Machine learning based predictive model and systems-level network of host-microbe interactions in post-COVID-19 mucormycosis

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A B S T R A C T

Mucormycosis, a rare infection is caused by fungi *Mucorales*. The affiliation of mucormycosis with Coronavirus disease (COVID-19) is a rising issue of concern in India. There have been numerous case reports of association of rhino-cerebral-orbital, angioinvasive, pulmonary, respiratory and gastrointestinal tract related mucormycosis in patients with history of COVID-19. The immune dysregulation, preposterous use of steroids, interleukin-6-directed therapies and mechanical ventilation in COVID-19 immunocompromised individuals hypothesizes and predisposes to advancement of mucormycosis. The gaps in mode of presentation, disease course, diagnosis and treatment of post-COVID-19 mucormycosis requires critical analysis in order to control its morbidity and incidence and for prevention and management of opportunistic infections in COVID-19 patients.

Our study performs machine learning, systems biology and bioinformatics analysis of post-COVID-19 mucormycosis in India incorporating multitudinous techniques. Text mining identifies candidate characteristics of post-COVID-19 mucormycosis cases including city, gender, age, symptoms, clinical parameters, microorganisms and treatment. The characteristics are incorporated in a machine learning based disease model resulting in predictive potentiality of characteristics of post-COVID-19 mucormycosis. The characteristics are used to create a host-microbe interaction disease network comprising of interactions between microorganism, host-microbe proteins, non-specific markers, symptoms and drugs resulting in candidate molecules. R1A (Replicase polyprotein 1a) and RPS6 (Ribosomal Protein S6) are yielded as potential drug target and biomarker respectively via potentiality analysis and expression in patients. The potential risk factors, drug target and biomarker can serve as prognostic, early diagnostic and therapeutic molecules in post-COVID-19 mucormycosis requiring further experimental validation and analysis on post-COVID-19 mucormycosis cases.

1. Introduction

Mucormycosis is a sporadic fatal fungal infection caused by *Mucorales* such as *Rhizopus, Rhizomucor, Mucor, Cunninghamella* and *Absidia*. The prevalence of mucormycosis is ~0.14 cases per 1000 in India [1].

The identification of mucormycosis in individuals with history of Coronavirus disease (COVID-19) is a rising problem of distress especially after second wave. COVID-19 presents with varying symptomatic patterns, ranging from mild to moderate to lethal such as immune modulation, dizziness, mood changes, weight gain, insomnia, muscle weakness, diabetes mellitus and secondary infections [2].

Multitudinous reports of presence of craniofacial, pulmonary, rhinocerebral, cutaneous, renal and gastrointestinal mucormycosis in cases post-COVID-19 in India have been published. Post-COVID-19 mucormycosis mainly develops in immunocompromised hosts and is stipulated

to be associated with the unreasonable use of steroids, diabetes mellitus, neutropenia, systemic corticosteroid therapy, stem cell transplant, haematological malignancy and other risk factors leading to tissue infarction, necrosis, adrenal suppression, residual pulmonary dysfunction, difficult airway and myocardial dysfunction [36].

COVID-19 leads to thrombosis and endothelial damage facilitating the Mucor spread. The attack of microorganisms in pancreas causes islet cell injury that leads to impaired insulin secretion and glucose intolerance. This downregulates angiotensin converting enzyme 2 (ACE2) increasing angiotensin levels impairing insulin secretion in diabetic cases. Steroids are immunosuppressive and increase levels of blood sugar leading to increased susceptibility. In immunocompromised cases, the overexpression of inflammatory cytokines and decrease in CD4$^+$ T and CD8$^+$ T cells is observed upregulating GRP78 receptor utilized by microorganisms for entering endothelial cells. The COVID-19 cases with

pneumonia allow mucormycosis involvement in sinuses and lungs due to alveolo-interstitial involvement. High glucose and acidic levels due to diabetes, hypoxic conditions and mechanical ventilation contribute to germination of fungal spores by providing an ideal environment [3,32].

Diagnosis is challenging and delayed because of non-specific clinical signs or symptoms pertaining severe morbidity and mortality requiring early suspicion, timely diagnosis and prompt treatment [4].

In the current era, the incorporation of systems biology and machine learning plays an important role for deciphering host-microbe interactions for diagnosis and prognosis of diseases. For example, a published study created a host-microbe disease network for Reactive Arthritis and associated Inflammatory Bowel Disease using an *In-silico* pipeline incorporating systems biology that incorporates potential signatures for prognosis, diagnosis and therapy. In another study, machine learning algorithms were implemented for classifying drug targets using host and pathogen drug and non-drug target proteins including host-pathogen network centrality characteristics for predicting drug targets involved in Microbe Associated Cardiovascular Diseases for prognosis, diagnosis and therapy. A study was carried out for improving *Clostridium difficile* infection pathogenesis, diagnosis, treatment and prevention by finding the interactions between gut microbiota and host immune markers and incorporating host-microbe data into machine learning classification models ([5,38,39].

Our study applies machine learning, systems biology and bioinformatics techniques namely text mining, host-pathogen interaction, host protein-marker interaction, host protein-symptom interaction, microbial protein-drug interaction and potentiality analysis in order to create a predictive disease model and host-microbe disease network of post-COVID-19 mucormycosis.

We hypothesize that the identified risk factors, drug targets and biomarkers in this study will help in understanding disease course/presentation, prognosis, early diagnosis and prompt treatment in post-COVID-19 mucormycosis.

2. Materials and methods

2.1. Text mining

Text mining was conducted to unveil the characteristics of post-COVID-19 mucormycosis cases using pubmed.mineR that operates in R (4.1.1), a command based software (https://www.r-project.org/). Pubmed.mineR comprises details from PubMed repository, consisting of greater than 32 million cited biomedical literature associated with NLM, MESH, MEDLINE, books, life science journals and more data sources [6]. The literature search utilized keywords (e.g. "Mucormycosis AND COVID-19 AND India") including Boolean operators (AND/OR/NOT). These characteristics were utilized for further bioinformatics analysis.

2.2. Machine learning based disease model

The characteristics were incorporated in machine learned based supervised logistic regression analysis of COVID-19 dataset taken from publicly available Kaggle dataset of COVID-19 that was filtered according to our study requirements (https://www.kaggle.com/imdevs kp/covid19-corona-virus-india-dataset?select=patients_data.csv). The regression analysis was conducted after preprocessing dataset using R software to create a predictive machine learning disease model of post-COVID-19 mucormycosis consisting of potential risk factors using methodology as per our published article [7].

2.3. Host-pathogen interaction

UniProtKB (https://www.uniprot.org/), a resource that contributes to exhaustive data regarding protein sequence and function [8], was used to retrieve reviewed proteins from genome of target microorganisms causing post-COVID-19 mucormycosis obtained via text mining as

well as microorganism leading to Coronavirus disease (COVID-19).

Host-pathogen interaction database (HPIDB) (https://hpidb.igbb.msstate.edu/), a curated database consisting of 69,787 (668 pathogen and 66 host) protein interaction entries obtained from numerous experimental detection methods [9]), was utilized to find interactions between microbial proteins and human host.

2.4. Host protein-marker interaction

Search tool for the retrieval of interacting genes/proteins (STRING) (https://string-db.org/), a database covering physical and functional protein-protein associations of 24,584,628 proteins from 5090 organisms derived from genomic, expression and high-throughput experiments [10], was employed to find interactions between interacting human proteins obtained via host-pathogen interaction and non-specific markers found using text mining.

2.5. Host protein-symptom interaction

GeneCards (https://www.genecards.org/), a knowledgebase integrating information from around 150 sources providing genomic, proteomic, transcriptomic, genetic, functional and clinical data on human genes [11], was used to find interactions between interacting human proteins obtained via host-pathogen interaction and symptoms found using text mining.

2.6. Microbial protein-drug interaction via docking

The interactions between interacting microbial proteins obtained via host-pathogen interaction and drugs found using text mining was carried out through docking studies using Schrödinger software as per methodology used in our published article [12].

The host-microbe interaction network was visualized using Cytoscape software [13].

2.7. Drug target potentiality analysis

The potentiality of candidate drug targets was observed by assessing their essentiality and homology. Database of Essential Genes (DEG) (http://origin.tubic.org/deg/public/index.php), a database consisting of experimentally identified essential genes in bacteria, eukaryotes and archaea [14] was utilized to find essentiality at identity ≥25% and Basic Local Alignment Search Tool (BLAST) (https://blast.ncbi.nlm.nih.gov/Blast.cgi) was utilized to find homology at E value of 0.0001 and identity ≥25% [15].

The methodology incorporated in our study is illustrated in Fig. 1.

3. Results

3.1. Text mining

Text mining search derives 14 relevant case reports indexed in PubMed consisting of post-COVID-19 mucormycosis patients from India.

After carefully studying and screening the case reports, the subsequent characteristics are acquired:

a. City:

The post-COVID-19 mucormycosis cases admitted are located in Bangalore, Bhopal, Chandigarh, Chennai, Delhi, Jodhpur, Karnataka, Mumbai, Pune, Punjab, Rajasthan and Uttar Pradesh.

b. Gender:

The post-COVID-19 mucormycosis cases are more in males as compared to females.
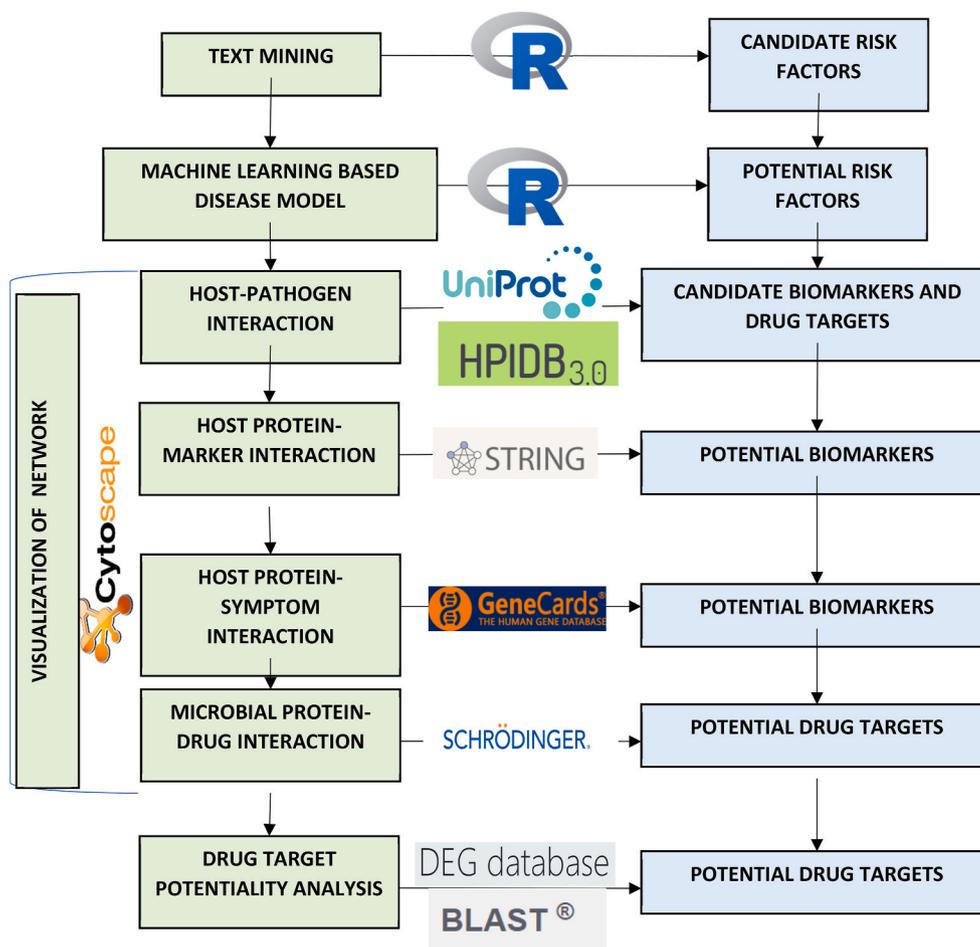
Fig. 1. | Outline of the approach used in the study for post-COVID-19 mucormycosis.

c. Age:

The post-COVID-19 mucormycosis cases are of age group of 28–73 years.

d. Symptoms:

The post-COVID-19 mucormycosis cases are showing symptoms/disorders namely abdomen distension, abdomen pain, abdomen tenderness, afebrile, anuria, asthma, breathlessness, chemosis, constipation, cough, diabetes, dyspnea, epistaxis, expectoration, eye cellulitis, eye edema, eye pain, eye swelling, face pain, face swelling, fever, flank edema, flank erythema, flank pain, headache, hematochezia, hypertension, hypotension, hypoxia, malaise, melena, micturition, neutropenia, neutrophilia, obstipation, ophthalmoplegia, palate ulcer, peritonitis, proptosis, ptosis, retinopathy, sepsis, tachycardia, tachypnea, thrombosis, vision loss and vomiting with more diabetic cases. These are observed after performing ultrasound, doppler, computed tomography, sonography, magnetic resonance imaging, radiography, angiography and other tests/examinations.

e. Clinical parameters:

The post-COVID-19 mucormycosis cases affected clinical parameters are ferritin, D-dimer, C-reactive protein, blood pressure, HbA1c, fetal bovine serum, Interleukin-6, neutrophil, lymphocyte, lactate dehydrogenase, glucose, albumin, polymorphs, haemoglobin, respiratory rate, pulse rate, aminotransferase, creatinine, blood urea nitrogen, platelet and white blood cells observed after performing laboratory investigations.

f. Microorganisms:

The post-COVID-19 mucormycosis cases histopathological analysis using palate, nasal, renal, necrotic and orbital tissue and biopsy samples/swabs incorporated fungal staining and microscopy showing hyphae of microorganisms namely *Rhizopus oryzae, Rhizopus arrhizus* and *Rhizopus microsporus.*

g. Treatment:

The post-COVID-19 mucormycosis cases underwent therapy consisting of amphotericin, analgesic, antibiotic, eye drops, fluid, heparin, inotrope, insulin, nebulizer, oxygen, steroid and surgery that treated few cases, improvised some cases and fatality is seen in rest of the cases.

The result obtained after performing text mining is depicted in Fig. 2 and the candidate characteristics were employed for further analysis.

3.2. Machine learning based disease model

The filtered dataset used in our study to create disease model of post-COVID-19 mucormycosis comprises of 107242 COVID-19 cases from India with characteristics including age, gender and state. After incorporating characteristics obtained via text mining, the preprocessed dataset consists of attributes/features namely gender (0: female; 1: male), state (1: Andaman and Nicobar Islands; 2: Andhra Pradesh; 3: Arunachal Pradesh; 4: Assam; 5: Bihar; 6: Chandigarh; 7: Chhattisgarh; 8: Dadra and Nagar Haveli and Daman and Diu; 9: Delhi; 10: Goa; 11:
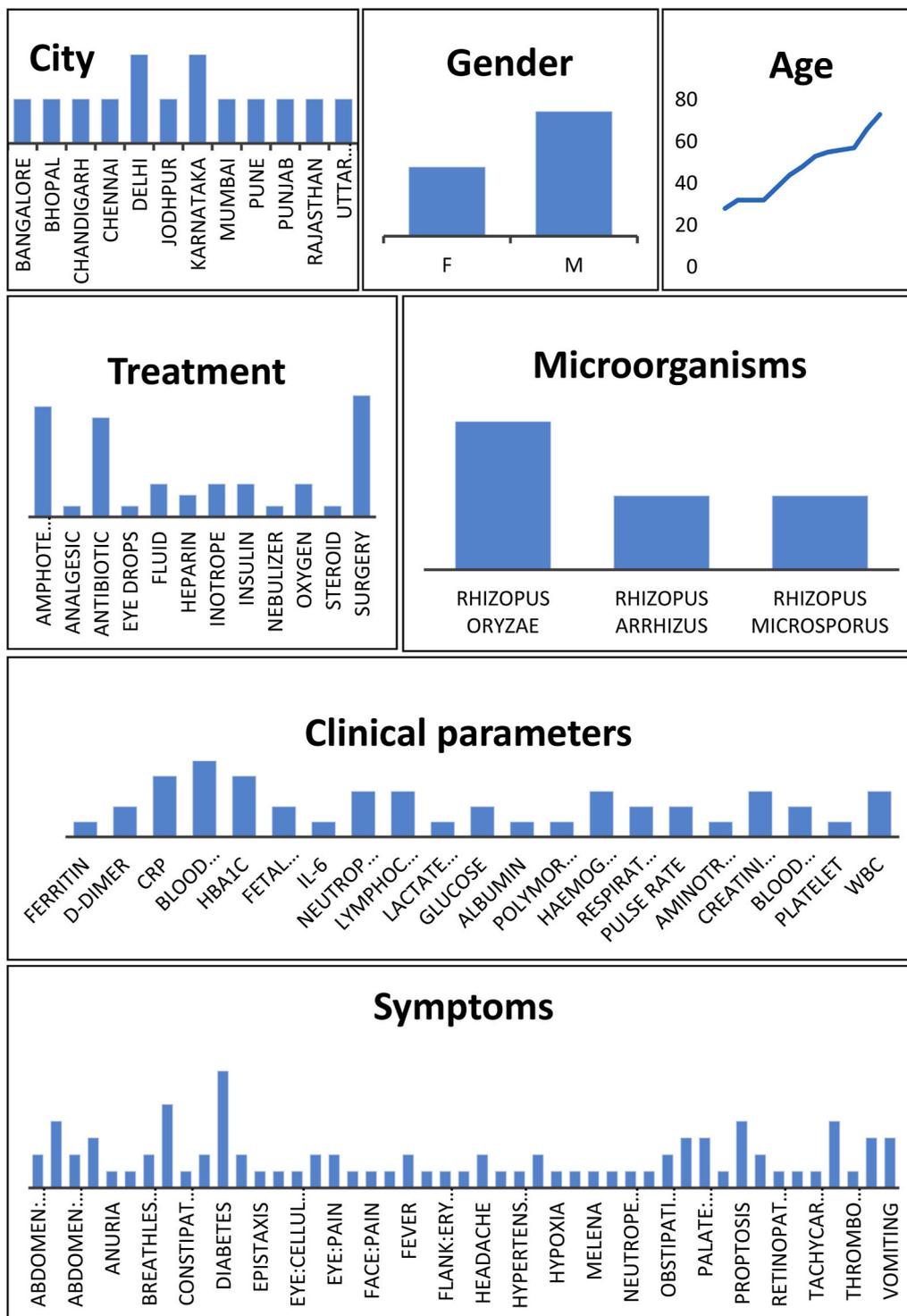
Fig. 2. | Text mining to retrieve characteristics of post-COVID-19 mucormycosis in India.

Gujarat; 12: Karnataka, 13: Kerala; 14: Madhya Pradesh; 15: Maharashtra; 16: Manipur; 17: Meghalaya; 18: Mizoram; 19: Odisha; 20: Puducherry; 21: Punjab; 22: Rajasthan; 23: Sikkim; 24: Tamil Nadu; 25: Telangana; 26: Tripura; 27: Uttar Pradesh; 28: Uttarakhand; 29: West Bengal) and age in years with target attribute mucormycosis (0: absent; 1: present).

The machine learning based predictive model shows 43934 COVID-19 cases having the risk of attaining mucormycosis (Fig. 3). The accuracy of training set is 99%. The statistical parameters of testing set are: Accuracy = 0.9998 (99%); Area under the receiver operator curve

(AUC) = 99% (95% CI = 0.9997, 0.9999); Sensitivity = 0.9997 (99%), and Specificity = 1.0000 (100%) showing potentiality of candidate characteristics.

3.3. Host-pathogen interaction

The reference genomes for SARS-COV-2, *Rhizopus oryzae/arrhizus* and *Rhizopus microsporus* are Severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2), *Rhizopus oryzae* (Mucormycosis agent) (*Rhizopus arrhizus* var. delemar), *Rhizopus oligosporus* (*Rhizopus*
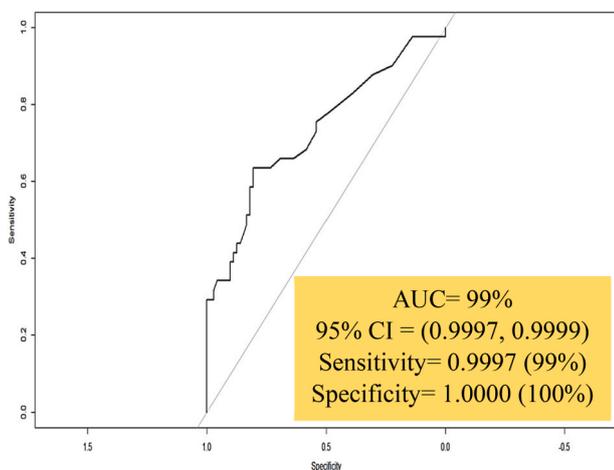
Fig. 3. | ROC curve of machine learning based disease model of post-COVID-19 mucormycosis.

microsporus var. oligosporus) and *Rhizopus azygosporus* (*Rhizopus microsporus* var. azygosporus) respectively. The proteins in SARS-COV-2 are 16, *Rhizopus oryzae/arrhizus* are 11 and *Rhizopus microsporus* are 5 as represented in Table 1.

The host-microbe interacting proteins for SARS-COV-2 are SPIKE (Spike glycoprotein), R1AB (Replicase polyprotein 1 ab), R1A (Replicase polyprotein 1a) and NCAP (Nucleoprotein) (microorganism) and ACE2 (Angiotensin Converting Enzyme 2), VATG1/ATP6V1G1 (ATPase H + Transporting V1 Subunit G1), RS6/RPS6 (Ribosomal Protein S6), SUMO1 (Small Ubiquitin Like Modifier 1) and ROA1/OPA6 (Optic Atrophy 6 (Autosomal Recessive) (human); for *Rhizopus oryzae/arrhizus* are FUMH (Fumarate hydratase, mitochondrial) and ATP9 (ATP synthase subunit 9, mitochondrial (Lipid-binding protein)) (microorganism) and UBC (Ubiquitin C) and UBQL1/UBQLN1 (Ubiquilin 1) (human); none are present for *Rhizopus microspores* (Table 1).

3.4. Host protein-marker interaction

The interaction of human proteins with non-specific markers of post-COVID-19 mucormycosis yields 26 interactions consisting of 10 proteins namely ACE2, RPS6, SUMO1, UBC, UBQLN1, CRP (C-Reactive Protein), HBA1 (Hemoglobin Subunit Alpha 1), IL-6 (Interleukin 6), LDHB (Lactate Dehydrogenase B) and ALB (Albumin). RPS6 is found to have maximum interactions with non-specific markers and can be regarded as

Table 1

| Proteins of target microorganisms and human obtained from UniProtKB and HPIDB.

Target microorganisms	Microorganism proteins from UniProtKB	Interacting microorganism proteins from HPIDB	Interacting human proteins from HPIDB
Severe acute respiratory syndrome coronavirus 2	16 (SPIKE, R1AB, R1A, NS7A, NCAP, AP3A, VME1, VEMP, NS8, NS6, ORF9B, NS7B, ORF3B, ORF9C, ORF3D, ORF3C)	4 SPIKE R1AB R1A NCAP NCAP	5 ACE2 VATG1/ ATP6V1G1 RS6/RPS6 SUMO1 ROA1/OPA6
Rhizopus oryzae/ arrhizus	11 (LIP, XYN2, FUMH, XYN1, CYB, AMYG, LDHA, LDHB, PYRF, ATP9, NU2M)	2 FUMH ATP9	2 UBC UBQL1/ UBQLN1
Rhizopus microsporus	5 (CHI2, CHI1, CHS2, CHS1, CARP)	N/A	N/A

a potential biomarker (Fig. 4).

3.5. Host protein-symptom interaction

The interaction of human proteins with symptoms of post-COVID-19 mucormycosis results in 91 interactions consisting of 30 proteins namely abdomen pain, asthma, constipation, cough, diabetes, dyspnea, epistaxis, eye pain, eye swelling, face pain, face swelling, fever, flank edema, flank pain, headache, hypertension, hypotension, hypoxia, neutropenia, ophthalmoplegia, peritonitis, proptosis, ptosis, retinopathy, sepsis, tachycardia, tachypnea, thrombosis, vision loss and vomiting. ACE2 is found to interact with 22 symptoms, SUMO1 with 19 symptoms, UBC with 19 symptoms, UBQLN1 with 8 symptoms and RPS6 with 23 symptoms i.e. maximum symptoms. RPS6 is found to have maximum interactions with symptoms and can be regarded as potential biomarker (Table 2).

3.6. Host protein-drug interaction via docking

The interacting candidate drug target R1A with potential biomarker RPS6, shows binding with Amphotericin drug used to control post-COVID-19 mucormycosis via docking analysis resulting in docking score −3.963 kcal/mol as depicted in Fig. 5.

The interaction between host-microbe interacting proteins, non-specific markers, symptoms and drug gives rise to a host-microbe interaction network consisting of candidate and potential molecules of post-COVID-19 mucormycosis comprising of 72 nodes and 152 interactions as depicted in Fig. 6 and Supplementary material 1.

3.7. Drug target potentiality analysis

The interacting candidate drug target R1A with potential biomarker RPS6, is found to be essential and non-homologous against human host as assessed from Database of Essential Genes (DEG) and identity ≥25% and Basic Local Alignment Search Tool (BLAST) at E value of 0.0001 and identity ≥25% and can be regarded as potential drug target.

4. Discussion

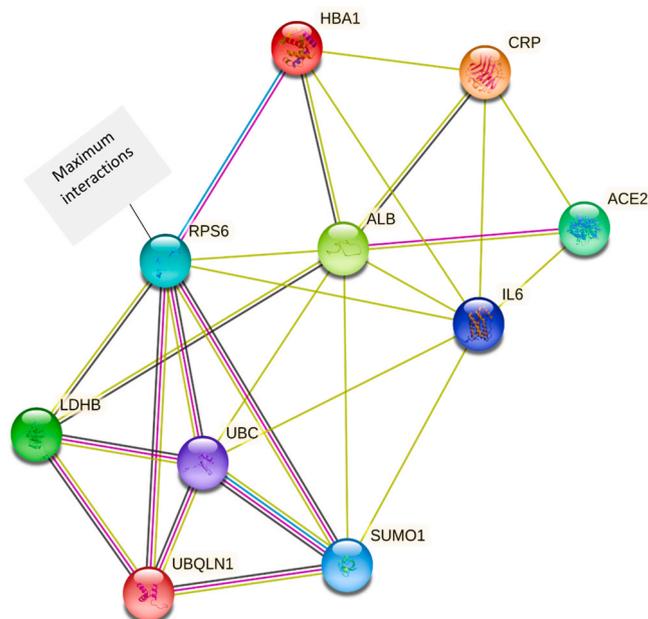Coronavirus disease (COVID-19) was first detected in China in

Fig. 4. | Host protein-marker interaction using STRING.

Table 2

| Protein-symptom interaction using GeneCards.

ACE2	RPS6	SUMO1	UBC	UBQLN1
Asthma	Abdomen:pain	Abdomen:pain	Asthma	Diabetes
Cough	Asthma	Constipation	Constipation	Dyspnea
Diabetes	Constipation	Cough	Cough	Eye:pain
Dyspnea	Cough	Diabetes	Diabetes	Face:pain
Eye:pain	Diabetes	Dyspnea	Eye:pain	Headache
Eye:swelling	Dyspnea	Epistaxis	Face:pain	Hypoxia
Face:pain	Epistaxis	Eye:pain	Fever	Ptosis
Face:swelling	Eye:pain	Face:pain	Flank:edema	Vomiting
Fever	Eye:swelling	Fever	Flank:pain	
Flank:edema	Face:pain	Flank:edema	Headache	
Flank:pain	Face:swelling	Flank:pain	Hypertension	
Headache	Fever	Hypertension	Hypoxia	
Hypertension	Flank:edema	Hypoxia	Ophthalmoplegia	
Hypotension	Flank:pain	Neutropenia	Proptosis	
Hypoxia	Headache	Ophthalmoplegia	Ptosis	
Peritonitis	Hypertension	Ptosis	Retinopathy	
Retinopathy	Hypoxia	Retinopathy	Sepsis	
Sepsis	Neutropenia	Vision loss	Vision loss	
Tachycardia	Ophthalmoplegia	Vomiting	Vomiting	
Thrombosis	Ptosis			
Vision loss	Tachypnea			
Vomiting	Thrombosis			
	Vomiting			
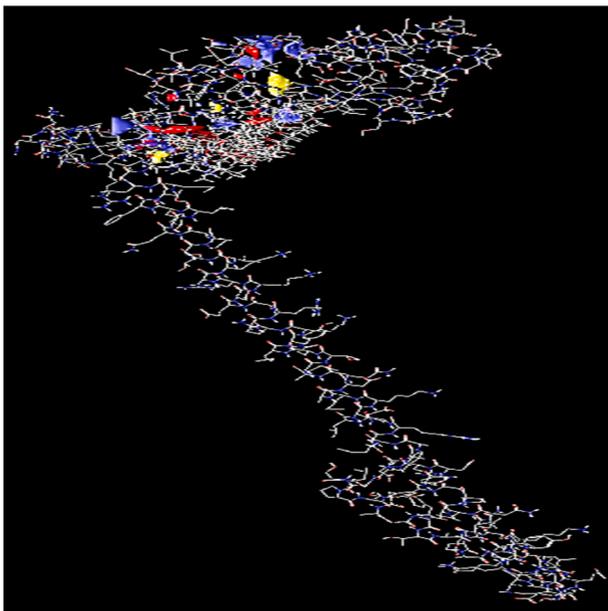
Fig. 5. Host protein-drug interaction via docking using Schrödinger.

December 2019 and was declared pandemic in March 2020. The first wave of COVID-19 was seen in India in mid-2020 peaking in September. The major associated symptoms were fatigue, fever, cough, headache and myalgia. Mortality was seen highest in elders with pre-existing comorbidities leading to hypoxia and multi-organ failure. India saw its second wave in March 2021 peaking in May with more severity due to mutations in virus strain affecting even the younger group without pre-existing comorbidities and with delayed complications (thrombo-embolic episodes and mucormycosis) despite of full recovery [16,17,33, 35]

Mucormycosis, an opportunistic fungal infection, caused by *Zygomycetes (Rhizopus, Rhizomucor* and *Cunninghamella)* has been observed as a complication in post-COVID-19 cases during the second wave of COVID-19 in India mainly involving rhinocerebral, pulmonary, cutaneous, gastrointestinal and encephalic areas. It leads to vascular invasion and gradually causes thrombosis and tissue damage. The

hypothesized pathophysiological causes of COVID-19 leading to fungal infections include immune dysregulation, ciliary dysfunction, thromboinflammation, cytokine storm, microvascular hypercoagulability, tissue necrosis, long standing and poorly controlled diabetes, chronic pulmonary disorder, renal failure, leukemia, lymphoma, neutropenia, organ transplant, prolonged use of steroids in severe cases, hyperglycemia, hypoxia, mechanical ventilation, unhygienic conditions in hospital stay and use of low-grade oxygen [1,2,18].

Non-specific diagnostic and therapeutic interventions are used to control the infection such as histopathological analysis for identifying hyphae of fungus in biopsy, surgical debridement of tissue, antifungal therapy and use of liposomal amphotericin B ([4,34]. A published report has mentioned the use of MSC-based therapy along with combination of short-term antifungal drugs for prospective treatment of post-COVID-19 mucormycosis [19].

Early diagnosis, prognosis and targeted treatment is necessary for prevention of related life-threatening complications and to reduce morbidity and mortality of post-COVID-19 mucormycosis.

Our study employed machine learning, systems biology and bioinformatics techniques such as text mining, host-pathogen interaction, host protein-marker interaction, host protein-symptom interaction, microbial protein-drug interaction and potentiality analysis to create a predictive disease model and host-microbe disease network of post-COVID-19 mucormycosis retrieving potential molecules of post-COVID-19 mucormycosis.

The recent articles regarding post-COVID-19 mucormycosis in India mostly focus on case reports, case-control studies and reviews. To the best of our knowledge, our research article is the first paper focusing on basic research utilising in-depth machine learning, systems biology and bioinformatics data creating a disease model and host-microbe interaction disease network to predict risk factors, drug targets and biomarkers that can be utilized by clinicians and researchers to improve the prognosis, diagnosis and treatment of post-COVID-19 mucormycosis cases in India requiring further substantiation.

Text mining indicates the candidate characteristics of post-COVID-19 mucormycosis consisting of 12 cities, more in males, age group 28–73 years, 47 symptoms with maximum diabetic cases, 21 clinical parameters, 3 microorganisms and 12 therapies. These have been ascertained from 14 case reports of post-COVID-19 mucormycosis in India having diverse demographic and clinical characteristics [3,20–30,35,37].

The machine learning based predictive model portrays the COVID-19 cases having the risk of attaining mucormycosis with 99% accuracy,

Fig. 6. | Host-microbe interaction network of post-COVID-19 mucormycosis.

99% sensitivity, 100% specificity and 99% area under the receiver operator curve showing the potentiality of the candidate characteristics that can be utilized for prognosis of post-COVID-19 mucormycosis.

The characteristics were incorporated for further bioinformatics analysis to create a host-microbe interaction disease network. 16, 11 and 5 proteins respectively were retrieved for target microorganisms obtained via text mining namely Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), *Rhizopus oryzae/arrhizus* and *Rhizopus microspores*. These microorganisms have been observed in post-COVID-19 mucormycosis cases after performing histopathological analysis using palate, nasal, renal, necrotic and orbital tissue and biopsy samples/swabs incorporating fungal staining. 4 SARS-COV-2 microbial proteins having interaction with 5 human proteins and 2 *Rhizopus oryzae/arrhizus* microbial proteins having interaction with 2 human proteins were obtained. 5 out of 7 human proteins had interaction among themselves and with 5 non-specific marker proteins namely CRP (C-Reactive Protein), HBA1 (Hemoglobin Subunit Alpha 1), IL-6 (Interleukin 6), LDHB (Lactate Dehydrogenase B) and ALB (Albumin) extracted via text mining observed after performing laboratory investigations in post-COVID-19 mucormycosis cases. The human proteins had interaction with 30 symptoms namely abdomen pain, asthma, constipation, cough, diabetes, dyspnea, epistaxis, eye pain, eye swelling, face pain, face swelling, fever, flank edema, flank pain, headache, hypertension, hypotension, hypoxia, neutropenia, ophthalmoplegia, peritonitis, proptosis, ptosis, retinopathy, sepsis, tachycardia, tachypnea, thrombosis, vision loss and vomiting extracted via text mining observed after performing ultrasound, doppler, computed tomography, sonography, magnetic resonance imaging, radiography, angiography and other tests/examinations in post-COVID-19 mucormycosis cases.

The interactions between microorganism, host-microbe proteins, non-specific markers, symptoms and drugs give rise to a host-microbe interaction disease network showing candidate and potential molecules of post-COVID-19 mucormycosis.

RPS6 was found to have maximum interactions with non-specific markers and symptoms associated with post-COVID-19 mucormycosis and has been found to be expressed in COVID-19 cases as per published studies [31]. R1A (Replicase polyprotein 1a), a microbial protein having

interaction with RPS6 shows interaction with Amphotericin used to control post-COVID-19 mucormycosis and is found to be essential and non-homologous protein against human host. Therefore, RPS6 and R1A can be regarded as potential biomarker and drug target respectively serving as early diagnostic and therapeutic molecules in post-COVID-19 mucormycosis.

Apart from these, parallel molecules for post-COVID-19 mucormycosis are present in host-microbe disease network created in our study that can be utilized further as disease determinants.

The information regarding the host-microbe interactions can serve as a vital indicator for prognostic, diagnostic and therapeutic interventions for post-COVID-19 mucormycosis requiring prospective experimental validation and substantiation in post-COVID-19 mucormycosis cases.

5. Conclusion

There is an upsurge in the occurrence of mucormycosis in the present COVID-19 pandemic situation. There are still gaps in the source and root cause of accelerated prevalence of post-COVID-19 cases. The postulated predisposing attributes such as immune dysregulation and suppression, diabetes mellitus, impertinent intake of immunomodulators and/or corticosteroids during COVID infection can cause thromboembolic events and opportunistic infections such as mucormycosis. High index of suspicion, awareness, sustained anticoagulation therapy, judicious use of immunosuppressants and long-term follow-up for opportunistic infections must be done for timely and early diagnosis and appropriate and adequate treatment in such patients. Prospective large-scale studies and research is required for prevention, management and to curtail morbidity in post-COVID-19 cases. The present work contributes the in-depth machine learning, systems biology and bioinformatic data creating a disease model and host-microbe interaction disease network. Candidate and potential risk factors, drug targets and biomarkers are retrieved that can be utilized by clinicians and researchers to improve the prognosis, diagnosis and treatment of post-COVID-19 mucormycosis requiring further substantiation in post-COVID-19 mucormycosis cases.

CRediT authorship contribution statement

Anukriti Verma: Supervision, Visualization, Writing – original draft, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software. **Bhawna Rathi:** Writing – review & editing, Supervision.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.micpath.2021.105324.

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