 2002;76(2):633–43. https://doi.org/10.1128/jvi.76.2.633-643.2002.
22. Chu H, Chan CM, Zhang X, Wang Y, Yuan S, Zhou J, et al. Middle East respiratory syndrome coronavirus and bat coronavirus HKU9 both can utilize GRP78 for attachment onto host cells. J Biol Chem. 2018;293(30):11709–26. https://doi.org/10.1074/jbc.RA118.001897.
23. Hardy B, Battler A, Weiss C, Kudasi O, Raiter A. Therapeutic angiogenesis of mouse hind limb ischemia by novel peptide activating GRP78 receptor on endothelial cells. Biochem Pharmacol. 2008;75(4):891–9. https://doi.org/10.1016/j.bcp.2007.10.008.
24. Luo S, Mao C, Lee B, Lee AS. GRP78/BiP is required for cell proliferation and protecting the inner cell mass from apoptosis during early mouse embryonic development. Mol Cell Biol. 2006;26(15):5688–97. https://doi.org/10.1128/mcb.00779-06.
25. Girona J, Rodríguez-Borjabad C, Ibarretxe D, Vallvé JC, Ferré R, Heras M et al. The Circulating GRP78/BiP Is a Marker of Metabolic Diseases and Atherosclerosis: Bringing Endoplasmic Reticulum Stress into the Clinical Scenario. J Clin Med. 2019;8(11). https://doi.org/10.3390/jcm8111793.
26. Wang Y, Wu H, Li Z, Yang P, Li Z. A positive feedback loop between GRP78 and VPS34 is critical for GRP78-mediated autophagy in cancer cells. Exp Cell Res. 2017;351(1):24–35. https://doi.org/10.1016/j.yexcr.2016.12.017.
27. Carlos AJ, Ha DP, Yeh DW, Van Krieken R, Tseng CC, Zhang P, et al. The chaperone GRP78 is a host auxiliary factor for SARS-CoV-2 and GRP78 depleting antibody blocks viral entry and infection. J Biol Chem. 2021;296:100759. https://doi.org/10.1016/j.jbc.2021.100759.
28. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019;5(1):26. https://doi.org/10.3390/jof5010026.
29. Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D. Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. Nat Cell Biol. 2000;2(6):326–32. https://doi.org/10.1038/35014014.
30. Pobre KFR, Poet GJ, Hendershot LM. The endoplasmic reticulum (ER) chaperone BiP is a master regulator of ER functions: Getting by with a little help from ERdj friends. J Biol Chem. 2019;294(6):2098–108. https://doi.org/10.1074/jbc.REV118.002804.
31. Gonzalez-Gronow M, Selim MA, Papalas J, Pizzo SV. GRP78: a multifunctional receptor on the cell surface. Antioxid Redox Signal. 2009;11(9):2299–306. https://doi.org/10.1089/ars.2009.2568.
32. Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. Microorganisms. 2021;9(3). https://doi.org/10.3390/microorganisms9030523.
33. Ismaiel WF, Abdelazim MH, Eldsoky I, Ibrahim AA, Alsobky ME, Zafan E, et al. The impact of COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. Am J Otolaryngol. 2021;42(6):103080. https://doi.org/10.1016/j.amjoto.2021.103080.
34. Danion F, Letscher-Bru V, Guitard J, Sitbon K, Dellière S, Angoulvant A, et al. COVID-19 associated mucormycosis

in France: a rare but deadly complication. Open Forum Infect Dis. 2021. https://doi.org/10.1093/ofid/ofab566.
35. Kumar M, Garg H, Gupta N, Sharma A, Kaushal S, Kumar R, et al. Glucose- regulated protein 78 (GRP78) in renal cell carcinoma: A novel biomarker for predicting tumor behavior. Heliyon. 2021;7(6):e07300. https://doi.org/10.1016/j.heliyon.2021.e07300.
36. Shumilov E, Bacher U, Perske C, Mohr A, Eiffert H, Hasenkamp J et al. In Situ Validation of the Endothelial Cell Receptor GRP78 in a Case of Rhinocerebral Mucormycosis. Antimicrob Agents Chemother. 2018;62(5). https://doi.org/10.1128/aac.00172-18.