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Editorial

Annals of National Academy of Medical Sciences (2022) ...An Appraisal

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Ann Natl Acad Med Sci (India) 2023;59:1–3.

The biology is a dynamic science. The life has evolved from one cell to fully evolved human being. It is a continuous process. The biology is evolving so is the medical sciences. Medical science has evolved from treatment remedies based on erroneous and philosophical assumptions to scientifically derived and validated research evidence. The therapeutics have also evolved over the year.

The modern medicine has evolved from a stage of prescientific development to an era of evidence-based medicine. The evidence-based interventions make the treatment outcome predictable. The evidence not only to be generated but also to be made available far and wide and beyond the human life by scientific writings and publications, then only it will be available to clinicians worldwide in providing evidence-based treatment and basis for future research.

Scientific journals play a big role in authenticating the research and spreading to every corner of the world. Each article submitted for publication to medical journals is scrutinized by blinded peer review. Once cleared and improved by peer review, the research is printed in a journal. It is regarded as a credible research to be used by clinicians for the benefit of patients and also becomes the basis of future research hypothesis and are included in meta-analysis.

Annals of National Academy of Medical Sciences (ANAMS) was established in 1965. We are publishing four issues every year and is a multispecialty journal. The ANAMS conducts quality peer review by fellows and members of NAMS who are stalwarts in their field. It is an open-access journal and can be downloaded free of cost. At the moment, it is included in Directory of Open Access Journals (DOAJ) and Union Grant Commission (UGC)-approved list of journals. We are taking various steps to make it widely indexed and sought after journal.

Manuscript Submission System and Peer Review: All manuscripts are submitted only on an online manuscripts submission (**https://anams.manuscriptmanager.net**/). Though in previous years, we were also accepting manuscripts online as well as on emails. All manuscripts of previous years were also uploaded on the online submission system. We enrolled new reviewers among members and fellows of National Academy. We revamped the editorial board also and included eight associate editors. This exercise is done to shorten manuscript submission and decision time.

The manuscript submission is increasing now over the years as depicted in ►**Fig. 1.** This year we recorded 23.1% increase in manuscript submission.

In 2019, we were getting manuscripts by emails and we started online submission system in later months of 2019.

In 2022, out of 163 manuscripts (►**Fig. 2**), 96 manuscripts (58.9%) were original articles, 28 (17.1%) review articles, 23 (14.1%) case reports, and other types of manuscripts.

The editorial team processed 194 manuscripts this year (►**Fig. 3**), out of which 120 were decided with acceptance rate of 18/120 (23.33%) and rejection rate of 92/120 (76.66%). Remaining 74 are in different stages of review process.

Early Decision: The editorial team of Annals believe that each and every piece of research paper should be fast tracked and published as soon as possible. Though present submission to decision time is approximately 16 to 20 weeks, it has improved subsequently from last many years. We shall ensure submission-decision time of 12 weeks and acceptance to e-first in next 8 to 10 weeks. Our current timeline to the flow on manuscript is now structured and standardized.

Regularity of Publications: We have published all the four issues for the year 2022. Although first issue of 2022 was late and could be published in the month of May, but fourth issue was released online on December 28, 2022.

This year over all 36 manuscripts have been published that include 17 (47.2%) original articles, 9 (25%) review articles, 2 brief notes, and 9 other articles. This represents balance mix

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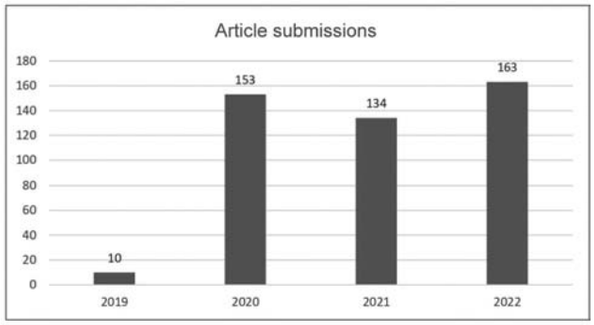

Fig. 1 Bar graph showing article submissions during last 3 years.

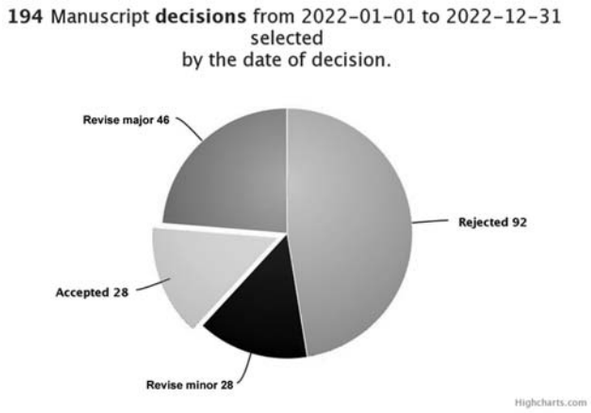

Fig. 3 Pie chart showing the progress of manuscripts in editorial process during 2022.

of every type of articles. Among important review articles, second issue published "Best practice guidelines for breast imaging" part 1 and 2 authored by Chakrabarthi et al for Breast Imaging Society.[1,2] Another article is on Patient Safety, Clinical Microbiology, and Collaborative Healthcare by Chugh et al.[3] We published two articles on mucormycosis and coronavirus disease 2019 (COVID-19) infection[4,5] and one each on COVID-19 vaccination and use of telemedicine in COVID-19 time.[6,7]

Global Reach: With the availability of ANAMS on web site and being open-access, the articles are read globally. This can be appreciated by constant increase in downloads of articles every year. In the year 2022, the download of full articles has increased by 12% (►**Fig. 4**). The visibility of ANAMS can be appreciated by the hits to see Annals on web site globally. ANAMS citations are increasing year by year **(►Fig. 5)** and during this year it has increased by 43.7% from the previous year.

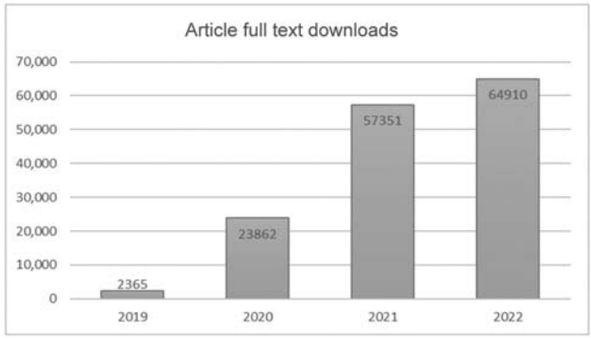

Fig. 4 Bar diagram showing downloading of published articles during last 3 years.

Future Projections: The editorial team is working hard on all-round progress of the journal. Prompt processing of manuscripts and early publication with open access policy will certainly attract authors. We plan to increase the pages in every issue and also to start thematic issues. We aim to include ANAMS in all important databases including Scopus,

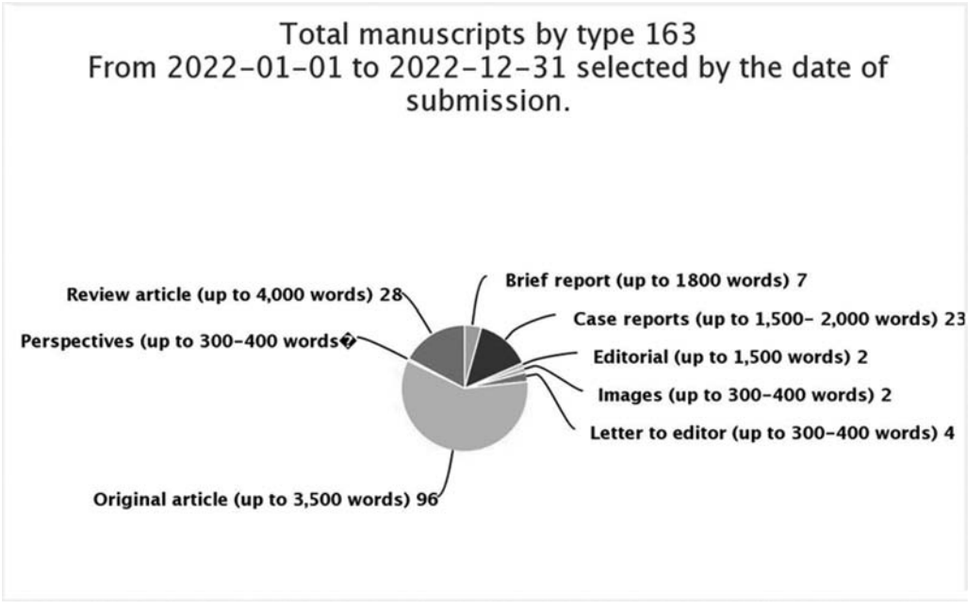

Fig. 2 Pie chart showing different types of manuscripts submitted in 2022.

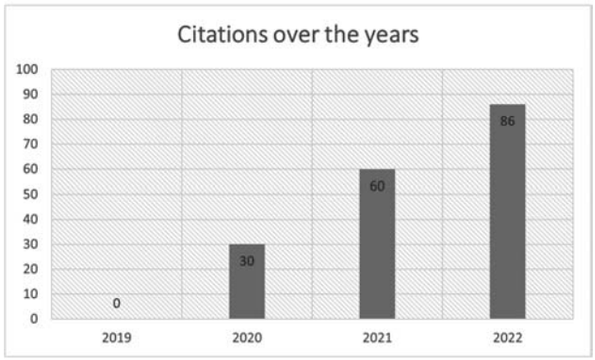

Fig. 5 Bar diagram showing citations for the last 3 years.

PubMed, and Science Citation Index (SCI) expanded. Annals is thankful to our authors, reviewers, readers, and members of editorial team for their support.

On behalf of editorial team of Annals of NAMS
Prof. Anil K. Jain
Editor-in-Chief

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Hepatokines and Adipokines in Metabolic Syndrome

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Abstract

Hepatokines and adipokines are secretory proteins derived from hepatocytes and adipocytes, respectively. These proteins play a main role in the pathogenesis of metabolic syndrome (MetS), characterized by obesity, dysglycemia, insulin resistance, dyslipidemia, and hypertension. Adipose tissue and liver are important endocrine organs because they regulate metabolic homeostasis as well as inflammation because they secrete adipokines and hepatokines, respectively. These adipokines and hepatokines communicate their action through different autocrine, paracrine and endocrine pathways. Liver regulates systemic homeostasis and also glucose and lipid metabolism through hepatokines. Dysregulation of hepatokines can lead to progression toward MetS, type 2 diabetes (T2D), inflammation, hypertension, and other diseases. Obesity is now a worldwide epidemic. Increasing cases of obesity and obesity-associated metabolic syndrome has brought the focus on understanding the biology of adipocytes and the mechanisms occurring in adipose tissue of obese individuals. A lot of facts are now available on adipose tissue as well. Adipose tissue is now given the status of an endocrine organ. Recent evidence indicates that obesity contributes to systemic metabolic dysfunction. Adipose tissue plays a significant role in systemic metabolism by communicating with other central and peripheral organs via the production and secretion of a group of proteins known as adipokines. Adipokine levels regulate metabolic state of our body and are potent enough to have a direct impact upon energy homeostasis and systemic metabolism. Dysregulation of adipokines contribute to obesity, T2D, hypertension and several other pathological changes in various organs. This makes characterization of hepatokines and adipokines extremely important to understand the pathogenesis of MetS. Hepatokines such as fetuin-A and leukocyte cell-derived chemotaxin 2, and adipokines such as resistin, leptin, TNF-α, and adiponectin are some of the most studied proteins and they can modulate the manifestations of

Keywords
- metabolic syndrome
- hepatokine
- adipokine
- type 2 diabetes
- obesity
- hypertension

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MetS. Detailed insight into the function and mechanism of these adipokines and hepatokines in the pathogenesis of MetS can show the path for devising better preventative and therapeutic strategies against this present-day pandemic.

Introduction

Metabolic syndrome (MetS) is a collection of related health issues that has a close association with T2D and cardiovascular diseases. It has turned into an epidemic disorder and describes many clinical and metabolic risk markers. MetS comprises abdominal adiposity and dyslipidemia characterized by insulin resistance, inflammation, low high density lipoprotein (HDL) cholesterol, high triglycerides, and blood pressure, which also correlate with cardiovascular disease (CVD).[1,2]

MetS has been defined in various aspects by the World Health Organization (WHO). Other groups working on epidemiology, endocrinology, basic science, public health have also proposed their definition on MetS.[3–5] In the present day definition, MetS has been framed according to NCEP-ATP III and other clinical and biochemical parameters.

Studies have shown a varying prevalence of MetS in people above the age of 20 years, ranging from around 20% to 39.3% in India, the USA, Tehran, Turkey and Saudi Arabia.[6,7] MetS is becoming more common due to an increase in the occurrence of obesity and may overtake smoking as the main cause behind heart disease in future.

The major risk markers of metabolic syndrome are described below and mentioned in ►**Fig. 1**.

1. **Adiposity**

Being overweight and deposition of abdominal fat is the root cause of MetS. Body fat deposits in different regions in females and males following separate patterns. These tendencies of fat deposition are called gynoid and android adiposity because women tend to deposit excess adipose tissue in outlying regions like legs, and pelvic region while men have tendencies to deposit adipose tissue in the central region (like abdomen). However, the position of adipose tissue is very complex because the regions of body fat deposition are common in men and women. Notably, deposition of adipocytes in abdominal region creates more complexities and lead to MetS. It leads to glucose intolerance, where the action of insulin is shunted.[8]

2. **Insulin resistance**

Insulin resistance (IR) is a key factor in MetS, linking the other components stated above. These metabolic abnormalities are the outcomes of the interaction between glucose utilization and storage in skeletal muscles and adipose tissue, culminating in increased insulin demand and hyperglycemia. Healthy women and men have fat content between 18% and 20% and 10 and 15% of body weight, respectively. MetS affects 30 to 40% of people, mainly due to an increase in weight, and intra-abdominal or ectopic fat accumulation. Reducing weight by 5 to 7% by diet and workout can lower MetS, risk of type 2 diabetes, and cardiovascular diseases. Moreover, anti-diabetic drugs that can improve insulin resistance, reduce the level of lipid and control weight gain are helpful for people with type 2 diabetes arising out of MetS. Bariatric surgery is another option for those with body mass index (BMI) greater than or at least 40 kg/m^2 or 35 to 40 kg/m^2 with significant co-morbidities.[9]

3. **Type 2 Diabetes (T2D)**

The possibility of T2D increases by five times in MetS patients. MetS and insulin resistance together have a cumulative effect because these patients are more prone to develop T2D. T2D is often linked to chronic inflammation. MetS in females, who have pregnancy-induced diabetes, also significantly escalates the likelihood of developing T2D.[10]

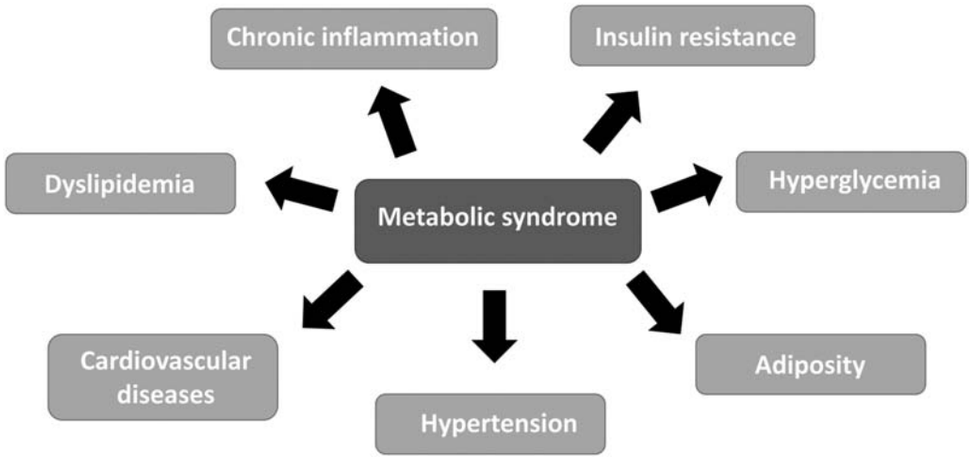

Fig. 1 Major risk markers of metabolic syndrome.

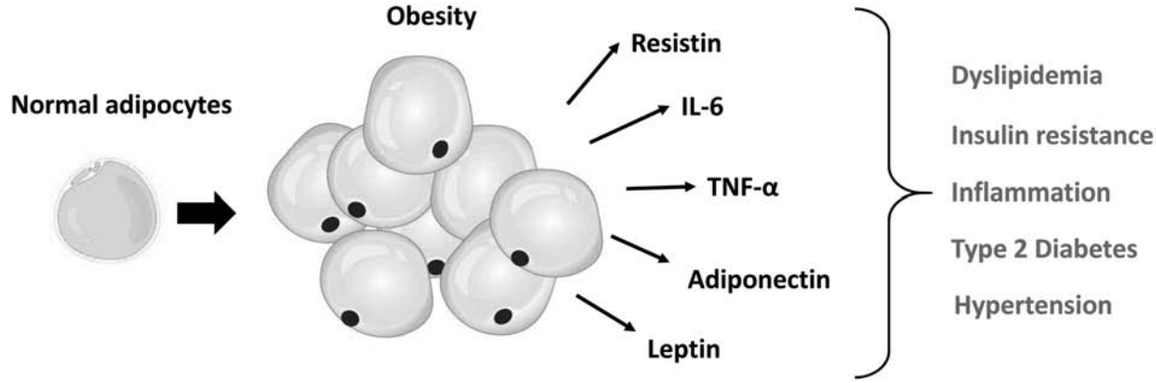

Fig. 2 Adipokines in metabolic syndrome: role of resistin, IL-6, TNF-α, adiponectin, and leptin in dyslipidemia, insulin resistance, inflammation, type 2 diabetes, and hypertension.

4. **Dyslipidemia**

In insulin-sensitive individuals, insulin inhibits adipose tissue lipoprotein lipase. Insulin resistance therefore enhances lipolysis in adipose tissue, resulting in FFA overproduction, increasing its plasma level and also uptake by hepatocytes. FFA increases liver triglyceride and cholesterol ester content. High level of triglycerides in blood TG content induces function of cholesterol ester transfer protein (CETP), that in turn stimulates removal of triglyceride from very low-density lipoprotein (VLDL) and adding to high-density lipoprotein (HDL), hence HDL clearance increases. It also stimulates the conversion of TG into LDL. LDL again in turn undergoes lysis, resulting in the formation of tiny and concentrated cholesterol less LDL particles, which increases the risk of cardiovascular diseases.[11]

5. **Hypertension**

Hypertension has become a global pandemic, developing countries facing the brunt of the problem, where the number of hypertensives are estimated to increase by 80% by 2025.[12] Approximately 1 billion people are affected globally by hypertension and associated heart and kidney disease. It is the one of the major causes behind global mortality. Hypertension is intricately linked to insulin resistance, high cholesterol, cardiovascular diseases, and MetS. Hyperinsulinemia or the increased insulin levels promote hypertension as a compensation for lesser insulin-mediated glucose uptake by skeletal myocytes. Moreover, resistin, and leptin secretion from adipocyte increases during hypertension and insulin resistance.[13,14]

Adipokines in Metabolic Syndrome

Adipokines have a wide variety of role in multiple physiological functions leading to abnormal characteristics of MetS. Anomalous production of adipokines from visceral fat contribute to a proinflammatory condition. An interplay of low adiponectin and high leptin and resistin contribute to dyslipidemia, hyperinsulinemia, and atherosclerosis. To date, only leptin has been developed into a drug.[15,16] Dipeptidyl peptidase-4 (DPP-4) has been recognised as an adipokine and DPP-IV inhibitors (gliptins) are already in use for the treatment of type 2 diabetes.[17,18] Extensive research is needed to identify the basic mechanism of action of adipokines such as apelin, chemerin and resistin. Deficiency in understanding the mechanism of action of these adipokines has retarded the development of adipokine-based therapeutic strategies.[19] Further research is needed to identify the specific adipokines with potential diagnostic and therapeutic properties. The role of different adipokines in MetS are discussed below and shown in ►**Fig. 2**.

1. Resistin

The most crucial point about resistin is that it counteracts insulin's action. Its expression is obstructed during adiposity as well as in T2D. This inhibition of the expression of resistin is mediated by increased expression of TNF-α. Under normal condition, resistin particularly decreases the repressive action of insulin so that gluconeogenesis can occur in the liver. When resistin does not function, circulatory glucose concentrations decreases and insulin sensitivity improves. The gene expression and secretion of resistin increases during adipogenesis in 3T3-L1, which in turn inhibits 3T3-LI adipogenesis.[20,21] Circulatory resistin remains high in obese and T2D patients.[22] However, in certain cases, resistin levels remain quite low in patients having adiposity as well as insulin resistance, which makes the role of resistin controversial. Hyperglycemia is caused by excess secretion of resistin due to increased hepatic glucose production. Resistin also subdues the activation of AMP-activated protein kinase (AMPK) in hepatocytes and muscle cells.[23,24] However, these restrictive actions of resistin upon the activation of AMPK do not occur in primary culture of murine muscle cells, advocating that this process requires release of other factors from other cell types.[25] Moreover, the level of resistin in circulation increases with increasing BMI in humans as well as rodents.[24] A recent meta-analysis showed circulatory resistin levels to be higher in hypertensive subjects compared to their normotensive counterparts, suggesting a pathogenic role of resistin in hypertension.[26] Nevertheless, additional investigation is necessary to identify the detailed function of resistin in MetS.

2. **Interleukin-6 (IL-6)**

Interleukin-6 (IL-6) is considered as a very important adipocytokine that regulates immune responses. It is produced by fibroblasts, monocytes, and adipocytes. Adipocyte-derived IL-6 makes up almost 15 to 35% of total circulating IL-6.[27] The receptor of IL-6 functions by regulating other signaling molecules.[28] It must be mentioned that plasma concentrations and adipocyte-derived IL-6 levels rise during obesity.[28] In high-fat diet (HFD) fed mice, elevated levels of IL-6 in adipocytes induce insulin resistance, inhibiting the function of insulin receptor via proteasomal degradation of insulin receptor substrate (IRS).[29] A key component related with IL-6 is C-reactive protein, and their concentrations are positively correlated.[30] The presence of IL-6 is found in a wide range in different fat or lipid deposition sites. For example, IL-6 levels in visceral adipocytes are higher than peripheral depositions. Altogether, the relation between IL-6 concentration and T2D is quite complicated. Level of IL-6 in circulation increases in obese and T2D patients with significantly enhanced concentrations in visceral adipocytes.[31] IL-6 activates AMPK-activated protein kinase in myotubes; however, the detailed signaling pathway involved in IL-6-mediated glucose uptake and other downstream elements in AMPK activation are not known.[32] Hence, IL-6, a pro-inflammatory cytokine, can be regarded as an indicator of insulin resistance, adiposity, and T2D.[33]

3. **Tumor Necrosis Factor-alpha (TNF-α)**

Just like IL-6, TNF-α is also highly expressed in visceral adipocytes than peripheral adipocytes. It is profusely released by macrophages. TNF-α levels in adipocytes increase with obesity, BMI, insulin resistance, and T2D.[34] TNF-α lowers the level of resistin and also impairs its function in 3T3-L1 adipocytes. Blocking of TNF-α affects other adipokines and improves inflammatory markers. It must be mentioned that TNF-α impairs insulin function in liver and adipocytes.[35] Incubation with TNF-α affects insulin-mediated glucose uptake in skeletal muscle cells. Moreover, TNF-α receptor-IgG chimeric protein restores phosphorylation and insulin signaling via its receptor and substrate (insulin receptor substrate-1/IRS-1) in adipocytes and skeletal muscle cells. Also, knockout of TNF-α or TNF-α receptor improves glucose homeostasis and increases insulin sensitivity in obese models but not in obese patients with T2D.[36,37] In short, TNF-α levels in adipocytes is positively correlated with fasting plasma glucose levels, insulin, and triglyceride levels in high fat-fed female subjects. It also increases adipocyte lipolysis.[38] Hence, TNF-α elevates insulin resistance because it stimulates the production of lipids from adipocytes. Macrophages that are produced from adipose tissue resident monocytes are another significant source of pro-inflammatory cytokines. Also, the ratio of pro-inflammatory and anti-inflammatory cytokines regulate insulin resistance, heart, and kidney diseases.[39]

4. **Adiponectin**

Adiponectin is a very crucial adipocyte-derived protein because it is a key regulator of obesity and T2D. While it can induce release of proinflammatory cytokines, it also has anti-inflammatory functions and affects nuclear factor (NF-kB). It also enhances the action of insulin in peripheral tissues. Adiponectin decreases glucose concentrations and induces liberation of fat without increasing insulin levels, hence acting as an endogenous insulin sensitizer. Adiponectin is circulation occurs in three forms: trimer, hexamer, and high molecular weight (HMW) 12-18-mer adiponectin.[40] It enhances energy expenditure in hepatocytes and skeletal muscle cells, while reducing tissue triglyceride content. Adiponectin restores insulin sensitivity through AMPK-induced reduction of gluconeogenesis in the liver and increased glucose uptake by muscles.[41] There are two major receptors for adiponectin-AdipoR1 and AdipoR2, having seven transmembrane domains. AdipoR1 is found in muscles, and AdipoR2 is found in the liver.[42] Increased plasma level of adiponectin is known to significantly reduce the risk of T2D. High molecular weight (HMW) adiponectin is an important biomarker for MetS, and mainly responsible for increased insulin sensitivity.[43] Hypoadiponectinemia is typical in metabolic and cardiovascular disease states such as T2D, non-alcoholic hepatic steatosis, hypertension, and heart disease. Genetic hypoadiponectinemia is mediated by a missense mutation. Decrease in adiponectin levels precede the progression of T2D, making it an important component behind the condition. Adiponectin levels affect the formation of glucose in the liver by decreasing gene expression of enzymes: phosphoenolpyruvate carboxykinase as well as glucose-6-phosphatase. These two enzymes are very important for gluconeogenesis. Adiponectin also aids in the formation of foam cells from macrophages and reduction of TNF-α production from macrophages.[44] Adiponectin induces weight loss and ameliorates dyslipidemia. Adiponectin expression is reduced in people with metabolically unhealthy adiposity (diabesity).[45] Increased adipocyte accumulation in the visceral region is linked to several health issues. Interestingly, individuals with higher visceral adipose tissue (VAT) have low level of circulatory adiponectin.[46] Adiponectin manifests glucose tolerance by insulin-sensitivity, energy utilization, and anti-inflammatory functions. Adiponectin also aids in the development of MetS in women after menopause.[47] A recent clinical study on postmenopausal women showed that a decrease in body weight significantly increased adiponectin levels and reduced insulin in circulation in fasting condition and also IR.[48] The most cost-effective way of increasing adiponectin, the major anti-inflammatory adipokine, is reduction of the adipose tissue mass by achieving around 5 to 7% weight loss through hypocaloric diet and physical exercise.[49–51] Also, recent studies have shown that GLP-1 agonists, i.e., semaglutide and liraglutide and dual GLP-1 and GIP agonist tirzepatide, can increase adiponectin and reduce pro-inflammatory cytokines, by inducing 10 to 20% weight loss.[52,53] PPAR-gamma agonists such as pioglitazone and rosiglitazone significantly improve insulin sensitivity by increasing adiponectin levels and reducing fetuin-A levels, albeit with loss of weight.[54,55]

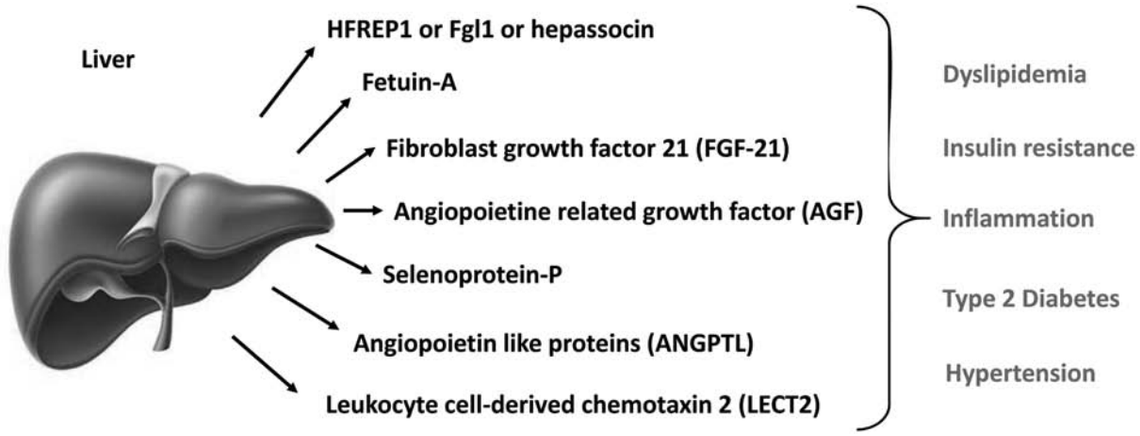

Fig. 3 Hepatokines in metabolic syndrome: role of Hepatocyte-derived fibrinogen-related protein 1 (HFREP1) or Fgl1 or hepassocin, Fetuin-A, fibroblast growth factor 21 (FGF-21), angiopoietin-related growth factor (AGF), angiopoietin-related growth factor (AGF), angiopoietin-like proteins (ANGPTL) and leukocyte cell-derived chemotaxin 2 (LECT2) in dyslipidemia, insulin resistance, inflammation, type 2 diabetes, and hypertension.

5. **Leptin**

Leptin is essentially a thinning hormone, inhibiting food intake by stimulating the hypothalamic satiety center. Leptin is secreted majorly from adipocytes. However, small quantities of leptin are secreted from skeletal muscle, liver, placenta, and fundus of the stomach. Leptin levels increase with increasing amount of fat deposition in body. High level of leptin is associated with obesity and T2D.[56] Leptin resistance leads to unregulated food intake and often co-exists with hypothalamic insulin resistance. The various mechanisms by which a loss of hypothalamic leptin signal leads to weight gain are induction of leptin by Suppressor of Cytokine Signalling-3 (SOC-3), decreased circulation to brain, and increased endoplasmic reticulum (ER) stress. The JAK-STAT pathway activated by leptin receptor is also an important regulator of increasing BMI and phosphoinositol-3-kinase is also regulated by leptin, which, in turn, controls glucose metabolism.[57] Circulatory leptin levels modulate nutritional status because its level decreases soon after fasting begins.[58] Leptin secretion is also dependent on body fat content. Also, 80% of total leptin production is from subcutaneous fat. Circulatory leptin levels, and its secretion from adipose tissue are positively correlated with obesity. Higher content of fat is linked to an increase in leptin resistance. Leptin is a crucial moderator in managing body weight. Hence, deficiency of leptin in blood leads to leptin resistance. Leptin resistance is a key player behind adiposity.[59] Leptin improves insulin sensitivity through AMPK. AMPK in turn decreases malonyl-CoA, thereby impairing acetyl-CoA carboxylase. This explains how leptin deficiency contributes to insulin resistance. It establishes that leptin resistance as a key factor behind adiposity and can be targeted to reduce insulin resistance. Bariatric surgery achieves these goals in a much more robust way, as it allows patients to achieve more than 20% weight loss. DiRECT trial, where participants were subjected to very low-calorie diets (600 calories), resulted in 12 to 15 kg weight loss.[60–63] This was associated with significant improvement in obesity-associated insulin and leptin resistance, secondary to favorable improvements in adipo-hepatokine profiles. Although the actual part played by leptin in regulating insulin resistance is unclear, the contribution of leptin along with other adipokines such as TNF-α, resistin, IL-6 in MetS is confirmed.[64] Finally, leptin is a major gate keeper of the initiation of puberty in girl. Adequate leptin levels tell the hypothalamic GnRH neurons that the body has acquired enough adipose tissue store to sustain pregnancy and child birth; the latter then triggers the onset of puberty.[65]

Hepatokines in Metabolic Syndrome

Liver, one of the major glands in human body, plays several functions such as regulating carbohydrate, fat, and protein metabolism. Hepatokines, the liver-derived secretory proteins, have been given the status of 'new hormones' having substantial role in MetS. The hepatokines regulate energy homeostasis by controlling glucose and lipid metabolism.[66] The high prevalence of type 2 diabetes has increased the need for drug development targeting the liver. Many glucose-lowering drugs are used as hepatokine blockers for treating liver diseases. Some known drugs are nuclear hormone receptor agonists such as peroxisome proliferator-activated receptor agonists, and farnesoid X receptor agonists, incretins, fibroblast growth factor-19/21 and sodium–glucose cotransporter inhibitors.[67] However, detailed studies on deciphering the mechanism is necessary to evaluate hepatokine induced tissue damage and the role of these drugs in metabolic syndrome. Several hepatokines have been identified that provide important knowledge in understanding the pathogenesis of MetS. These hepatokines pose to be the possible targets for treating obesity and other related diseases. The role of all these hepatokines in MetS are as follows and shown in ►**Fig. 3**:

1. Fetuin-A

Fetuin-A (AHSG), is a liver-derived protein and is one of the major culprits behind T2D via blocking the function of insulin receptor and promoting secretion of cytokines. Fetuin-A reduces adiponectin secretion, in adipocytes and

monocytes, which is a main protein that plays important role against MetS. Fetuin-A secretion increases with increased hepatic fat accumulation and sub-clinical atherosclerosis while it is negatively associated with insulin sensitization.[68] The position of fetuin-A gene is 3q27. Single nucleotide polymorphisms (SNPs) in human *AHSG* gene is linked to T2D.[69] The role of excess fetuin-A is reported in obesity, MetS, and T2D. Fetuin-A can be a potential bio-marker for T2D.[69] Interestingly, plasma fetuin-A levels can be reduced by calorie restriction.[70] Pioglitazone, an insulin sensitizer, decreases fetuin-A mRNA expression in liver tissue.[54] Regular exercise or workout has variety of action on circulatory fetuin-A levels; and it has been proven that exercise can reduce serum fetuin-A concentration in T2D while increasing serum adiponectin levels. Lowering fetuin-A level in obese subjects can lead to improvement in IR. Increased serum fetuin-A levels following weight loss after 6 months of aerobic training in healthy overweight old men has been shown to be cardioprotective.[71] Altogether, fetuin-A is a very promising drug target for preventing and treating T2D.[66]

2. Hepatocyte-derived fibrinogen-related protein 1 (HFREP1)

Hepatocyte-derived fibrinogen-related protein 1 (HFREP1, or Fgl1 or hepassocin), is produced from the liver and can lead to progression of T2D through ERK1/2. HFREP1 is also secreted in adipocytes where it controls lipid homeostasis. Plasma HFREP1 levels correlate positively with insulin desensitization and the rate of progression of prediabetes to T2D.[72]

3. Fibroblast growth factor 21 (FGF-21)

FGF-21, another hepatokine, is a strong energy regulator and an essential hormone needed for adaptive starvation. FGF21 is also a myokine and an adipokine. It also affects the level of reactive oxygen species (ROS), ER stress, and other cellular processes and exerts a favorable effect on controlling body weight and triglyceride and cholesterol levels. FGF21 increases GLUT-1 expression in the skeletal muscle and insulin-mediated glucose uptake and serum insulin concentrations in diabetes patients.[73] LY2405319, an FGF-21 agonist, highly improves lipid content in blood in T2D subjects with direct effect on controlling BMI, circulatory insulin levels, and production of adiponectin. FGF21 regulates metabolic balance by enhancing PPAR-γ actions by inducing the formation of beige or brown adipose tissue from white adipose tissue (WAT).[74] Browning of WAT is a crucial balance involving two important factors-FGF-21 and irisin. Irisin is another prominent skeletal muscle-derived protein that has a significant role in MetS. Nutrition status has a direct effect on FGF-21 level in MetS. It suppresses the production and function of adiponectin and promotes the secretion of leptin and cytokine IL-6 in maturing adipocytes.[75,76] High-sensitivity C-reactive protein (hsCRP, a popular indicator of inflammatory diseases) has intricate connection with FGF-21 in T2D subjects. Also, transcription and secretion of FGF-21 can be decreased by TNF-α. Circulatory FGF-21 concentrations are also linked to hypertension, making a role of FGF-21 in MetS quite significant. While pre-clinical studies were highly promising in terms of improving insulin sensitivity, the clinical development of FGF-21 as a drug was given up, as human studies showed significant FGF-21 resistance in T2D, undermining its efficacy in clinical T2D.[77]

4. Angiopoietin-related growth factor (AGF)

Angiopoietin-related growth factor (AGF) is produced from the liver and has crucial function in maintaining lipids and carbohydrates in our body. AGF deficiency is directly linked to, adiposity, T2D and fat depot formation in various organs. AGF also decreases hepatic gluconeogenesis. Serum AGF level increases in T2D patients and also in MetS patients. AGF increases with progression of T2D, while the level of HDLc in circulation decreases.[78]

5. Selenoprotein-P (SeP)

Selenoprotein-P is another crucial hepatokine. High level of SeP is found in T2D or fatty liver patients, or patients having visceral adipocyte accumulation. Such excess concentration of SeP is significantly correlated with IR, hsCRP, and triglyceride level. However, SeP in circulation is low in MetS subjects, particularly those with heart ailments.[79,80] Moreover, excess concentrations of SeP decreases the risk of MetS in children. Adiponectin and salsalate inhibit SeP and this inhibition is mediated by AMPK-Forkhead box protein O1a (FOXO1 a) and its downstream proteins, thereby reducing hepatic glucose output.[81] Serum SeP level shows inverse relation to serum adiponectin concentrations in T2D subjects. SeP can be a potent target for the management of IR-associated diseases.[82]

6. Angiopoietin-like proteins (ANGPTL)

Angiopoietin-like proteins (ANGPTL 1-8), are a group of proteins, secreted from the liver. These have a crucial role in maintaining lipid content in the body. First, we shall discuss about angiopoietin-like protein 4 (ANGPTL4). ANGPTL4 is also secreted from muscle cells and adipocytes. ANGPTL4 primarily regulates the storage of lipid in cells and its spilling. Because the lipid content is directly dependent on food intake, ANGPTL4 secretion is controlled by several factors such as the amount and time of food intake, nutrients present in food, and lifestyle.[83] Nutrients in food, particularly fatty acids, can control gene expression of ANGPTL4 via PPARs. ANGPTL4 stimulates lipid breakdown within adipocytes through cAMP. ANGPTL4 is directly associated with IR. Excess production of ANGPTL4 is required to regulate insulin sensitivity; however, sometimes it may lead to excess lipid spillage in circulation and deposition of fat in various organs. ANGPTL4 concentration in circulation decreases in T2D patients, which implies that low level of ANGPTL4 can be a reason behind T2D. AGPTL4 has a key role in maintaining ROS level and inflammation.[84] ANGPTL8 (also known as lipasin) is another newly studied liver-derived protein that regulates lipid metabolism. ANGPTL8 and HDL-cholesterol have a negative association, while ANGPTL8 and triglyceride level has a positive association. All the effects of ANGPTL8 are moderated by blocking the action of lipoprotein lipase and also ANGPTL3 by increasing the production of very low-density lipoprotein from hepatocytes. The expression of ANGPTL8 is directly related to an increased

expression of hsCRP which in turn increases the prevalence of MetS. Plasma ANGPTL8 begin to increase in pre-diabetic patients and continue to increase until the progression of T2D.[85] ANGPTL8 is also considered to be an indicator of kidney and insulin resistance. Increased secretion of ANGPTL8 occurs in MetS patients with hypertension along with increased expression of ANGPTL4.[86] So, for future investigations ANGPTLs can be targeted by pharmaceuticals to treat hyperlipidemia.

7. Leukocyte cell-derived chemotaxin 2 (LECT2)

Leukocyte cell-derived chemotaxin 2 (LECT2), another hepatokine, is a key protein that can recognize energy demand in our body. It is connected to inflammation in the liver and natural killer T cells. LECT2 is also linked to fat accumulation and glucose transport impairment in skeletal muscles. Positive correlation exists between circulatory LECT2 concentrations, body weight, T2D, and increasing fat depot in the liver and other organs. Calorie-rich diet or fat-containing diet and workout or calorie expenditure exert opposite effects on LECT2 levels, increasing and decreasing its level, respectively, via blocking or activation the AMPK pathway.[87] LECT2 treatment can increase inflammation by increasing the secretion of cytokines and other inflammatory molecules. LECT2 also increases insulin resistance, accumulation of fat, and phosphorylation of mammalian target of rapamycine (mTOR) in hepatocytes, making its role in MetS prominent.[88]

Conclusion

Taken altogether, adipokines and hepatokines likely contribute to insulin resistance, adiposity, T2D, cardiovascular diseases, dyslipidemia, hypertension, and inflammation, leading to MetS and its sinister consequences. Most adipokines and hepatokines are novel proteins. Several adipokines and hepatokines have crosstalk not only amongst themselves but also with other myokines or organokines. Better knowledge of all these proteins is the need of the hour to help us improve the preventive and therapeutic strategies to be adopted for MetS. The easiest and most effective way to restrain or suppress MetS is by making changes in our mode of lifestyle. Living a healthy life with proper food habits and exercise can delay the onset of MetS or aid in curing MetS along with medications.

Conflict of Interest

Dr. Satinath Mukhopadhyay reported Grants or contracts from AM is thankful to Science & Engineering Research Board (SERB), Department of Science & Technology, Govt. of India, for her research fellowship (Grant No. ECR/2017/001028/LS). SM and SAM are thankful to the Department of Science and Technology, Government of West Bengal, Bikash Bhawan, Bidhan Nagar, Kolkata, India [853 (Sanc.)/ ST/P/S&T/9G-2/2011] for funding.
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Association of Metformin with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis

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Abstract

Studies have demonstrated high prevalence of mortality in coronavirus disease (COVID-19) patients with type 2 diabetes mellitus; however, the effects of antidiabetic pharmacotherapy on COVID-19 complications need further exploration. The aim of the study was to explore the association of metformin use and mortality in COVID-19 patients. A literature search was conducted using the databases Medline (via PubMed) and Cochrane Central Register of Controlled Trials until February 09, 2021. Nine studies were included in the meta-analysis, including 12,684 COVID-19 patients. The meta-analysis suggested 37% lower risk of mortality in patients receiving metformin (risk ratio: 0.63; 95% confidence interval: 0.50–0.78; $p < 0.001$). However, no significant difference in hospitalization days between the two groups ($p = 0.197$) was observed. The analysis revealed significantly lower risk of having obesity ($p < 0.001$), hypertension ($p < 0.001$), heart failure ($p < 0.001$), and cerebrovascular disease ($p = 0.015$) in the group receiving metformin. The analysis also demonstrated significantly lower risk of using anticoagulants ($p = 0.015$), diuretics ($p < 0.001$), and antiplatelets ($p = 0.010$) in patients receiving metformin. Our findings suggest that metformin use decreases mortality in COVID-19 patients. However, randomized studies demonstrating the consequences of metformin use are needed to understand the magnitude of the beneficial effects of metformin.

Keywords
- COVID-19
- hospitalization
- metformin
- mortality
- meta-analysis
- type 2 diabetes
- SARS-CoV-2

Introduction

The novel coronavirus disease (COVID-19), now a worldwide public health concern, is associated with varied fatality.[1] Some of the recognized risk factors for poor prognosis of COVID-19 patients include age (>65 years), chronic obstructive pulmonary disease (COPD), hypertension, cardiovascular disease, and type 2 diabetes mellitus.[2] Although type 2 diabetes mellitus has been reported as a risk factor for COVID-19, the effect of pharmacologic agents used to treat type 2 diabetes mellitus on COVID-19 outcomes remains unclear.

Metformin, the first-line treatment for type 2 diabetes mellitus with adequate safety profile, is being suggested for treatment of COVID-19 as a host-directed therapy.[3] A retrospective study highlighted metformin use to be associated

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with a higher risk of severe COVID-19.[3] On the contrary, some retrospective cohort studies have revealed a significant reduction in mortality with metformin use in type 2 diabetes mellitus patients diagnosed with COVID-19.[1,4–6] The mechanism by which metformin seems to reduce the mortality risk of COVID-19 patients remains unclear. However, its anti-inflammatory actions are hypothesized to be one of the mechanisms.[7–9]

Several studies have demonstrated higher prevalence of mortality in type 2 diabetes mellitus patients with COVID-19[1,4–6]; however, the effects of antidiabetic pharmacotherapy on COVID-19 complications need further exploration. Studying the probable effects of pharmacologic agents on clinical prognosis may provide an important understanding to design further studies related to mitigating the risk factors.[2] Thus, in this systematic review and meta-analysis, we aimed to explore the association of metformin use and mortality in COVID-19 patients. We hypothesized that mortality would be lower in COVID-19 patients receiving metformin.

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for systematic reviews[10] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE)[11] guidelines in designing, conducting, and reporting of this systematic review. The systematic review protocol was registered at PROSPERO (registration ID: CRD42020204384).

Data Sources and Searches

We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials using the keywords "COVID-19 and metformin" and "2019 novel coronavirus and Metformin." Additional search was done on LitCovid using the keyword "Metformin" until February 08, 2021. We also searched gray literature using Google Scholar and reference list of eligible articles.

Inclusion and Exclusion

The studies comparing the effect of metformin use on mortality in COVID-19 patients with existing type 2 diabetes mellitus were included. We excluded duplicate publications, reviews, editorials, case reports, letters, meta-analysis, protocols, and studies not reporting the required data. Studies in language other than English were also excluded because of lack of understanding of the data. First author (RP) searched the databases and screened articles for eligibility. Another author (PM) double checked all the included articles and any dispute was resolved by consensus.

Quality Assessment

Two reviewers (RP and RL) assessed the quality of data in the included studies using the National Institutes of Health (NIH) quality assessment tools.[12] The NIH tool is comprehensive and widely accepted for assessment of data quality specially in observational study designs. The tools are specific to individual types of included study designs and are designed to assist reviewers in focusing on concepts that are key to critical appraisal of the internal validity of a study. The tools include items for evaluating research question, objective and study population, selection of subjects, sample size justification, exposure, and outcome measures. Quality reviewers could select "yes," "no," or "cannot determine/not reported/not applicable" in response to each item on the tool. The overall quality of included studies was rated as good, fair, and poor, and the results were incorporated in the meta-analysis.[12]

Data Extraction

Data were extracted using a standardized data extraction in Excel and independently checked by a second reviewer (PM) for accuracy. The following variables were extracted: name of the first author, year of publication, study design, age, gender, number of mortalities, comorbidities, and concomitant medications.

Data Synthesis

An exploratory meta-analysis was performed to understand the magnitude and direction of effect estimate. For dichotomous outcomes, risk ratios (RRs) were calculated and presented with respective 95% confidence intervals (CIs). Mantel–Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool RRs.[13] Continuous outcomes are presented using mean difference (MD) and 95%CIs and pooled using the inverse variance approach. Meta-analysis for each continuous outcome was processed using a random effects model (using DerSimonian and Laird method) since heterogeneity among studies was expected. Heterogeneity between studies was assessed using the χ^2-based Cochran's Q statistic ($p < 0.1$ considered as the presence of heterogeneity) and I-squared (I^2) statistics (>50% representing moderate-high heterogeneity).[13] Forest plot was produced, and subgroup analysis was conducted according to the study design. The 95% prediction interval (PI) was calculated, which estimates the uncertainty bounds for a new study evaluating that same association by considering between-study heterogeneity.[13] Across the meta-analysis, the statistical significance was set as a p-value of <0.05. Publication bias was not assessed as the total number of included studies in meta-analysis was less than 10.[14]

Results

Search Results

The systematic search yielded a total of 135 publications using the keyword "Metformin and COVID-19." After removing duplicates, 86 articles were found to be potential publications for screening. A total of 76 articles (42 review articles and 14 not reporting the required data) were excluded after the application of predefined inclusion and exclusion criteria. Ten studies[4,15–23] were included for systematic review, while 9[4,15–18,20–23] were included in the meta-analysis (►**Fig. 1**). All included studies were retrospective cohort studies.

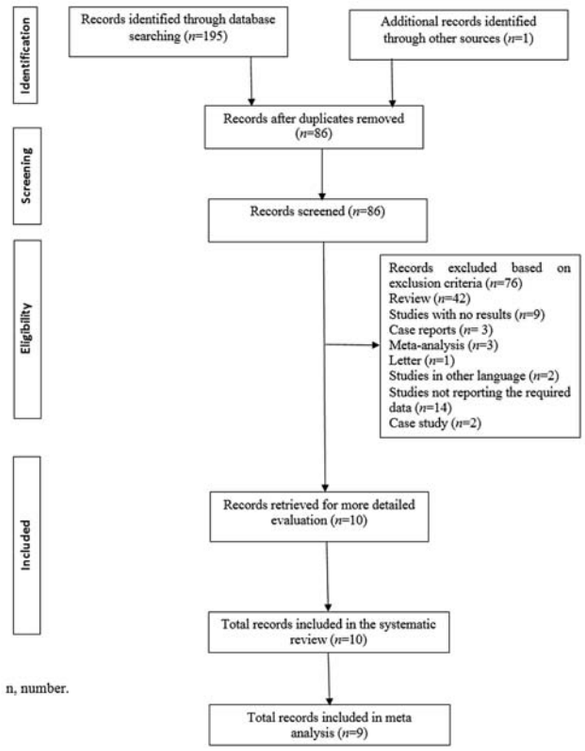

Fig. 1 Prisma flowchart. n, number.

Study Characteristics

All the included studies were retrospective cohort studies.[4,15–20,22,23] Most of the studies were conducted in China. The studies enrolled a total of 12,684 patients (metformin group: 5,819; no-metformin group: 6,865). The sample size of the studies varied from 120 to 6,250. The study characteristics are provided in ►**Table 1**.

Quality Assessment

We assessed the quality of data in the included studies using the NIH quality assessment tools. The quality assessment indicated that included studies were of acceptable quality. All the papers clearly stated the research question or objective, the study population was clearly specified and defined, and all the subjects were selected from the same or similar populations. The detailed result of the quality assessment is provided in the **Supplementary File** (available in the online version).

Association between Metformin Use with Mortality and Hospitalization Days

The analysis of the nine retrospective cohort studies suggested that metformin is associated with lower mortality rate (RR: 0.63; 95% CI: 0.50–0.78; $p < 0.001$; I^2: 73.9%) with substantial heterogeneity in individual study estimates. The results highlight that mortality was 37% lower in patients receiving metformin (►**Fig. 2**), while Cheng et al[19] reported no significant difference in the mortalities of individuals between the metformin and the no-metformin groups (adjusted hazard ratio [HR]: 0.87; 95%CI: 0.36–2.12; $p = 0.757$). Univariate analysis by Pérez-Belmonte et al[18] showed significant association of metformin with mortality (RR: 0.73; CI: 0.58–0.90; $p = 0.004$). However, the multivariate analysis revealed no significant association (RR: 1.10; CI: 0.76–1.60; $p = 0.616$). Multiple logistic regression analysis by Crouse et al[16] revealed that metformin use is an independent factor affecting mortality in COVID-19 patients. Lally et al[23] showed that the patients taking metformin were at significantly reduced hazard of death (adjusted HR: 0.48; 95%CI: 0.28–0.84). Multivariate analysis by Luo et al[15] showed that the use of metformin was negatively correlated with the mortality of type 2 diabetes mellitus patients. Four studies qualified for quantitative analysis of hospitalization days. The analysis revealed no significant difference in hospitalization days between the two groups (MD: 1.07; 95%CI: –0.55 to 2.69; $p = 0.197$; I^2: 0.0; ►**Table 2**).

Association between Metformin Use and Laboratory Parameters

The analyzed hematological parameters included white blood cells, neutrophils, lymphocytes, monocytes, platelets, glucose, and eosinophils. The eosinophil level was higher in the group receiving metformin (MD: 0.02; 95%CI: 0.002–0.04; $p = 0.034$). However, no difference was observed in other hematological parameters (►**Table 2**). Additionally, higher levels were observed for albumin (MD: 2.23; 95%CI: 1.04–3.43; $p < 0.001$), HbA1c (%; MD: 0.70; 95%CI: 0.27–1.13; $p = 0.001$), HbA1c (mmol/L; MD: 1.77; 95%CI: 0.98–2.56; $p \leq 0.001$), and estimated glomerular filtration rate (eGFR; MD: 3.43; 95%CI: 0.55–6.32; $p = 0.020$) in the group receiving metformin (►**Table 2**).

Association between Metformin Use with Comorbidities, Clinical Severity, and Oxygen Support

The analysis revealed that the risk of having obesity (RR: 0.53; 95%CI: 0.43–0.65; $p < 0.001$), hypertension (RR: 0.93; 95%CI: 0.91–0.96; $p < 0.001$), heart failure (RR: 0.41; 95%CI: 0.33–0.51; $p < 0.001$), cerebrovascular disease (RR: 0.48; 95% CI: 0.27–0.87; $p = 0.015$), and COPD (RR: 0.71; 95%CI: 0.62–0.81; $p < 0.001$) was significantly lower by 48, 7, 59, 53, and 30%, respectively, in the group receiving metformin. No significant difference was observed in clinical severity between the two groups. The risk of using nasal canula was significantly higher in the group not receiving metformin (RR: 1.44; 95%CI: 1.06–1.97; $p = 0.02$; ►**Table 3**).

Association between Metformin Use and Concomitant Treatments

The analysis revealed that the risk of using anticoagulants (RR: 0.70; CI: 0.53–0.94; $p = 0.015$), diuretics (RR: 0.69; C95%CI: 0.63–0.76; $p < 0.001$), and antiplatelets (RR: 0.91; 95%CI: 0.84–0.98; $p = 0.010$) was significantly lower by 30, 32, and 10%, respectively, in patients receiving metformin (►**Table 3**).

Discussion

Emerging evidence suggest that the presence of comorbidities increases the mortality risk in COVID-19 patients.

Table 1 Study characteristics

Study	Study design	Patient population	Country	Groups	Sample size	Age[a]	Male, *n* (%)	Main outcome
Pérez-Belmonte et al[18]	Retrospective cohort	T2DM	Spain	Metformin	825	74.9 (8.4)	1647 (61.9)	Use of metformin showed no significant association with in-hospital deaths
				No metformin	663			
Bramante et al[17]	Retrospective cohort	T2DM or obesity	United States	Metformin	2333	73.0 (66.0, 80.0)	1204 (51.6)	Metformin use not significantly associated with decreased mortality in the overall sample
				No metformin	3923	76.0 (67.0, 84.0)	1750 (44.6)	
Chen, 2020[4]	Retrospective cohort	T2DM	China	Metformin	43	62.0 (56.0–69.0)	421 (46.57)	Multivariable regression analyses indicated no association of metformin with in-hospital death
				No metformin	77	67.0 (57.5–73.0)		
Cheng et al[19]	Retrospective cohort	T2DM	China	Metformin	678	62.0 (55.0–68.0)	365 (53.8)	Metformin was not associated with increased mortality
				No metformin	535	64.0 (58.0–70.0)	267 (49.9)	
Crouse et al[16]	Retrospective cohort	T2DM	United States	Metformin	76	NA	NA	Mortality risk is reduced in subjects taking metformin. Multiple logistic regression analysis revealed metformin to be an independent factor affecting mortality
				No metformin	144	NA	NA	
Jianget al[21]	Retrospective cohort	T2DM	China	Metformin	100	64.0 (56.5–70.0)	49 (49.0)	No significant association between metformin use and mortality
				No metformin	228	67.0 (60.0–70.0)	125 (54.8)	
Jinghong, 2020[32]	Retrospective cohort	T2DM	China	Metformin	37	64.6 ± 11.2	22 (59.5)	Significant association between metformin use and survival. Multivariate analysis revealed metformin to be an independent predictor of survival
				No metformin	94	67.7 ± 11.7	52 (55.3)	
Lalauet al[22]	Retrospective cohort	T2DM	France	Metformin	1496	68.5 ± 11.9	1000 (66.8)	Metformin use is associated with a lower risk of death in patients with diabetes
				No metformin	953	74.6 ± 12.5	568 (59.6)	
Lally et al[23]	Retrospective cohort	T2DM/ non-T2DM	United States	Metformin	127	72.3 (8.3)	125 (98.4)	Subjects taking metformin were at significantly reduced hazard of death
				No metformin	69	75.6 (9.2)	68 (98.6)	
Luo et al[31]	Retrospective cohort	T2DM	China	Metformin	104	63.0 (55.8–68.3)	53 (51.0)	Metformin use was significantly associated with decreased mortality
				No metformin	179	65.0 (57.5–71.0)	103 (57.5)	

Abbreviations: *N*, number of subjects; NA, not available; T2DM, type 2 diabetes mellitus.
[a]Data presented as mean (standard deviation [SD]) or median (interquartile range [IQR]).

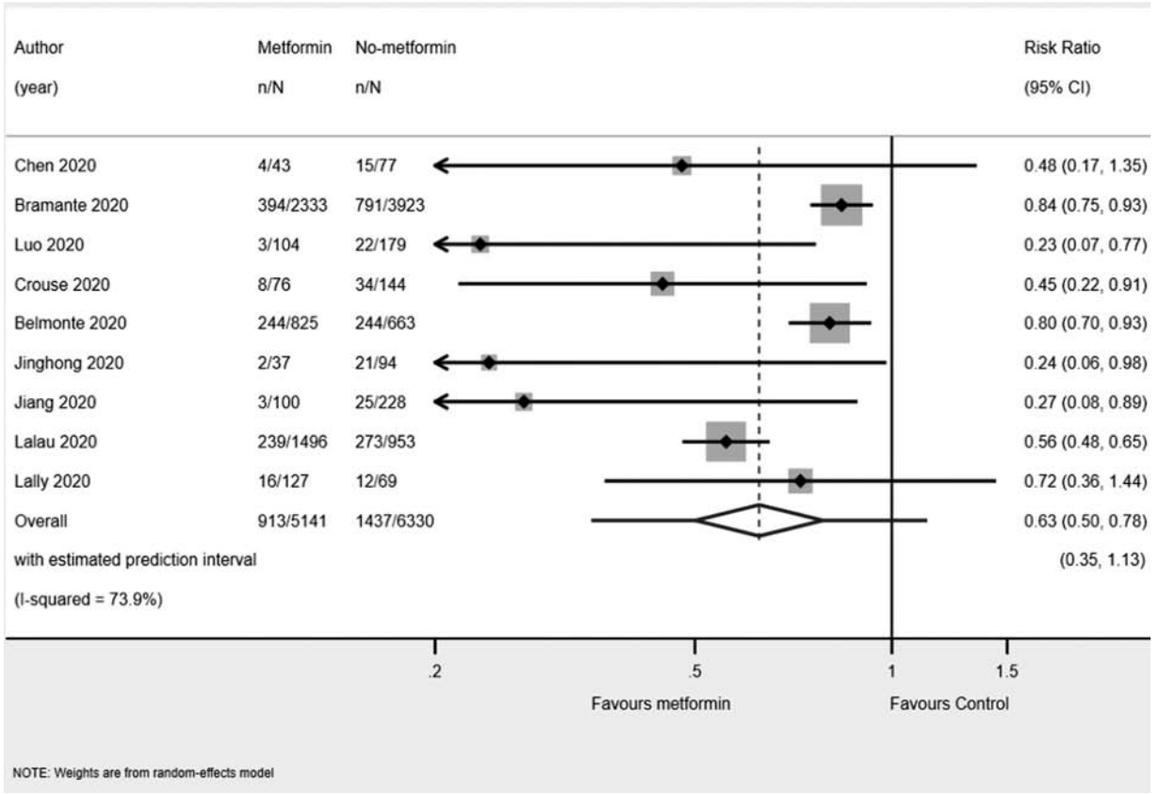

Fig. 2 Association of metformin use and mortality in covid-19 patients.

Table 2 Random-effects meta-analysis results between metformin and control groups for hospitalization and laboratory parameters

Outcomes	No. of studies	Sample size	MD	95% CI	*p*-value	I-squared (%)	Heterogeneity statistic (*p*-value)
Hospitalization (d)	4	1,646	1.07	−0.55 to 2.69	0.197	0.0	0.18 (0.758)
Hematologic parameters (10^9/L)							
White blood cells	3	731	0.01	−0.29 to 0.31	0.953	0.0	1.79 (0.409)
Neutrophils	2	403	−0.11	−0.48 to 0.26	0.561	0.0	0.61 (0.436)
Lymphocytes	3	731	0.12	−0.02 to 0.28	0.085	39.2	3.29 (0.193)
Monocytes	2	403	−0.02	−0.08 to 0.05	0.650	51.7	2.07 (0.150)
Platelets	2	403	12.57	−12.46 to 37.57	0.324	45.8	1.84 (0.174)
Eosinophils	1	283	0.02	0.002 to 0.04	0.034	–	–
Biochemical parameters							
ALT (U/L)	3	731	0.02	−2.27 to 2.31	0.986	0.0	0.41 (0.815)
AST (U/L)	3	731	−1.66	−6.11 to 2.78	0.464	78.3	9.20 (0.010)
Urea (mmol/L)	2	403	−0.65	−1.49 to 0.19	0.129	53.8	2.16 (0.141)
LDH (U/L)	1	328	−12.30	−28.79 to 4.19	0.144	–	–
Ferritin (μg/L)	1	328	78.47	−53.00 to 209.94	0.242	–	–
Albumin (g/L)	1	328	2.23	1.034 to 3.433	<0.001	–	–
Triglyceride (mmol/L	1	131	0.12	−0.18 to 0.42	0.432	–	–
FBG (mmol/L)	2	611	1.00	−0.59 to 2.58	0.218	71.7	3.53 (0.060)
HbA1c (%)	1	328	0.70	0.27 to 1.13	0.001	–	–

(*Continued*)

Table 2 (*Continued*)

Outcomes	No. of studies	Sample size	MD	95% CI	*p*-value	I-squared (%)	Heterogeneity statistic (*p*-value)
HbA1c (mmol/L)	1	131	1.77	0.98 to 2.56	<0.001	–	–
eGFR (mL/min)	1	1,213	3.43	0.55 to 6.32	0.020	–	–
γ-Glutamyltransferase	1	283	−0.23	−5.33 to 4.86	0.928	–	–

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; LDH, lactic dehydrogenase; MD, weighted mean difference.

Table 3 Random-effects meta-analysis results between metformin and control groups for comorbidities, clinical severity, oxygen support and treatments

Outcomes	No. of studies	Sample size	RR	95% CI	*p*-value	I-squared (%)	Heterogeneity statistic (*p*-value)
Comorbidities							
Overweight	1	28	0.56	0.24–1.32	0.184	–	–
Obese	1	465	0.53	0.43–0.65	<0.001	–	–
Weight loss	1	26	0.63	0.31–1.29	0.210	–	–
Hypertension	4	5,873	0.93	0.91–0.96	<0.001	0.0	1.85 (0.603)
Heart failure	2	282	0.41	0.33–0.51	<0.001	0.0	0.38 (0.536)
Cerebrovascular disease	1	45	0.48	0.27–0.86	0.015		
Dementia	2	1,071	0.81	0.58–1.13	0.213	88.1	8.39 (0.004)
COPD	4	1,241	0.71	0.62–0.81	<0.001	9.3	3.31 (0.346)
Clinical severity							
Moderately ill	1	66	1.19	0.78–1.83	0.421	–	–
Seriously ill	1	207	0.98	0.84–1.13	0.768	–	–
Critically ill	1	10	0.43	0.09–1.99	0.280	–	–
Severe	1	103	0.81	0.56–1.17	0.265	–	–
Nonsevere	1	225	1.10	0.94–1.27	0.237	–	–
Oxygen support							
Ambient air	1	66	1.19	0.78–1.83	0.421	–	–
Noninvasive oxygen support	1	211	0.97	0.84–1.12	0.667	–	–
Invasive ventilation	1	9	0.62	0.13–3.02	0.551	–	–
Nasal canula	1	69	1.44	1.06–1.97	0.020	–	–
Nonrebreathing mask	1	7	0.17	0.01–2.85	0.216	–	–
High-flow oxygen	1	7	0.42	0.05–3.39	0.419	–	–
Room air	1	26	0.76	0.33–1.75	0.521	–	–
Noninvasive ventilation	1	19	0.68	0.24–1.91	0.461	–	–
Concomitant medications							
Insulin	4	3,427	0.85	0.59–1.22	0.386	96	75.33 (<0.001)
Other oral antidiabetic treatment	4	1,948	1.50	1.22–1.85	<0.001	85.8	21.06 (<0.001)
Chloroquine/hydroxychloroquine	2	80	0.75	0.31–1.83	0.522	65.4	2.89 (0.089)
Anticoagulants	4	2,977	0.70	0.53–0.94	0.015	93	42.67 (<0.001)
Glucocorticoids/steroids	4	1,948	0.80	0.56–1.16	0.240	90.7	32.14 (<0.001)
B-blockers	2	4,268	0.82	0.61–1.11	0.203	96.6	29.17 (<0.001)
Antibacterial treatment	2	1,058	1.00	0.90–1.10	0.975	0	0 (0.986)

Table 3 (*Continued*)

Outcomes	No. of studies	Sample size	RR	95% CI	*p*-value	I-squared (%)	Heterogeneity statistic (*p*-value)
Statins	3	5,698	1.15	1.05–1.27	0.004	65.4	5.79 (0.055)
Diuretics	1	989	0.69	0.63–0.756	<0.001	–	–
ARBs and/or ACE inhibitors	2	5,137	1.22	1.01–1.46	0.037	95.2	20.64 (<0.001)
Antiplatelet	2	1,999	0.91	0.84–0.98	0.010	0	0.26 (0.611)
Antivirals	3	796	1.08	1.03–1.13	0.001	0	1.24 (0.5307
Overall	33	30,325	0.95	0.86–1.04	0.276	96.8	1,008.44 (<0.001)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

Diabetes forms an important risk factor to predict the adverse outcomes.[1] Several studies have demonstrated high mortality rate in type 2 diabetes mellitus patients[1,5,6,24]; however, the effect of antidiabetics on the mortality remains to be elucidated.[25] Thus, the present meta-analysis was conducted to assess the association of metformin use with mortality in COVID-19 patients. The present meta-analysis was based on data from nine studies on COVID-19 patients. The analysis demonstrated lower mortality in the group receiving metformin; however, no significant difference in hospitalization days was observed between the two groups. The analysis also revealed significant difference in the prevalence of obesity, hypertension, heart failure, cerebrovascular disease and COPD. No significant difference was observed in clinical severity between the two groups.

Several retrospective cohort studies have demonstrated low mortality in patients receiving metformin.[15,17,24,25] In line with our findings, other meta-analysis have revealed a significantly lower mortality in patients receiving metformin.[7,26] Retrospective cohort studies have shown metformin use to be an independent factor associated with mortality.[16,20] However, retrospective cohort studies have revealed no difference in hospitalization days.[20,21] Additionally, no difference in the clinical severity between the groups receiving and not receiving metformin was revealed in retrospective cohort studies.[15,21] Furthermore, retrospective cohort studies have reported a lower number of patients with obesity,[17] hypertension,[17,22] heart failure,[19,22] cerebrovascular disease,[19] and COPD[22] in patients receiving metformin.

The potential mechanisms underlying the reduction of mortality by metformin in COVID-19 patients remain unclear.[7] However, several mechanisms have been proposed for the same. Metformin is thought to increase the expression of angiotensin converting enzyme 2 (ACE2),[2,27–29] a receptor for severe acute respiratory syndrome coronavirus 2.[2] Metformin has been demonstrated to activate adenosine monophosphate-activated protein kinase (AMPK) in in vitro and in vivo experiments,[2,7] thus regulating ACE2 and protein stability.[2] Activation of AMPK further leads to the inhibition of nuclear factor kappa B (NF-kB), which is a transcription regulator involved in inflammation. Inhibition of NF-kB subsequently inhibits the production of proinflammatory cytokines, such as interleukins 8 and 1α.[7] Metformin is also suggested to have antithrombotic effects. Evidence suggests excessive inflammatory responses as well as disseminated thromboembolic events are associated with increased mortality in COVID-19 patients.[30] Therefore, metformin is suggested to have beneficial effect by its antifibrinolytic activities[30] and inhibiting the cytokine storm in COVID-19 patients.[7] Additionally, metformin induces autophagy, thus controlling inflammation and activating innate and adaptive immunity.[31] Furthermore, metformin is suggested to act on Na^+/H^+ exchangers and vacuolar ATPase, subsequently inhibiting viral infection by raising the cellular pH leading to interference with the endocytic cycle.

This study had several limitations. A small number of studies have been included in the meta-analysis; retrospective cohort studies were included, and substantial heterogeneity was observed among the studies, which poses a significant limitation for the conclusions drawn. Although an extensive search was done, studies might have been missed inadvertently. Exclusion of studies in languages other than English might have resulted in missing of relevant studies.

Conclusion

To conclude, our findings suggest that metformin may contribute to reduced mortality in COVID-19 patients. However, randomized studies demonstrating the effects of metformin in COVID-19 are needed to support clinical recommendations of metformin in high-risk population. Further investigations are warranted to look into the likelihood of metformin improving prognosis of COVID-19.

Authors Contribution

All the authors contributed in conception or design. RP, PM, and RL contributed in acquisition of data. RB and NA contributed in data analysis and interpretation. All the authors contributed to the preparation of manuscript or critically revising the manuscript and gave their final approval for the manuscript.

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Conflict of Interest
None declared.

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Adherence and Cost Effectivity of Home-Based Prophylaxis Over Institutionalized Prophylaxis in Patients with Hemophilia

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Abstract

Purpose: Home-based prophylaxis in hemophilia facilitates the treatment of patients with hemophilia (PwH) at home resulting in an improved quality of life, experiencing less pain and greater flexibility in daily activities. This literature studies the cost effectivity and adherence to prophylaxis treatment after the implementation of home-based prophylaxis therapy in PwH registered under the Hemophilia Treatment Centre (HTC) of Assam Medical College and Hospital.

Materials and Methods: PwH and their parents were advised for self/home infusion after being trained by a medical professional for 6 months. Data were collected on the skip in prophylaxis treatment by PwH and their traveling cost to access the prophylaxis treatment before and after the implementation of home infusion, through questionnaire and telephonic interview.

Results: The mean number of days of skip in prophylaxis was significantly reduced from 25 (±11) to 4 (±2) days after implementation of home infusion. The mean transportation cost was also found to be significantly decreased from Rs. 3297 (±2251) to 440 (±279). Before home/self-infusion, 77% of the registered PwH were found to skip prophylaxis doses more than 12 times a year but after home infusion, no PwH were found to skip more than 12 doses a year.

Conclusion: Home therapy facilitates the PwH to strictly adhere to the prophylaxis regime significantly reducing the skipping of doses to be administered to the PwH. The risks of regular traveling and the burden of transportation expenditure to avail the prophylaxis treatment was also found to be reduced significantly.

Keywords
- home care
- self-infusion
- prophylaxis treatment
- economic and traveling burden

Introduction

Hemophilia, a sex-linked inherited disorder characterized by recurrent bleedings due to the deficiency of clotting factor VIII (hemophilia A) and IX (hemophilia B) in blood, manifests mostly in males though it is occasionally seen in females too. In one-third of the cases, spontaneous mutation has been reported. Frequent bleeding into the joints, muscles, or soft tissues may cause severe problems which may later cause serious disabilities in the joints. Excessive bleeding following

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trauma and surgery can be life threatening. Hemophilia is treated with factor concentrate according to the deficient factor in the blood. Treatment may be on demand but prophylaxis therapy minimizes the chances of emergency bleeding, pain and disability. Hemophilia treatment needs lifelong clotting factor replacement.[1] Prophylaxis therapy is the gold standard and home therapy particularly empowers patients with hemophilia (PwH) with effective management.[2] The World Federation of Hemophilia (WFH) guidelines recommend home management for PwH where appropriate and possible.[1] Home treatment refers to the prevention, evaluation, and treatment of bleeding at home by the PwH or their family members. It facilitates immediate and early treatment, reducing pain and the risk of deformity and hospitalizations associated with complications.[3,4] Intravenous infusion of factor concentrate is one of the most important home therapies. Early treatment of bleeds due to home infusion can reduce the long-term effect of joint haemorrhages.[5] Another problem of treating hemophilia is the burden of huge expenses the patients and their family members has to bear to avail the treatment. Of all expenses, the cost of factor concentrate is the keystone of management shares 90% of the economic load.[6] However, now a days factor concentrate are being served free for treatment by the government of various states. Thus, this issue no further seems to be a burden in the management of hemophilia. However, some other new challenges in affording the treatment comes into view that includes expenditures for medical care, transportation charges in repeated clinical visits, and non-medical home services. In our study, some of the PwH are from remote areas of Arunachal Pradesh, Nagaland, and Dimapur and they experiences financial problem in affording the transportation cost for regular prophylaxis in the Hemophilia Treatment Centre (HTC) of Assam Medical College and Hospital. Traveling long distances to avail the treatment may risk their health for which there may be negligence in the treatment. Thus, we conceptualized the idea of home therapy and later during the lockdown of 2020 due to the novel coronavirus, home therapy was aggressively up taken by almost all the PwH and their parents as it became a necessary for the continuation of regular prophylaxis at their home. This study provides an insight of implementation of self/home infusion and its impact in the adherence to the prophylaxis regime by PwH/CwH. It also focuses on the transportation cost that a PwH and their parents has to bear to avail the treatment to continue prophylaxis. Studies found that children on home treatment experienced decreased hospitalization and better adherence to the prophylaxis regime, less days of absence from school, better integration with peer groups, and less pain.[5,7,8] Adult men reported better quality of life as well, including greater feelings of self-sufficiency and self-confidence, less work absenteeism, more employment stability, and less negative emotions such as fear, anger, and depression.[9–12] In this study, we wanted to evaluate the adherence to prophylaxis treatment in PwH after implementation of home infusion therapy. We also wanted to evaluate the cost effectivity of home infusion therapy.

Materials and Methods

This is a retrospective study conducted over a period of 5 years with 94 PwH registered under HTC of Assam Medical College and Hospital. The HTC of Assam Medical College includes a team of hematologists, pediatricians, trained nurses, social workers, physiotherapists, orthopedists, and dentists to provide necessary care to the PwH. OPDs are conducted bimonthly, where necessary treatments were provided to the PwH/CwH. Factor concentrate doses are provided to them for the treatment of bleed and continuation of prophylaxis regime.

The study included 94 subjects registered under Hemophilia Treatment Center (HTC) of Assam Medical College and Hospital, undergoing prophylaxis treatment, aged between 8 and 35years. All subjects and their parents were trained for self or home infusion by trained medical professionals at HTC for 6 months. PwH were trained for self-infusion, and the parents of CwH were trained to infuse their child as per the calculated dose prescribed by doctors of HTC. In case of any emergency bleeding, the PwH and their parents were advised to infuse factor at the very first suspected sign of clinical bleeding. Along with factor infusion, the PwH and their parents were also trained for appropriate documentation of the treatment records of factor dosage used, correct storage, and handling of the products, careful preparation of factor concentrate and disposal of infusion equipment. During the training period, positive home therapy experiences were shared among the PwH and their family members to increase their self confidence in executing home therapy and function effectively in the face of any emergency. The PwH and the parents were first allowed for infusion under the supervision of medical professionals and after four or five successful infusion at HTC, they were supplied with the required amount of factors for home infusion. Data were collected based on a questionnaire and telephonic interview for doses of factor used by them for prophylaxis in HTC or local medical centers before they were being trained for home infusion. Proper consent was obtained from each PwH after providing the detailed information about the study. A questionnaire was prepared that included personal history, family history, socioeconomic status, travel details, details of financial expenditure incurred during hospital visits, joint bleeding (ABR-annual bleeding rate), HJHS (hemophilia joint health score), functional assessment that were obtained from each PwH enrolled for the study. Records of self/home infusion were obtained from the record book maintained by the PwH and their parents when they perform factor infusion at home according to the provided prophylaxis regime by the physician. Bleeding rates and cost of transportation per prophylaxis treatment in HTC were also recorded by the PwH. Transportation cost was calculated by taking into account the cost of transport per unit distance travelled in rupees per month. Records of the skip in prophylaxis treatment were collected from the maintained records books of the PwH/CwH. Although PwH executes home therapy after proper training, all the PwH were called at least once every month to the treatment center for clinical

examination by doctors, physiotherapists, dental surgeons to minimize any possible internal bleeds or to improve the joint health. Orthopedic expert opinion was taken on individual case-based issues as and when needed.

Statistical Analysis

Statistical analysis was done using SPSS 16 (available at the institution where the study was carried on). Data have been summarized as mean and standard deviation for numerical variables and numbers (percentage) for categorical variables. Chi square test and paired - sample *t*-test were used for the test of significance between two groups. Probability (p) value <0.001 was considered statistically significant.

Results

Distribution of studied population across Assam and nearby states (Arunachal Pradesh and Nagaland) was shown in the map by Google My Maps (►**Fig. 1**). During the study period, 77% of the PwH were found to involve actively in home infusion by 2020 (►**Table 1**), out of which 43% were involved in self infusion of factor, i.e., the PwHs of this category could inject factor concentrates by themselves. They usually included school going children and teenagers. Also, 34% depends on their family members (parents, guardians, etc.) for factor infusion at home, and they were categorized as the PwH with home infusion. They included mostly the small children. Rest 23% had to depend on health professionals to avail the treatment (►**Fig. 2**). After the implementation of home therapy, a significant reduction in transportation cost was seen. Before the practice of home infusion, the mean cost of transportation to avail the treatment was Rs. 3297 (2251), which got significantly reduced to Rs. 440 (279) (►**Table 2**).

Table 1 Table showing the implementation of home Infusion in the above years

Year	% of implementation of Home/self-infusion
2016	2
2017	4
2018	5
2019	9
2020	77

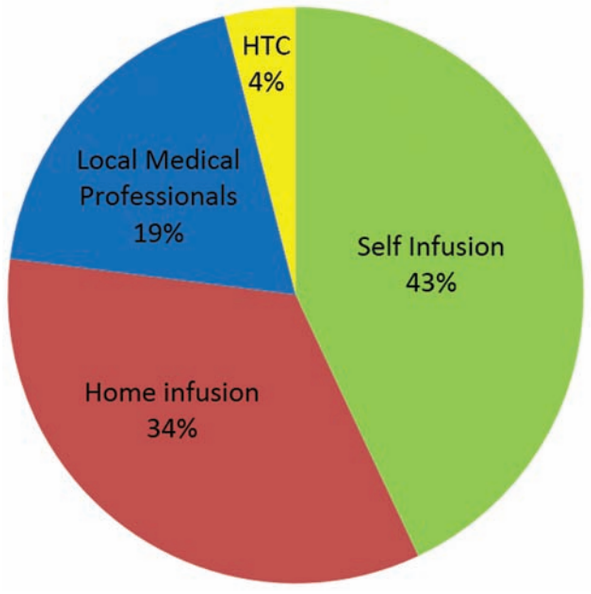

Fig. 2 Proportion of PwH undergoing prophylaxis treatment based on factor infusion.

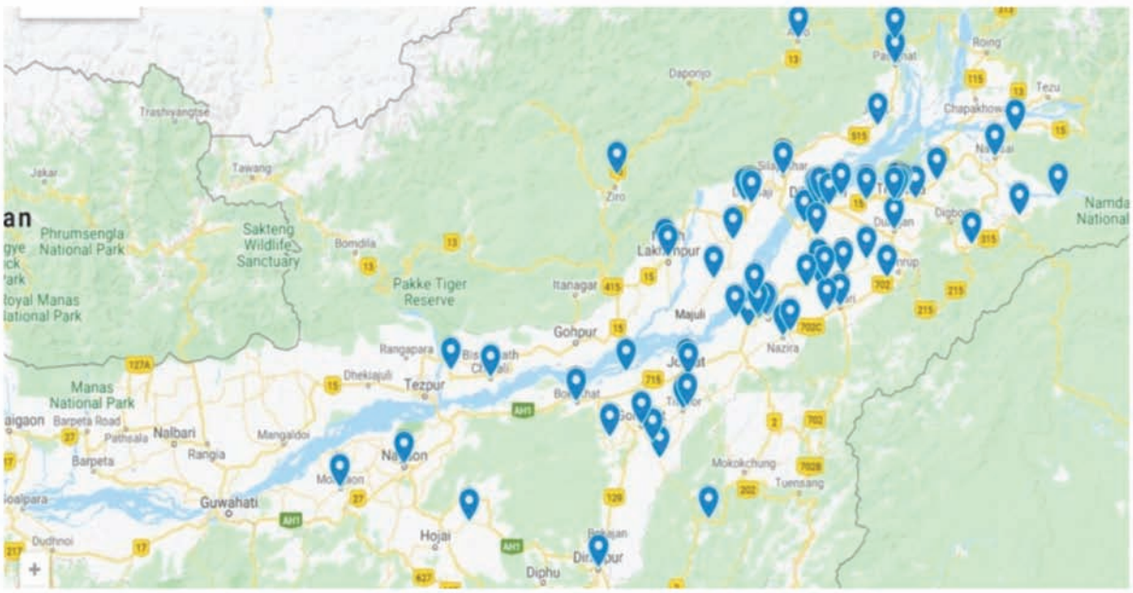

Fig. 1 Geographical distribution of patients across upper Assam and neighboring states (Arunachal Pradesh and Nagaland). Google My Maps: Google LLC, Amphitheatre Parkway, Mountain view, CA 94043, USA.

Table 2 Mean and standard deviation of transportation cost and skip in prophylaxis treatment before and after implementation of home infusion

Parameters	Before home infusion Mean (±SD)	After home infusion Mean (±SD)	*P*-value
Skip in day of prophylaxis treatment	25 (±11)	4(±2)	<0.001
Transportation cost in Rupees	3297(±2251)	440(±279)	<0.001

Note: Values are presented as mean (±standard deviation).
p-Value calculated by paired simple *t*-test.

Also, 48 (51%) of the registered PwH has an expenditure of more than 2400 rupees per month in receiving prophylaxis treatment while after home infusion, no PwH were found to expend more than Rs 2400 in a month in transportation to continue prophylaxis and 83 (88%) were found to expend below Rs 800, which was the minimum transportation cost per distance that a PwH has to bear (►**Table 3**). It is because regular visit to the HTC for prophylaxis factor infusion was not required after the implementation of home infusion. Earlier PwH/CwH solely depend on medical professionals, and they visit HTC twice a week along with their parent or relative for factor infusion for which the cost of transportation was very high but after implementation of home infusion their visit to HTC got reduced to once a month, which significantly reduced the cost.

Home infusion also reduced the number of days of skip in prophylaxis treatment, significantly from 25 (11) days to 4 (2) days (►**Table 2**). Also, 56 (60%) of the subjects did not skip any prophylaxis doses after the implementation of home infusion, strictly adhering to the prescribed treatment regime (►**Table 4**). Then, 72 subjects were found to skip prophylaxis treatment prescribed by the physician more than 12 times a year before the practice of home infusion whereas after implementing it, no subjects were found to skip more than 12 prophylaxis treatment in a year. This indicates that home-infusion facilitated the PwH/CwH to stick to the prophylaxis regime more strictly, skipping less doses. However, it can be seen from the table that 38 (40%) studied subjects were still found to skip doses of prophylaxis treatment, with a maximum of one to three skip per year by 21 (22%) PwH/CwH.

Discussion

The benefits of prophylaxis treatment in decreasing the bleeding rates, joint damage, and improving the quality of life are dependent on adherence to the prescribed treatment regimie.[13–15] Patients with low adherence rates are found to experience more bleeds.[16] Although home infusion has improved the quality of life of these PwH to a large extent but still it could be seen that 19% of PwH are still dependent on medical personnel and 4% still visits HTC for factor infusion. This may be due to the lack of confidence due to failed venipunctures and insufficient knowledge in using the venous access device. Some PwH also stated that they were

Table 3 Transportation fare in PwH before and after implementation of home infusion

Transportation cost (Rs)	No. of PwH, before implementation of home infusion, *n* (%)	No. of PwH, after implementation of home infusion *n* (%)	*p*-Value
₹0-₹800	11 (12)	83 (88)	<0.001
₹801-₹1600	13 (14)	9 (10)	
₹1601-₹2400	22 (23)	2 (2)	
more than ₹2400	48 (51)	0 (0)	
Total	94 (100)	94 (100)	

Note: Values are presented as number and percentage.
p-Value calculated by chi-square test.

Table 4 Skip in prophylaxis doses before and after implementation of home infusion

(Number of Skip/year)	No. of patient undergoing prophylaxis at HTC *n* (%)	No. of patient undergoing prophylaxis at home *n* (%)	*p*-Value
No skip	0 (0)	56 (60)	<0.001
1-3 skip	1 (1)	21 (22)	
4-6 skip	4 (4)	6 (6)	
7-9 skip	3 (3)	5 (5)	
9- 12 skip	14 (15)	6 (6)	
More than 12 times skip	72 (77)	0 (0)	

Note: Values are presented as number and percentage.
p-Value chi square test.

afraid of self-infusion without proper guidance. However, literature shows nonadherence to prophylaxis treatment regime may be intentional where patients makes a deliberate decision of not taking factors or it may be unintentional usually due to forgetting.[16] PwH with mild bleeding phenotypes suffer from less bleeds and therefore they are more relaxed and less concern about the treatment and the possible severe outcome of illness.[17]

Another critical challenge of skipping prophylaxis is the cost of treatment, which also proved to be one of the significant barrier.[18] PwH intentionally skip prophylaxis treatment to reduce the economic burden. Socioeconomic factors including family size, family structure, social support, income, literacy, and culture norms also affects the family's ability to understand the disease and its consequences and patient willingness to accept treatment recommendations.[19]

These challenges can be overcome by repeated education about the need of prophylaxis treatment for improving the disease consequences. Self-care and home infusion must be promoted for better adherence to the prophylaxis treatment and management of bleeding episodes. Continuous practice of self-infusion under the supervision of medical professionals, adequate education, training, and support from HTC can encourage them to take responsibility for their own health and risk behaviors. Patient awareness camp should be done to advocate the PwH and their family members about hemophilia to access the safe and effective treatments and benefits of the prophylaxis treatment and how the strict adherence to it can help the PwH to lead a normal and healthy life.

The families of PwH in the study were seen to approve the benefits of training for home therapy. They believed home infusion facilitated early treatment minimizing the emergency problems and their life are better controlled than before. During the ongoing pandemic and prevailing lockdown, the PwH and their parents were bound to self-infuse the factor concentrates and thus could minimize their bleeding episodes to a great extent. Studies also showed that the number of hospitalization due to emergency bleeds decreases after implementing the home infusion of factors.[4] Previous study on regular prophylaxis showed less absenteeism from work and school, more active social participation, and more employment stability in PwH.[20,21] Home infusion was also found to be cost beneficial to the PwH and their families. It substantially reduced the transportation cost that PwH has to bear for prophylaxis treatment at HTC. PwH from remote and distant areas found difficulties in travelling mainly during active bleeds, which compelled them for home infusion. Earlier PwH were found to travel twice a week to receive their prophylaxis doses, which substantially reduced to once a month after full implementation of home infusion.

A 2-year crossover study of home versus hospital-based treatment in 36 children with hemophilia A and B found that more products were used during home care and that it was given with significantly shorter delay from the onset of bleeding.[22] Children missed only 2.5 days of school for each bleeding episode treated at home, compared with 6.2 days for hospital-based care.[3] Studies demonstrated the success of home therapy in reducing the bleeding episodes that have created a boon to the life of PwH.[5,7,8,21]

For effective implementation of home infusion for a better quality of life, hemophilia nurses could set the example of those patients and families as peer educators who had carried out better home therapy and conduct peer education focused on experience-sharing. Peer-based home therapy education may compensate for the lack of confidence and doubts and therefore may be an appropriate approach to promote the self/home infusion in these PwH.

Home infusion facilitated a cost beneficial treatment. Repeated visit to HTC for prophylaxis is a burden to PwH and their families. Distance and cost are the barriers for most of the PwH belonging to the remote areas during emergency bleed and they found home infusion has helped them to reduces the time of treatment and cost of transportation they have to bear for continuing prophylaxis treatment.

The burden of routine traveling for prophylactic infusion of factor concentrates during the pandemic of COVID 19 was reduced due to home infusion. Most PwH could perform home/self-infusion with ease. Home infusion training increased the confidence level of the patient and their parents as they became a part of the treatment. Although home infusion/self-infusion was mainly adopted as the only way of treatment during the pandemic but this strategy was continued to be encouraged by our treatment center for their obvious benefits in number of ways. A routine monthly checkup of each PwH by the health experts of HTC also helped them to reduce the emergency bleeding episodes and improved the joint bleeds. Moreover, by adopting home infusion of factor concentrates, these PwH became proactive and also encourage new PwH and their family members to execute home therapy, which can benefit them to a great extent at the time of emergency and lead a normal healthy life.

Conclusion

Home management care in hemophilia improves the quality of life in PwH as it helped in better adherence to the treatment regime that resulted in less pain and greater flexibility in daily activities, less financial burden, less absenteeism from school and work, and can engage more actively on their daily activities without the fear of being bleeding unconsciously.[5,7,8,21] The success of home infusions shifted the dependency of PwH on health professionals to their family members and also reduced the expenditure cost, time, and potential risk of health of PwH belonging to distant area. Although similar studies were carried out in different parts of the world but the results of this study will reinforce such treatment options in difficult areas such as hilly and remote areas of North Eastern part of India.

Author's Contribution

All authors have substantive intellectual contributions to this study.

Anupam Dutta contributed to the planning and conducting the study.

Dipjyoti Boruah contributed to the collection of data and preparation of the manuscript.
Angshuman Boruah contributed to statistical analysis.
Arijit Das contributed to the collection of data.

Statement of Institutional Review Board Approval

Research of the following manuscript has been approved and recommended by Institutional Ethics Committee (H), Assam Medical College, Dibrugarh. (Reg. No. ECR/636/Inst/AS/2014) on September 22, 2021. For authentication, the document of recommendation by institutional ethics committee has been attached in the PDF format.

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Conflict of Interest

None declared.

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A Study on the Impact of Diabetes Mellitus on the Severity of COVID-19-Associated Mucormycosis

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Abstract

Objectives: Diabetes mellitus (DM) seems the most common predisposing factor for rhino-orbito-cerebral mucormycosis (ROCM). This study aimed to study the impact of DM on the severity of COVID-19-associated ROCM (CAM).

Methods: This was a retrospective analytical study performed over a period of 3 months to assess the impact of DM on the severity of CAM in 100 patients and association of clinical correlates of DM with severity of CAM.

Statistical analysis: The data collected using the study tools were converted into a computer-based spreadsheet and analyzed. The statistical analysis comprised a descriptive analysis that involved calculating means, standard deviations, and proportions. For calculating the significance of the difference of mean between two groups, Student's *t*-test was applied. In addition, chi-square test (or Fisher's *t*-test if applicable) was applied to study the significance of association of clinical correlates of DM with severity of CAM for categorical variables and *t*-test for continuous variables.

Results: The prevalence of DM was 67%. The average presenting blood sugar level was 245.9 ± 99.86 mg%. Glycated hemoglobin level between 4.5 and 6.5% was observed in 57 patients and over 6.5% in 43 subjects. A high body mass index (BMI) of 25 and above was noted in 52 patients. A significantly higher level of presenting blood sugar and a longer duration of hospital stay was noted in patients having stage 3b or higher ($p < 0.05$) when compared with those having stage 3a or below. No significant correlation was observed in patients in stage 3a or below and those presenting with stage 3b or higher in terms of BMI, waist to hip ratio, or total cholesterol levels. There

Keywords
- ROCM
- COVID-19
- orbital mucormycosis
- diabetes mellitus
- corticosteroids

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was a strong correlation between blood sugar level at presentation, severity of DM with the severity of ROCM, and a strong inverse correlation noted between HDL level and severity of ROCM.

Conclusion: A poor metabolic control is associated with a higher risk of a severe disease with intracranial involvement.

Introduction

A recent increase in the number of cases of rhino-orbito-cerebral mucormycosis (ROCM) amidst the COVID-19 pandemic is a matter of concern. Most cases were observed in patients suffering from diabetes mellitus (DM) especially in the ones who had poor metabolic control of diabetes and/or had severe underlying COVID-19.[1] Mucormycosis is a potentially fatal disease characterized by vascular invasion due to saprophytic fungi that belong to the order Mucorales. The fungus is ubiquitously present in the environment, flourishes in the Indian soils, and therefore India has the highest number of cases of mucormycosis in the world with a prevalence of 0.14 cases per 1000 population.[2]

Rhizopus arrhizus (most common), *Rhizopus microspores*, and *Rhizopus homothallicus* are among the common species responsible for causing mucormycosis in India and the rest of the world.[3] The commonest type of mucormycosis observed in India include ROCM (45 – 74%), followed by cutaneous form (10 – 31%), pulmonary (3 – 22%), gastrointestinal (2 – 8%), disseminated and renal type (0.5 – 9%).[3] However, rhino-orbital (ROM) and ROCM account for the majority of cases (89%) of mucormycosis presenting in India amidst the COVID-19 pandemic. Pulmonary and disseminated types are also observed (10%).[4,5]

A recent study by John et al reported a series of ROM in patients who were documented to be nondiabetic prior to contracting COVID-19 and later diagnosed with diabetes mellitus of recent onset. Diabetes mellitus was uncontrolled in about 67% of the patients and 94% of the patients had a mean glycated hemoglobin (HbA1c) of 10% reflecting a poor control of DM. Mucormycosis is aptly addressed as diabetes-defining illness. Recently, it was reported that about 77% cases of ROCM are observed in patients diagnosed with diabetes mellitus.[3] Data from 18 countries reiterated the fact that diabetes is the predominant risk factor (95.2%) responsible for causing COVID-19 associated rhino-orbito-cerebral mucormycosis (CAM) cases in India, with uncontrolled or poorly controlled diabetes (80.3%) being the commonest presentation and diabetic ketoacidosis (DKA) was observed in 41% of cases.[6] A systematic review of 101 cases of CAM further strengthened the observation that the majority (81%) of the cases were from India and 83% of the subjects had underlying hyperglycemia at presentation. Diabetic ketoacidosis was seen in 15% of the cases. Also, 76.3% of the patients received corticosteroid therapy for treatment of COVID-19.[7]

Materials and Methods

This study aimed to evaluate the impact of DM and its clinical correlates on the severity of CAM. The primary objective of the research was to assess the prevalence of DM in patients with CAM. The secondary objective was to assess the impact of diabetes mellitus on the severity of CAM and determine the association of clinical correlates of DM with the severity of CAM. The study was conducted in the Department of Ophthalmology, Department of Medicine, and Department of Otorhinolaryngology at a tertiary care center in Delhi. The records of the patients who got admitted between August 2021 and October 2021 were analyzed. This was a retrospective, analytical study. Institutional Ethics Committee–Human Research (IEC-HR) approval was taken and subject confidentiality and anonymity was maintained in all cases. The study was conducted according to the principles of the Declaration of Helsinki. There are no conflicts of interest or financial disclosures. The patients included in the study comprised confirmed cases/suspected cases of COVID-19 who presented with either clinical, radiological, microbiological, cytopathological, or histopathological evidence suggestive of mucormycosis. The patients excluded from the study were those with no clinical, radiological, microbiological, cytopathological/histopathological evidence suggestive of ROM; patients with HIV-positive status; patients on any form of immunosuppression including cancer chemotherapy and those under the age of 18 years.

All hospital records of subjects fulfilling the inclusion criteria over a time period between August 2021 and October 2021 were retrieved and studied. Hospital records with only complete information on the variables of interest of the current study, with no missing data, were analyzed eventually. There was no sampling involved. The number of such case records during the stipulated period was approximately 100. The patients were placed in two groups based on the severity of mucormycosis for the purpose of statistical analysis. The groups were divided into stage 3a and below and those with stage 3b (diffuse orbital involvement) and/or higher. Further patients with nasal and/or sinus involvement (Stages 1 and 2 as per classification—less severe variety) were compared with those presenting with orbital and/or intracranial extension (Stages 3 and 4), being the more severe variety. The diagnosis of DM was decided on the basis of patient history or the HbA1c values. The diagnosis of Diabetes was done as per American Diabetes Association (ADA) guidelines- Fasting blood sugar (FBS) $\geq$ 126 mg/dL, 2 hours post prandial blood sugar (PPBS) $\geq$ 200 mg/dL or HbA1c $\geq$ 6.5%.[8] The recent onset diabetes mellitus was defined as FBS $\geq$ 126 mg/dL or 2 hours PPBS $\geq$ 200 mg/dL, which was diagnosed first time during the present illness with a negative history of diabetes or a history of normal glycated hemoglobin level and no history of steroid use.[9] The steroid

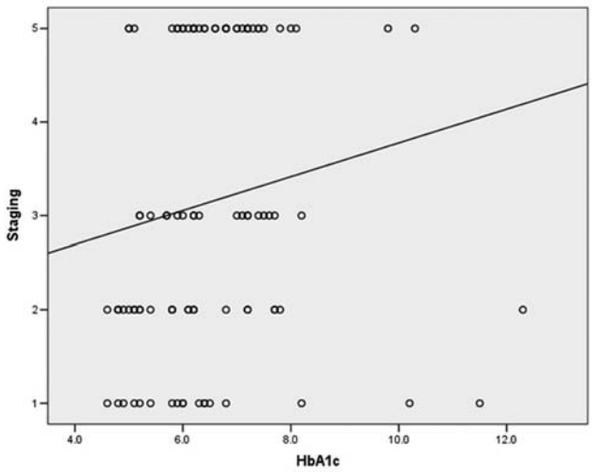

Fig. 1 Correlation between severity of diabetes (as measured by the HbA1c level) and severity of Rhino-orbital mucormycosis (as measured by the stage).

induced diabetes mellitus was diagnosed as FBS $\geq$ 126 mg/dL or 2 hours PPBS $\geq$ 200 mg/dL diagnosed first time during the present illness with the history of use of steroids with no prior history of diabetes or raised glycated hemoglobin levels.[10]

Clinical history of the cases including history of COVID-19, comorbidities were obtained as per records. General physical examination including blood pressure, measurement of body mass index (BMI), waist circumference as clinical correlates of diabetes were tabulated based on the records. Reports of the routine biochemical test including glycemic control indices (fasting blood sugar, postprandial blood sugar, HbA1c), serum lipid profile, and HIV status of the cases was retrieved from records. The severity of mucormycosis was staged based on the classification proposed by Honavar et al.[11]

Stage 1 (1a, 1b, 1c) had involvement of the nasal mucosa
Stage 2 (2a, 2b, 2c, 2d) had involvement of the paranasal sinuses
Stage 3 had orbital involvement:
Stage 3a- Nasolacrimal duct, medial orbit, vision unaffected; 3b-diffuse orbital involvement, vision unaffected;
Stage 3c-central retinal or ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of the superior or inferior orbital fissure, orbital apex with loss of vision; Stage 3d-bilateral orbital involvement
Stage 4-had involvement of the central nervous system (CNS) with the disease.

The outcome measures of the study were ascertained based on the difference in severity grading of CAM at presentation among patients with DM and those without diabetes. Further the hospitalization duration, requirement of critical care, surgical intervention, and mortality between the patients with DM was studied.

Statistical analysis: The data that were collected using the study tools were converted into a computer-based spreadsheet and analyzed. The statistical analysis comprised a descriptive analysis that involved calculating means, standard deviations, and proportions. For calculating the significance of difference in the mean HbA1c level between the groups based on the severity of CAM, Student's *t*-test was applied. In addition, chi-square test (or Fisher's *t*-test if applicable) was applied to study the significance of association of clinical correlates of DM with severity of CAM for categorical variables and *t*-test for continuous variables.

Results

The prevalence of diagnosed DM was 67% in this study, ignoring the recent onset and the steroid induced DM ($n = 11$). All diagnosed DM patients were of type 2 DM and the average duration of diabetes was 3.78 years (30.4 days–-24 years). Twenty-two subjects were not diabetic. Out of a total of 100 patients (male-61, female-39) included in the study population with an average age of 52.1 $\pm$ 11.29 years (25 to 78 years), 31 were aged 60 years or above (geriatric population) and 69 were under the age of 60 years. ►**Table 1** shows the demographic profile of the patients. Stage wise distribution was performed based on the staging criteria in 100 patients (stage 2-18, stage 3a-25, stage 3b-19, stage 3c-23, stage 4-15). Positive history for COVID-19 or positive testing on RTPCR/RAT was observed in 49 patients. Thirty-five patients had a history of steroid consumption for COVID-19. Sixty-four patients were receiving oral hypoglycemic medications, three were on insulin and six were on combination therapy of both oral medications and insulin for control of the blood sugar levels. Recently diagnosed DM or DM as a result of steroid administration was noted in three (27.3%) and eight (72.7%) patients respectively. The average presenting blood sugar level was 245.9 $\pm$ 99.86 mg% (100–578 mg%). Glycated hemoglobin level between 4.5 and 6.5% was observed in 57 patients and over 6.5% in 43 subjects. The average HbA1c level in 100 patients was 6.5 $\pm$ 1.37% (4.6–12.3%). ►**Figure 1** shows the correlation between the severity of diabetes as measured by the HbA1c level and the severity of ROCM as measured by the stage. Body mass index (BMI) of 25 and above was considered as being overweight that got observed in 52 patients. Total cholesterol, high density lipids and serum triglycerides were raised in 2, 100, and 38 patients, respectively. Based on the World Health Organization (WHO) criteria, a waist to hip ratio of over 102 in men and over 88 in women was considered abnormal.[12]

For Asians, a level of (men >90, female> 80) was considered as abnormal. This was raised in 53 and 98 patients based on the WHO and Asian criteria, respectively. Ninety-six patients underwent sinonasal debridement (external and/or endoscopic) and 17 were subjected to orbital exenteration. ►**Table 2** highlights the mean value for various parameters that were studied. T**able 2** also gives the correlation between severity of diabetes and severity of rhino-orbital mucormycosis and association of severity of ROM with other cofactors. Various parameters were compared for patients having stage 3a and below, i. e., stage 2 when compared with stage 3b and higher. A significantly higher level of presenting blood sugar levels (value = 0.017) and a

Table 1 Profile of patients presenting with CAM

Parameter $n = 100$	Observation
Geriatric	Yes–31, No-69
Gender	Male-61, females-39
Stage of ROCM	Stage 2-18 Stage 3a-25 Stage 3b-19 Stage 3c-23 Stage 4-15
Diabetes mellitus (DM)	Diagnosed DM- 67/100 (67%); Recent-onset and steroid induced- 11; No DM -22
Comorbidities	
Hypertension	No- 87, Yes- 13
Coronary artery disease; Hypothyroidism; Past tuberculosis; Hepatitis B; HIV	Yes- 4, No- 96; Yes-3, No-97; Yes-2, No-98; Yes-1, No-99; HIV positive -1
Positive history for COVID-19/currently positive	Yes-49, No-51
History of steroid intake	Yes-35, No-65
Type of steroid intake	Oral-9 Intravenous-19 Both Oral/IV-7
Antidiabetic medication	Oral-64 Insulin-3 Oral and insulin-6
Insulin requirement during hospitalization	Yes-83, No-17
HbA1c	Level 4.5-6.5%- 57 Level > 6.5%- 43
Body mass index (BMI)	< 25-48/100 (48%) ≥ 25-52/100 (52%)
Cholesterol > 200 High density lipid (HDL)-men > 40, female > 50 Triglyceride (TG) level >150	Total cholesterol Elevated-23 Normal-77 HDL Low levels-100 TG Elevated-38, Normal-62
Waist to hip ratio (WHO criteria) men >102, Female > 88; for Asians (men > 90, female > 80)	Following WHO criteria- Increased–53 Not increased- 47 Following Asian criteria Increased-98 Not increased-2
Treatment	
Status of treatment	Critical care-16 Routine management without critical care-84 Discharged-97 Death-3
No operative procedure Endoscopic sinonasal debridement (SND) External SND/maxillectomy Exenteration Neurosurgical procedure	No operative procedure-2 No surgery done as was unfit for Surgery-1 Endoscopic sinonasal debridement (SND)-19 Endoscopic and external SND-2 External SND/maxillectomy-59 External SND and exenteration-16
Exenteration Done	Yes-17, No-83

Table 2 Mean values for various parameters and their correlation with severity of diabetes

	Mean	Std. deviation	Minimum	Maximum
Various parameters				
Age ($n = 100$)	52.1	11.29	25	78
Interval between COVID-19 and mucormycosis for those who had known history of COVID-19 ($n = 48$)	28.0	15.48	3	65
Hospital stay for COVID-19 for those who had some hospital stay ($n = 25$)	15.6	10.66	5	45
Blood sugar at presentation	245.9	99.86	100	578
HbA1c	6.5	1.37	4.6	12.3
Total hospital stay	66.7	14.68	42	102
BMI	25.6	4.40	16.81	38.14
TG	142.8	47.57	52	315
HDL	28.1	5.50	19	45
Total cholesterol	166.0	44.52	62	280

longer duration of hospital stay ($p = 0.00$) was noted in patients having stage 3b or higher ($p < 0.05$) when compared with those having stage 3a or below. The patients with stage 3b, 3c, or 4 had a significantly lower levels of high-density lipoprotein when compared with the patients having stage 3a or below ($p = 0.020$). A significantly higher number of patients ($n = 50$ [61.7%]) who had DM had presentation with stage 3b or above ($p = 0.049$). Further the patients who had diagnosed DM [n = 42 (62.7%)] presented with stage 3b or above ($p = 0.021$). A significantly ($p = 0.005$) higher level of presenting blood sugar over 200 mg% was noted in patients (n = 40 [69.0%]) who presented with stage 3b or higher as were significantly higher levels ($p = 0.008$) of HbA1c over 6.5% ($n = 31$ [72.1%]) at presentation (►**Table 3**). No significant correlation was observed in patients in stage 3a or below and those presenting with stage 3b or higher in terms of BMI, waist to hip ratio, or total cholesterol levels. 53.5% of those with high HbA1c ($\geq 6.5\%$) were overweight (as per the WHO classification) or obese (as per recommended classification for Asian Indians, JAPI, Misra et al, 2009).[12] Also, 60.5% had central obesity, by waist circumference (by the WHO cutoffs of 102 cm for males and 88 cm for females) (98.0% if we take as per the recommended classification for Asian Indians, JAPI, Misra et al, 2009). Those with higher HbA1c were significantly more likely to have Stage > 3a (3b or higher) (72.1%) as compared to those with normal HbA1c (45.6%), *p*-value for difference = 0.008. Two deaths were reported as outcome among the 57 patients with elevated HbA1c ($\geq 6.5\%$), as compared to one death among the 43 patients with normal HbA1c. Regression analysis was performed adjusting for confounding effect of BMI and gender and it was observed that HbA1c remained a strong correlate with severity of DM.

There was no statistically significant correlation between patients who underwent exenteration when compared with their age, gender, presence/absence of DM, positive history/currently positive status for COVID-19 on testing, HbA1c levels, or HIV status ($p > 0.05$). However, when subjects presenting with stage 2 and below were compared with stage 3 and 4, the patients with stage 3, 4 had a significantly higher BMI ($p = 0.058$), waist to hip ratio ($p = 0.020$), higher cholesterol level ($p = 0.011$) and almost significantly higher levels of presenting blood sugar ($p = 0.070$). As far as the secondary objectives of the study are concerned, there was a strong correlation between blood sugar level at presentation and the severity of ROM (Spearman's rho = 0.260, $p = 0.009$) and so was a strong inverse correlation noted between HDL level and the severity of ROM (Spearman's rho = −0.237, $p = 0.018$). All ROCM patients had low HDL levels. The correlation between severity of diabetes (as measured by the HbA1c level) and severity of rhino-orbital mucormycosis (as measured by the stage) was found to be statistically significant (Spearman's rho = 0.282, $p = 0.004$). The association was direct in nature, higher HbA1c was associated with a higher stage).

Discussion

It is now established that diabetes is associated with a poor prognosis of COVID-19.[13,14] Several epidemiological studies have reported that patients suffering from diabetes mellitus are at a greater risk of getting hospitalized and also getting admitted to critical care alongwith a higher risk of mortality as a result of COVID-19.[15–17] Mortality following the COVID-19 pandemic is noted to be 1.49 to 3 times higher in the individuals suffering from diabetes.[18,19] It is also observed that individuals from black, Asian and minority ethnic (BAME) backgrounds are at a relatively higher risk of contracting SARS CoV-2 and the risk of death was also observed to be higher in the UK in those individuals suffering from type 1 and type 2 diabetes. This possibly could be a confounding factor in the regional differences and higher prevalence of CAM observed in India after the second wave of COVID-19.[20–23] Newly diagnosed DM is commonly observed

Table 3 Association between various parameters with the stage of mucormycosis

Association between different variables and stage of mucor [0- Stage 2, 3a; 1- Stage 3b, 3c, 4)					
Variable	Type of variable	Stage 2,3a		Stage 3b, 3c, 4	*p*-Value
Geriatric age (y)	Age < 60 Age ≥ 60	31 (44.9%) 12 (38.7%)		38 (55.1%) 19 (61.3%)	0.561
Gender	Female Male	16 (41.0%) 27 (44.3%)		23 (59.0%) 34 (55.7%)	0.750
Diabetes mellitus	No DM DM present	12 (63.2%) 31 (38.3%)		7 (36.8%) 50 (61.7%)	0.049
Hypertension	No Yes	39 (44.8%) 22 (44.9%)		30 (58.7%) 27 (55.1%)	0.340
Positive history for COVID-19	No Yes	21 (41.2%) 62 (63.9%)		Yes- 75 (64.1%) Yes- 35 (36.1%)	0.707
Whetder received steroids	No Yes	26 (40.0%) 17 (48.6%)		39 (60.0%) 18 (51.4%)	0.409
Diabetes mellitus	No DM Recent or Steroid induced	15 (68.2%) 3 (27.3%)		17 (31.8%) 8 (72.7%)	0.021
	Diagnosed DM	25 (37.3%)		42 (62.7%)	
Blood sugar at presentation (Random blood sugar > 200 mg %)	No Yes	25 (59.5%) 18 (31.0%)		17 (40.5%) 40 (69.0%)	0.005
HbA1c	4.5-6.5% >6.5%	31 (54.4%) 12 (27.9%)		26 (45.6%) 31 (72.1%)	0.008
BMI	< 25 ≥25	18 (37.5%) 25 (48.1%)		30 (62.5%) 27 (51.9%)	0.286
Waist to hip ratio Men >102, Female> 88	Normal High	19 (40.4%) 24 (45.3%)		28 (59.6%) 29 (54.7%)	0.624
Total cholesterol	<200 >200	33 (42.9%) 10 (43.5%)		44 (57.1%) 13 (56.5%)	0.958
	Staging [Stage 3a and below (0) when compared witd Stage 3b and higher (1)]	***N***	**Mean**	**Std. deviation**	***p*-Value**
Blood sugar at presentation	0	43	218.67	98.976	0.017
	1	57	266.53	96.338	
HbA1c	0	43	6.270	1.7013	0.101
	1	57	6.725	1.0334	
Total hospital Stay	0	43	60.86	12.176	0.000
	1	57	71.21	14.929	
BMI	0	43	26.1342	4.29388	0.385
	1	57	25.3553	4.50383	
HDL	0	43	29.60	5.368	0.020
	1	57	27.04	5.392	

in COVID-19 patients as reported in the literature.[24,25] A systematic review and meta-analysis of eight studies is reported with regard to the proportion of newly diagnosed diabetes in COVID-19 patients.[26] Newly diagnosed diabetes in this study was defined as new-onset diabetes without any prior history of diabetes with fasting plasma glucose (FPG) ≥ 7.0 mmol/L or random blood glucose (RBG) ≥ 11.1 mmol/L and HbA1c < 6.5% or previously undiagnosed diabetes (FPG ≥ 7.0 mmol/L or RBG ≥ 11.1 mmol/L and HbA1c ≥ 6.5% or HbA1c ≥ 6.5% only.[27] This is supported by reports showing exceptionally high insulin requirements in severely or critically ill COVID-19 patients with diabetes.[24,28] There exists a complex mechanistic and clinical interplay between DM and COVID-19.

The management guidelines for the treatment of COVID-19 seem nonuniform in different centers/regions of the country. This is reflected in routine clinical practice where patients with different severity of COVID-19 receive intravenous and oral steroids where the same may not be warranted.[29–31] Although dexamethasone gave a survival benefit by reducing mortality in the patients affected with COVID-19, the administration of corticosteroids remains a

double-edged sword. This indiscriminate use of corticosteroids apart from other multiple factors has resulted in an epidemic of COVID-19-associated mucormycosis, specifically the cases of ROCM. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is no longer an exclusive pulmonary disease. It is shown to have involved the kidneys, brain, cardiovascular system (heart), eyes in the form of conjunctivitis, gastrointestinal and other endocrine organs.[29–31]

It is reported that the destruction of the pancreatic β-cell due to infection with the SARS CoV-2 causes dysregulation of the metabolism resulting in the diabetogenic effect of the virus.[32] Involvement of the exocrine part of the pancreas presents as pancreatitis, enlargement of the pancreas, and alteration in the serum levels of amylase or lipase.[33] COVID-19 also accounts for impairment of insulin receptor signaling along with a high degree of peripheral insulin resistance. All these disturbances in the physiology of the pancreas manifest in the form of elevated blood glucose levels in previously nondiabetic individuals who contract COVID-19. At 6 months after being infected with COVID-19, an increase in the burden of DM and use of oral hypoglycemic agents (OHA) is reported.[34] Recently, studies are reported in previously non-diabetic individuals who contract COVID-19 presented with CAM and have now developed diabetes mellitus of recent onset.[35–37] A global registry (COVIDiab) is set up to characterize the uncommon features of new-onset DM that are observed in COVID-19. In series of cases published on reviewing the literature, the average age of patients is reported to be from 35.9 to 60.5 years.[37] The development of CAM in previously healthy patients who do not have underlying DM and are immunocompetent gives a pointer to the fact that there exist possibly other etiopathogenetic mechanisms that are responsible for this manifestation. Alterations in the mucosal immunity in the nasal cavity due to infection with SARS CoV-2 and loss of ciliary function causing a reduction in the nasociliary clearance might result in the proliferation of the fungal spores in the paranasal sinuses and nasal cavity, the primary sites that harbor spores of mucor.[38,39] About 90.5% of patients suffering from CAM in Egypt had underlying diabetes on admission. In another study by Singh et al that had individuals mostly from India, about 80% had diabetes mellitus and 76.3% were administered corticosteroids.[40] Dysregulation of the immune system, cytokine storm, coagulation in the microvasculature apart from thrombo-inflammation and immune exhaustion are noted as result of diabetogenic state due to COVID-19. Further, immunosuppression due to COVID-19 results in an altered function of the $CD4^+/CD8^+$ T cells and antigen-presenting dendritic cells. These factors are conducive for the proliferation of the fungus and development of ROCM.[27,41,42] Platelet-driven immunosuppression is increasingly being recognized as a key factor in the etiopathogenesis of excessive COVID-19-related systemic inflammation that results in systemic co-infections apart from generalized immunosuppression.[42,43]

The existing literature on the research conducted on dyslipidemia and COVID-19 is limited; however, it is shown that dyslipidemia may play a role in the severity of COVID-19 infection.[44] Future studies are needed. Further dyslipidemia in diabetes is observed in the form of high plasma triglyceride, low HDL cholesterol and increase in the concentration of small dense LDL cholesterol levels. A higher concentration of total cholesterol levels was noted in individuals with stage 3 and above and also was a higher mean HDL cholesterol level noted in patients with stage 3b and above. This could be a correlate of diabetes due to the associated dyslipidemia with the disease or could possibly be a result of COVID-19-associated dyslipidemia. Because the pre-COVID-19 lipid levels in these patients are not available with the authors, it seems uncertain to attribute this increase in the level of lipids to DM or COVID-19. However, it is certain that higher levels of total and HDL cholesterol were associated with a worse stage of ROCM at presentation.

High mortality amongst the affected individuals due to ROCM is known. About 60% mortality is reported despite aggressive treatment and 46% of the subjects have permanent blindness who survive.[6] Surprisingly, the mortality rate due to CAM (36.5%) is lower when compared to the literature pertaining to the Indian population prior to the COVID-19 pandemic when the mortality reported was 52%.[4] The lower mortality rate is attributable to the improvement in the diagnostic facilities and multidisciplinary management. Early sinonasal debridement is the key component of the management apart from prompt initiation of the systemic antifungal therapy, in the form of liposomal amphotericin B (10 mg/kg/day) intravenous for 6 weeks, constitutes the first-line treatment while the patient awaits surgery. If the patient is allergic to liposomal amphotericin B, intravenous/oral posaconazole (300 mg BID on day 1 followed by 300 mg/day for 6 months) is administered. Metabolic control primarily of the blood sugar levels is indispensable. Involvement of the CNS carries poor prognosis as reported in the literature.[6]

The study is novel as it highlights the occurrence of severe ROCM in patients who did not have a history of steroid consumption for management of COVID-19. Further, only one previous study exists that correlates serum lipid profile with the severity of CAM, wherein the authors concluded that a positive correlation exists between serum lipid profile and staging of ROCM and a negative correlation is observed between lipid levels with duration between onset of COVID-19 to onset of ROCM. This study concludes that a higher cholesterol level was noted in individuals presenting with a more severe stage of ROCM and a strong inverse correlation noted between HDL level and the severity of ROM wherein all ROCM patients had low HDL levels. Comparison of BMI and waist–hip ratio with severity of ROCM in this cohort of patients is also a new parameter that was evaluated. A large number of patients presenting to a single tertiary care center is also a key highlight of this research.

The results of the study show a high prevalence of DM in patients infected with mucormycosis who develop this fatal disease in the background of COVID-19. A spurt in the number of cases of ROCM to epidemic proportions was observed by the authors at the tertiary care center catering to over 300 patients who presented amidst the COVID-19

pandemic. The study was, however, limited by the fact that complete data for all patients was not available in the medical records due to the retrospective nature of the study and hence could not be evaluated completely.

Conclusions

A high prevalence of DM observed in this study reiterates that ROCM is a diabetes-defining disease and the incidence of ROCM increases in patients infected with SARS CoV-2. A poor metabolic control is associated with a higher risk of intracranial involvement. Prompt metabolic control with medical management with antifungal medications along-with sinonasal debridement with or without orbital exenteration is indispensable in reducing the mortality of the disease.

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Conflict of Interest
None declared.

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Health Literacy and Clinic-Epidemiological Profile of Patients with COVID-19-Associated Mucormycosis: A Questionnaire-Based Study

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Abstract

Background The patient partnership is desirable for the optimal management of comorbidities. This became significant more so during the coronavirus disease 2019 (COVID-19) crisis wherein health infrastructure was overburdened.

Objectives The aim of this study was to estimate the clinicoepidemiological profile, health literacy regarding predisposing risk factors, and disease management in patients with COVID-19-associated mucormycosis (CAMCR).

Materials and Methods A structured questionnaire-based study on randomly chosen 100 microbiologically proven patients of CAMCR, consisting of 38 multiple choice questions, was designed with each answer having a patient and assessor response to it.

Results A male predilection was seen (68%) with rhino-orbital (73%) being the commonest anatomic site. Forty-nine percent of the study participants had pre-existing diabetes of which 62% did not carry out regular blood sugar monitoring and in 18%, blood sugars were controlled prior to COVID-19. Thirty-five percent of patients with mild COVID-19 illness were treated with unwarranted steroids and 56% of patients had fluctuating blood sugar levels, during COVID-19 illness.

Seventy-nine percent of patients were not vaccinated against COVID-19, 16% only partially vaccinated. Seventy-one percent of patients were not aware of red flag signs and of mucormycosis with 8% presenting early, on noticing nasal symptoms.

Conclusion This study observed diabetes as the most common comorbidity in patients with CAMCR. A lacuna in the health literacy of diabetics presenting with CAMCR was found. Additionally, knowledge regarding glycemic control during COVID-19 illness with or without the use of steroids and awareness of the "red flag" signs of CAMCR were mostly lacking. Interventions to improve awareness amongst patients with diabetes should help in optimal glycemic control, and avoid potential complications like severe COVID-19 illness, and mucormycosis.

Keywords
- awareness
- diabetes
- epidemiology
- patient education

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Introduction

Mucormycosis (MCR) referred to as "black fungus" results from inhalation of fungal spores in patients with a weakened immune system.[1] The second wave of coronavirus disease 2019 (COVID-19) in India resulted in an unprecedented outbreak of MCR.

India has had the maximum disease load of MCR even in pre-COVID-19 times, although it remained largely unrecognized.[2] Rhino-orbitocerebral mucormycosis (ROCM) is the most common clinical form and diabetes mellitus (DM) is the biggest risk factor,[3] so much so that MCR has become a diabetes-defining illness.[4] It became a "notifiable disease" in May 2021.[2] India has a major global burden of uncontrolled diabetes.[5] It leads to mortality and morbidity associated with diabetes.[6] It increases the risk of COVID-19 infection and also complications. COVID-19, in turn, can induce acute-onset diabetes in some individuals with no history of diabetes.[7,8] India contributed to approximately 71% of the global cases of MCR in patients with COVID-19 based on published literature from December 2019, to the start of April 2021.[9] Diabetes has been identified as the most common comorbidity in COVID-19 patients in India.[10]

The patient partnership is desirable for optimal management of comorbidities, and health awareness for prevention and timely identification of potential disease complications. This became significant more so during the COVID-19 crisis wherein health infrastructure was overburdened.

Patients presenting early have MCR limited to the nose and paranasal sinuses and can be salvaged with antifungals accompanied by endoscopic surgery.[1,5] Owing to this, sound patient knowledge of predisposing risk factors and early symptom identification should lead to early detection and timely intervention, thereby improving patient outcomes.[5] The second wave of COVID-19 in India provided flourishing grounds for MCR.[9] Its association with COVID-19 is an entity demanding further research.

In the literature search, studies in various developing countries with a high diabetic burden reported awareness in less than half of their study participants and also highlighted the importance of patient awareness and their participation in the effective management of diabetes and prevention of its potential complications.[11,12] However, studies to assess awareness of MCR per se have been found lacking.[13]

Studies analyzing adverse health complications in diabetes revealed decreased incidence in patients where prevention and early detection of diabetes were practiced.[14]

However, studies evaluating the impact of awareness in MCR prevention among diabetic patients are deficient in literature.

In the present study, we aimed to provide a comprehensive assessment of MCR in the backdrop of COVID-19, to highlight the clinicoepidemiological profile, effect of health literacy on predisposing risk factors, and disease management in patients with COVID-19-associated mucormycosis (CAMCR), during the second wave of COVID-19 pandemic in India.

Materials and Methods

This cross-sectional study was conducted using a structured questionnaire in a tertiary care government hospital, during June-August 2021. Institutional ethics committee approval was obtained, IECHR-2021-50-S-R2, and the study was registered under Clinical Trial Registry of India, CTRI/2021/09/036452.

On the basis of a pilot study, 15 to 50% of patients had reasonable knowledge about various factors associated with CAMCR. Taking this value as reference, minimum required sample size with a 10% margin of error and 5% level of significance was 97 patients. To reduce the margin of error, total sample size taken was 100.

The formula used was:

$$N \geq (p(1 - p))/(ME/z_{\alpha})^2$$

Where, Z_{α} = value of Z at a two-sided alpha error of 5%, ME = margin of error, and p = proportion of patients who had reasonable knowledge about various factors associated with the disease.

The inclusion criteria were microbiologically proven MCR, serologically confirmed cases of COVID-19, and age group of 18 to 70 years. Exclusion criteria were MCR not associated with COVID-19, other fungal infections, and patients on invasive ventilation. One-hundred study participants were randomly chosen patients, and written and informed consent obtained. They answered a questionnaire (with 38 questions) with input from his/her attendant, if and when required. All the answers were then verified through the file and other available records by an assessor who was one of the investigators of the study. The structured questionnaire was prepared by the investigators using the existing literature on the awareness and knowledge of patients about their comorbidities and their complications. This was reviewed by senior investigators of the institutional ethics committee and a statistical validation was obtained (►**Annexure 1**). A pilot study was carried out and the questionnaire (►**Annexure 2**) was subsequently modified according to the responses obtained by the participants, so as to optimally simplify the questions for laymen and remove any ambiguity. The questionnaire was bilingual (Hindi and English) with both verbal and written consent forms. Blood sugars were defined as "controlled" when blood sugar values were 80 to 140 mg/dL before meals and less than 200 mg/dL, 2 hours after meals.

Presentation with MCR was defined as "early," when a patient presented to a clinician on noticing the symptoms of nasal cavity involvement.[5]

Awareness of symptoms of MCR was considered complete when being aware of red flag symptoms and considered incomplete if aware only of the advanced symptoms.[5] The assessor's response obtained following verification of health records, where ever available and applicable, was taken as the final response. In case of unavailability of records to verify a patient's response, the patient's response was documented and used in data analysis. In cases where neither the patient was able to recall nor the records were available to verify, the response was documented as "no records."

Statistical Analysis

The data entry was done in a Microsoft Excel spreadsheet and the final analysis was done using the Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, United States, version 21.0. Percentages were calculated for descriptive statistics. For statistical significance, a *p*-value of less than 0.05 was considered.

The inter-kappa agreement analysis was done to ascertain the association between the responses obtained from the patient and from the assessors, thereby mitigating any potential recall bias at the patient's end and also verifying the completeness of the hospital record keeping. Kappa's score derived ranged from poor to very good (0.20–1.00).

Results

The study participants were constituted of 21% young adults (18–39 years of age), 48% middle-aged (40–59 years age), and 31% old adults (≥ 60 years of age). The mean age with CAMCR was 50.85 years (24–77 years). Male predilection was seen, forming 68% of the study population. 41% of patients had wage-earning jobs, and 29% were housewives. The majority of patients hailed from upper lower (34%) and lower-middle (30%) socioeconomic strata of modified Kuppuswamy classification[15] (►**Table 1**). The most common anatomical site seen was rhino-orbital (73%; ►**Table 2**).

The most common chronic medical condition encountered was DM, seen in 49% of patients, either alone or in combination with other comorbidities (►**Table 3**). Sixty-two percent of the pre-existing diabetics in our study sample did not carry out regular blood sugar monitoring, while 38% did. Among the latter, 51% had uncontrolled blood sugars and in 18%, blood sugar was controlled. Moreover, 31% of patients were unaware of blood sugar values and also could not produce any health records (►**Table 4**). Fifty-nine percent of study subjects received systemic steroids during COVID-19 illness. Twenty-nine percent subject were unaware and did not have health record-keeping regarding steroid use (►**Annexure 2**).

The association between COVID-19 disease severity and steroid treatment was assessed by Fisher's exact test (►**Table 5**). It showed that 35% of study patients with mild COVID-19 disease were treated with systemic steroids. In addition, 45% of patients with mild disease were unaware and did not have health records to ascertain steroid

Table 1 Sociodemographic profile of study subjects

Sociodemographic characteristics	*n* (%)/ Mean ± SD
Age (years) Young adults (18–39 years age), middle-aged adults (40–59 years age), old adults (≥ 60 years age).	50.86 ± 12.67 21% 48% 31%
Gender, *n* = 100	
Male	68%
Female	32%
Occupation, *n* = 100	
Blue collar	41%
Housewife	29%
White collar	16%
Business	9%
Farmer	59%
Socioeconomic status, *n* = 100	
Upper	2%
Upper middle	28%
Upper lower	34%
Lower middle	30%
Lower	6%

Abbreviation: SD, standard deviation.

Table 2 Clinical presentations

Clinical form, *n* = 100	
Rhino	3
Cerebral	1
Rhinocerebral	2
Rhino-orbital	73
Rhino-orbital-pulmonary	10
Rhino-orbital-cerebral	11

Table 3 Chronic medical illness in study subjects

H/o Chronic medical illness, *n* = 100	%
DM1	1
DM2	33
DM2 + HTN	11
DM2 + HTN + CAD	1
DM2 + HTN + COAD	1
DM2 + HTN + HepC	1
DM2 + HTN + hypothyroid	2
HTN	5
Hypothyroid	1
No comorbidity	44

Abbreviations: CAD, coronary artery disease; COAD, chronic obstructive airway disease; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; Hep C, hepatitis C; HTN, hypertension.

Table 4 Blood sugar control among pre-existing diabetics

n = 49	%
Blood sugar controlled	18
Uncontrolled	51
No records	31

Table 5 Association of steroid treatment with disease severity

Steroid treatment	Mild ($n = 40$)	Moderate ($n = 24$)	Severe ($n = 36$)	Total	*p*-Value
No	8 (20%)	2 (8.33%)	2 (5.56%)	12 (12%)	0.001[a]
Yes	14 (35%)	16 (66.67%)	29 (80.56%)	59 (59%)	
Don't know	18 (45%)	6 (25%)	5 (13.89%)	29 (29%)	
Total	40 (100%)	24 (100%)	36 (100%)	100 (100%)	

Abbreviation: COVID-19, coronavirus disease 2019.
[a]The association between COVID-19 disease severity and steroid treatment was assessed by Fisher's exact test and was statistically significant with *p*-value of 0.001.

Table 6 Association of COVID-19 vaccination with the severity of COVID-19 illness

COVID-19 vaccination	Mild ($n = 40$)	Moderate ($n = 24$)	Severe ($n = 36$)	Total	*p*-Value
No	30(37.97%)	23(29.11%)	26(32.91%)	79(100%)	0.009
1 dose	8(50%)	0(0%)	8(50%)	16(100%)	
2 doses	2(40%)	1(20%)	2(40%)	5(100%)	
Total	40(40%)	24(24%)	36(36%)	100(100%)	

Abbreviation: COVID-19, coronavirus disease 2019.
Of the unvaccinated study participants, 37.97% had a mild COVID-19 illness and 32.91% had a severe disease.
In the fully vaccinated category (5 patients), 2 patients suffered severe disease. The association was statistically significant with a *p*-value of 0.009.

treatment in them. The association showed a statistically significant *p*-value (0.001). In 47% of the study patients, blood sugar monitoring was done during COVID-19 illness with or without a history of steroid use. In 36%, no blood sugar monitoring was done and 17% patients were unaware and had no pertaining records (►**Annexure 2**).

Fifty-six percent of study subjects had fluctuating blood sugar levels during COVID-19 illness with or without steroid use. Nine percent of them had blood sugars in the normal range. Thirty-five percent of patients were unaware of the blood sugar values and had no health record-keeping (►**Annexure 2**).

Mild and moderate COVID-19 illness was found in 40 and 24% of study subjects respectively, being severe in 36% (►**Annexure 2**). Sixteen percent of the study subjects received only 1 dose of COVID-19 vaccination and 5% had received both doses.

The association between COVID-19 vaccination status and severity of COVID-19 disease was analyzed (►**Table 6**). Of the unvaccinated, 32.91% had severe disease. In the fully vaccinated category (5 patients), two patients suffered severe disease. The association was clinically significant with a *p*-value of 0.009.

Knowledge about the initial symptoms of MCR was lacking in 71% of subjects. Eleven percent had incomplete information about the red flag signs of MCR and were aware only of the symptoms of the advanced disease, while 18% reported awareness of red flag symptoms and signs of MCR (►**Annexure 2**).

Eight percent of the subjects presented early with symptoms of MCR. Initiation of treatment within 5 to 10 days of symptom onset of MCR was done in 25% of the study patients (►**Annexure 2**). A significant *p*-value (< 0.0001) and very good kappa score (0.896) in agreement analysis regarding the onset of symptoms and initiation of treatment for MCR (►**Table 7**).

The agreement analysis between patient and assessor for blood sugar monitoring (►**Table 8**) and blood sugar control (►**Table 9**) during COVID-19 illness and or while on steroid treatment showed a significant *p*-value (<0.001) and a very good kappa agreement (0.882 and 0.714 respectively). The analysis regarding the severity of COVID-19 illness (►**Table 10**) was good ($k = 0.798$).

Discussion

The study patients presenting with CAMCR were more commonly middle-aged, males, belonging to the upper-lower class of modified Kuppuswamy classification, doing wage-earning jobs. The most frequently involved anatomical site was rhino-orbital (►**Tables 1**, **2**). DM was the most common underlying illness (►**Table 3**).

Studies have identified male predilection[2,16–19] and middle age group (45–55 years) as most commonly affected with MCR in pre-COVID-19 times similar to that for our patients with CAMCR,[16,17] as well as for other studies involving patients with CAMCR.[5,20]

Jeong et al in a global meta-analysis in non-COVID-19 times observed ROCM as the most common presentation, in 34% of patients.[11] Likewise, ROCM was also the most common clinical variant globally when associated with COVID-19 but in increasingly higher numbers, in 76%.[18] This was unlike in the pre-COVID-19 times wherein a disparate presentation was seen in the clinical distribution of MCR, with ROCM as the most common variant in developing countries,[2,17,20,21] but not the developed countries.[22]

Thus, we observed that the epidemiology and clinical form (►**Table 2**) of patients with MCR in correlation with

Table 7 Inter-rater kappa agreement between patient and assessor for the duration between mucormycosis symptom onset and initiation of treatment

Patient	Assessor							Total	*p*-Value	Kappa
	0–5 D ($n=6$)	5–10 D ($n=14$)	10–15 D (n = 20)	15–20 D ($n=10$)	20–30 D ($n=4$)	30–40 D ($n=5$)	40–50 D ($n=2$)			
0–5 D	6 (9.84%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (9.84%)	<0.0001	0.896
5–10 D	0 (0.00%)	14 (22.95%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	15 (24.59%)		
10–15 D	0 (0.00%)	0 (0.00%)	19 (31.15%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (32.79%)		
15–20 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (14.75%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	10 (16.39%)		
20–30 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.92%)	1 (1.64%)	0 (0.00%)	4 (6.56%)		
30–40 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (6.56%)	1 (1.64%)	5 (8.20%)		
40–50 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.64%)	1 (1.64%)		
Total	6 (9.84%)	14 (22.95%)	20 (32.79%)	10 (16.39%)	4 (6.56%)	5 (8.20%)	2 (3.28%)	61 (100.00%)		

Inter-kappa agreement could be carried out in 61 patients, since the pertaining health records were not retrievable in remaining 39 patients.
A significant *p*-value (< 0.0001) was derived with a very good kappa score (0.896) in agreement with analysis regarding the onset of symptoms and initiation of treatment for mucormycosis.

Table 8 Inter-rater kappa agreement between patient and assessor for blood sugar monitoring during COVID-19 illness/steroid use

Value of K	Strength of agreement
< 0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

COVID-19 were similar to that for MCR in a pre-COVID-19 era in India.[2,3,22]

DM was identified as most common underlying disease in patients affected by MCR in pre-COVID-19 times globally[2] as well as in India.[17,19] Jeong et al in a large meta-analysis showed 40 versus 73.5% diabetics globally and in India, respectively, thus, highlighting a much higher prevalence of diabetes with MCR in India.[16] Bala et al prior to the COVID-19 pandemic observed DM to significantly increase the odds of contracting ROCM.[18] Although during COVID-19 pandemic, hyperglycemia due to pre-existing DM or new-onset diabetes has been studied as most important risk factor for CAMCR even in cases outside India.[19,20]

Retrospective studies in India on CAMCR[5,23,24] noted diabetes as the single major comorbidity with Bhanuprasad et al[24] observing diabetes in 97% of CAMCR patients, 40% of which were newly detected. This is in concordance with our findings amongst CAMCR patients (►**Table 3**).

Patel et al[21] observed uncontrolled diabetes to be the most common underlying disease in 67 versus 60.4% in non-CAMCR and CAMCR, respectively. COVID-19 was the only underlying disease in 32.6% of CAMCR patients, comparable to 44% in our study (►**Table 3**). This suggests a possibility of either new-onset diabetes with COVID-19 infection since it induces a diabetogenic state[4] and also increases the risk of associated complications. Furthermore, it may have likely worsened hyperglycemia in pre-existing but undiagnosed diabetics, thereby unmasking diabetes in them[7] which could have been in high number considering abysmal health awareness among Indian population.[6] Thus, DM continues to be the most common underlying illness in MCR both with and without association with COVID-19, with a higher prevalence of uncontrolled diabetes in CAMCR.

India is the diabetic capital of the world, not surprisingly considering dismal health literacy, and health access.[9] This is

Patient	Assessor		Total	*p*-Value	Kappa
	No ($n=16$)	Yes ($n=17$)			
No	15 (45.45%)	0 (0.00%)	15 (45.45%)	<0.0001	0.882
Yes	1 (3.03%)	16 (48.48%)	17 (51.52%)		
Can't Say	0 (0.00%)	1 (3.03%)	1 (3.03%)		
Total	16 (48.48%)	17 (51.52%)	33 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be done for 33 patients since pertaining health records were not retrievable in the other 67 patients.
The agreement analysis between patient and assessor for blood sugar monitoring during COVID-19 illness and/or while on steroid treatment showed a significant *p*-value (<0.0001) and a very good value of kappa agreement (0.882).

Table 9 Inter-rater kappa agreement between patient and assessor for blood sugar control during COVID-19 illness/steroid use

Patient	Assessor		Total	*p*-Value	Kappa
	No ($n = 19$)	Yes ($n = 3$)			
No	16 (72.73%)	0 (0.00%)	16 (72.73%)	0.0002	0.61
Yes	1 (4.54%)	3 (13.64%)	4 (18.18%)		
Can't say	2 (9.09%)	0 (0.00%)	2 (9.09%)		
Total	19 (86.367%)	3 (13.64%)	22 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be carried out in 22 patients, since pertaining health records were not retrievable in the remaining 78 patients.
The agreement analysis between patient and assessor for blood sugar control during COVID-19 illness and/or while on steroid treatment showed a significant *p*-value (<0.0002) and a good value of kappa agreement 0.61.

Table 10 Inter-rater kappa agreement between patient and assessor for the severity of COVID-19 illness

Patient	Assessor				*p*-Value	Kappa
	Mild ($n = 24$)	Moderate ($n = 17$)	Severe ($n = 27$)	Total		
Mild	22 (32.35%)	5 (7.35%)	2 (2.94%)	29 (42.65%)		
Moderate	1 (1.47%)	12 (17.65%)	0 (0.00%)	13 (19.12%)		
Severe	0 (0.00%)	0 (0.00%)	25 (36.76%)	25 (36.76%)	< 0.0001	0.798
Can't say	1 (1.47%)	0 (0.00%)	0 (0.00%)	1 (1.47%)		
Total	24 (35.29%)	17 (25.00%)	27 (39.71%)	68 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be carried in 68 patients, since pertaining health records were not retrievable in remaining 32 patients.
The agreement analysis regarding the severity illness of COVID-19 was obtained as good (k= 0.798).

also reflected in our study with the fact that 62% of pre-existing diabetics were found not carrying out regular blood sugar monitoring. Furthermore, 51% of pre-existing diabetics had uncontrolled blood sugars, and 31% were both unaware of their glycemic control and also did not maintain health records (►**Table 4**). Though hemoglobin A1c aids in better defining diabetes blood sugar control, it was available in the medical records for a few patients only and hence was not used. However, when available, it was found to be abnormal.

Another major risk factor identified is corticosteroid use, especially in diabetics resulting in complex immune dysregulation.[25,26] In pre-COVID-19 times, Skiada et al[22] noted MCR with corticosteroid use in 46% of patients. It was noted to be the most common predisposing factor in a meta-analysis by Jeong et al.[16] John et al[20] observed the use of systemic corticosteroids in 97.56% of patients with CAMCR. In our study, 59% of patients had been treated with steroids, while they were positive for COVID-19. Out of the 51 non-diabetics, 59% had received steroids for COVID-19. Twenty-nine percent of patients were neither aware of steroid use nor had records for the same.

However, 29% of patients had no awareness and also maintained no health records to provide information on steroid medication prescription (►**Annexure 2**). The association between COVID-19 disease severity and steroid treatment was assessed and was statistically significant with *p*-value of 0.001(►**Table 5**).

We observed that 35% of patients with mild disease had been treated with systemic steroids. Furthermore, 45% of patients with mild COVID-19 illness had neither awareness nor documents pertaining to steroid use. These findings highlight the unwarranted and unrestrained use of steroids. COVID-19 scare and restricted access to a health facility during the COVID-19 crisis may have resulted in self-treatment with over-the-counter steroids.

In 47% of study subjects, blood sugar monitoring was carried out during COVID-19 illness with or without treatment with steroids. Seventeen percent of the patients were unaware and had no record-keeping to verify their glycemic monitoring. Furthermore, 56% of study subjects had fluctuating blood sugar levels during COVID-19 illness, while 9% of them had blood sugars in the normal range. Thirty-five percent of patients were unaware of the blood sugar values and had no health record-keeping (►**Annexure 2**).

Our observations are corroborated by Gianchandani et al[27] who found very high blood sugar levels in CAMCR patients. The inter-kappa analysis on blood sugar monitoring during COVID-19 illness with or without treatment with systemic steroids shows a significant *p*-value and a very good kappa agreement (0.81–1.00; ►**Table 8**). This further signifies that the information obtained from patients was accurate and also a good record keeping as retrieved from the case sheets of the patients.

Mulakavalupil et al[28] showed that low-dose steroids with strict glycemic control completely eliminated risk of MCR in

COVID-19. On assessing the disease severity, mild and moderate COVID-19 illness was found in 40 and 24% of subjects, respectively (►**Annexure 2**).

Even mild COVID-19 can induce a proinflammatory milieu, which can further lead to lowering insulin sensitivity.[29] Prolonged hospitalization, broad-spectrum antibiotics, intensive care unit admission, intubation/mechanical ventilation, and surgery are usually seen with severe COVID-19 illness and associated with MCR.[30] Sixty percent of the study patients required hospitalization for a COVID-19 illness of which 30% remained hospitalized for 11 to 20 days.

Primary prevention in the form of vaccination remains the mainstay for mitigating the risks associated with COVID-19 in patients with DM.[31] Seventy-nine percent of the study participants were not vaccinated against COVID-19. A correlation between COVID-19 disease severity and vaccination status of the participants was studied and findings revealed that 33% of unvaccinated patients had severe disease, 38% had mild disease, and 29% had moderate disease. The association was statistically significant with a *p*-value of 0.009 (►**Table 6**). COVID-19 vaccination has been shown to reduce the disease severity. In a retrospective, analysis by Li et al[32] on COVID-19 patients to estimate the effectiveness of vaccination in preventing disease progression, it was concluded that risk of pneumonia and severe disease was lower in fully vaccinated individuals than unvaccinated people. In a case–control study by Tenforde et al,[33] to ascertain the association between prior vaccination and hospitalization for COVID-19 and its progression, the authors concluded that the outcome of mechanical ventilation and death among the vaccinated was less likely. These findings are in concordance with the present study and suggest that the risk of developing severe COVID-19 disease is less with prior vaccination and thus complications like COVID-19-associated mucormycosis are also infrequent. Hence, mild disease does not require hospitalization or steroid treatment thereby immunosuppression and hospital-acquired infections are circumvented. Vaccination has a dual beneficial effect for COVID-19 disease on its severity as well as its further complications like COVID-19-associated MCR that were rampant during the second wave in India.

Average to poor sanitary surroundings during isolation and treatment period was reported by 58% of study subjects. Individuals who have recently recuperated from COVID-19 should ensure stringent personal hygiene.[34] Sixty-nine percent of patients reported wearing cloth protective masks and 9% used no masks, with 21% of patients using soiled masks (►**Annexure 2**). The All India Institute of Medical Sciences had issued guidelines on MCR alerting the public on the alarming symptoms to be watched for to detect early disease.[35]

Seventy-one percent of the study participants had no knowledge and 11% had knowledge only about advanced stage symptoms and could not relate their initial symptoms to the disease (►**Table 1**). In 18% of the aware cases, media through television and newspaper helped spread awareness. Only 6% of patients were alerted to the red flag signs of MCR by their clinicians. Thirty-two percent of patients reported face swelling including eyes as the initial symptom with nasal symptoms in only 11%. Hence, patients presenting with early disease limited to the nasal site were few (8%; ►**Annexure 2**).

Management for MCR was initiated in 25% of the patients within 5 to10 days of the symptom onset. Only in 8% of patients, management was initiated within 5 days of symptom onset. The agreement analysis shows a very good kappa score regarding the onset of symptoms and initiation of management of MCR, further nullifying a recall bias (►**Table 7**).

A delay in the establishment of the diagnosis of MCR resulted in rapid disease progression thereby necessitating more aggressive treatment. Seventy-five percent of the study participants received both medical and surgical treatment by the time they answered the questionnaire (►**Annexure 2**).

Strengthening efforts to enhance health awareness among the general public in various aspects of diabetes care is the key to keeping the associated threats in check. It is prudent to have early initiation of treatment of mucormycosis on strong clinical and radiological suspicion without waiting for tissue confirmation to enable improved outcomes in this rapidly progressive highly debilitating, fatal disease.

The present study having a questionnaire-based design had the limitations of being time-consuming, with participants getting disinterested at times, affecting the essence of the results obtained. Additionally, open-ended questions though few might have been difficult for less educated participants to answer. Other limitations specific to the study entailed records pertaining to the information on pre-existing illnesses, blood sugar charting, and management of MCR were incomplete and missing for so. Follow-up of the patients regarding outcome was not done; therefore, the underlying potential risk factors of the disease could not be correlated to the disease outcome.

The message to take home is that the health literacy of patients having a chronic disease like diabetes plays a key role in optimal control of comorbidity and preventing the associated complications. COVID-19 in its progression and severity affects immunocompromised patients with greater virulence. Hence, strengthening patient education and also health awareness in the general population is paramount to reducing complications entailing COVID-19 such as immunosuppression and MCR. In addition, vaccination against COVID-19 should be encouraged with the use of masks and social distancing should be actively practiced.

Conclusion

Clinicoepidemiological profile of COVID-19-associated MCR was found similar to that not associated with COVID-19, although diabetes was more commonly seen in patients with CAMCR in our study. Health literacy among diabetics had lacunae that resulted in impaired glycemic control. Additionally, awareness for blood sugar monitoring and control during COVID-19 illness with or without the use of steroids was mostly lacking. Knowledge of the "red flag" signs of MCR was incomplete, thereby hampering early disease

recognition. Interventions to improve awareness amongst patients with diabetes should help in optimal glycemic control, and avoid potential complications including severe COVID-19 illness, MCR.

Conflict of Interest
None declared.

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Annexure 1:

We conducted principal component analysis with Varimax rotation to divide the items into factors. The number of factors retained was derived by considering the magnitude of the eigenvalues, Kaiser's (1960) eigenvalues (> 1) rule, the proportion of variance extracted, item content, and the interpretability of the resulting factors. As for factor loading after the Varimax rotation, items with a factor loading less than 0.5 on all factors were excluded. We investigated the internal consistency by calculating Cronbach's alpha and by calculating item-total correlations for each factor that was identified with the factor analysis, and alpha greater than 0.70 was considered acceptable, and optimal item-total correlation was considered to be between 0.2 and 0.5.

Results from the factor analysis indicated that each factor accounts for approximately 40% of the variance. Cronbach's alpha coefficients for various questions in the questionnaire were greater than the accepted number of more than or equal to 0.70.

Calculation of internal consistency (Cronbach's alpha 0.703-0.834) and cross-validation provided evidence of reliability and lack of redundancy of items.

We found that the number of factors, the factor structure, and factors loadings were for the greater part comparable between the first randomly created subsample ($n = 25$) and the total sample ($n = 100$).

Annexure 2: Patient questionnaire with responses

S No	Question	Possible answers	Replies obtained
1	How many days prior to developing symptoms of "Black fungus," did you have COVID-19 or COVID-19 like illness? $n = 100$	0–10 days	33%
		11–20 days	36%
		21–30 days	18%
		31–40 days	9%
		$>$ 40 days	4%
2	Where did you get treated for COVID-19? $n = 100$	Home	38%
		Hospital	38%
		Home +Hospital	24%
3	How was the overall hygiene of the place of stay while being isolated? $n = 100$	Good	42%
		Average	50%
		Poor	8%
4	How many days did you stay at a hospital/COVID-19 care center? $n = 100$	<10 days	23%
		11–20 days	28%
		21–30 days	9%
		31–40 days	2%
		NA	38%
5a	Were you treated with steroids like Dexona/ Predmet/Medrol/ Wysolone, $n = 100$	Yes	59%
		No	12%
		No records	29%
5b	If yes, you took steroids, $n = 59$	As prescription	97%
		As self-medication	3%
5c	If taken steroids as a prescription, prescribed for what duration? ($n = 57$)	<10 days	30%
		>10 days	68%
		No Records	2%

(*Continued*)

S No	Question	Possible answers	Replies obtained
5d	If taken steroids as a prescription, took $n = 57$	More no. of days	1%
		More than the prescribed dose	1%
		More days+ More dose	1%
		None	60%
		No records	18%
		NA	19%
6a	Was blood sugar monitored during COVID-19 illness with or without steroid use? $n = 100$	Yes	47%
		No	36%
		Don't know	17%
6b	Was the blood sugar controlled during COVID-19 illness with or without steroid use? $n = 100$	Normal range	9%
		Fluctuating	56%
		No records	35%
7a	Treatment prescribed for blood sugar control during COVID-19 illness with or without steroid use? $n = 100$	OHA	18%
		OHA + insulin	17%
		Insulin	29%
		None	18%
		No records	18%
7b	If OHAs were used then medication names? $n = 35$	Single drug	31%
		Double drug	23%
		Triple drug	6%
		No records	40%
8	How severe was the illness? $n = 100$	Mild RR < 20, Spo2 > 93%	40%
		Moderate RR 20-30, Spo2 > 90%	24%
		Severe RR > 30, Spo2 < 90%	36%
9	What was the CTSS score if you remember, if the CT chest done? n = 100; CTSS score 7 or less (mild) $n = 0$; CTSS score 8–17 (moderate) $n = 22$; CTSS score 18 or more (severe) $n = 11$	10	3%
		11	1%
		12	4%
		13	2%
		14	3%
		15	4%
		16	2%
		17	3%
		18	3%
		19	2%
		20	1%
		21	2%
		22	1%
		23	1%
		24	1%
		NA	36%
		No records	31%

(*Continued*)

(*Continued*)

S No	Question	Possible answers	Replies obtained
10a	Did you receive oxygen therapy? ($n = 100$)	Yes	56%
		No	43%
		Can't say	1%
10b	If yes, received at $n = 56$	Home	4%
		Hospital	80%
		Home +Hospital	16%
10c	Was the oxygen dry or moist? $n = 56$	Moist	80%
		Dry	0%
		Can't say	20%
10d	What type of humidification was used (hospital/home)? $n = 56$	Packaged water/RO water	19%
		Distilled water	7%
		Tap water	6%
		Can't say	13%
		NA	55%
11	Mode of oxygen therapy used? $n = 56$	Simple face mask	38%
		Tight mask with straps (Bipap)	13%
		Nasal prongs	5%
		NA	44%
12	Any other treatment received?	Remdesivir	9%
		Any other treatment	35%
		No records	56%
13	For what duration was treatment taken for COVID-19, including hospital & home? $n = 100$	<7 days	22%
		7–14 days	36%
		15–30 days	34%
		>30 days	8%
14	COVID-19 vaccination received? $n = 100$	1 dose	16%
		2 doses	5%
		Not vaccinated	79%
15a	Do you have pre-existing diabetes or any other disease for which you have been taking long term medication prior to COVID-19 illness? $n = 100$	Yes	56%
		No	44%
15b	If yes please specify the disease DM/malignancy/HTN/thyroid disorder/CKD/ chemotherapy/immunosuppressants? $n = 56$	DM 1	1%
		DM2	33%
		DM2 + HTN	11%
		DM2 + HTN + CAD	1%
		DM2 + HTN + COAD	1%
		DM2 + HTN + Hep c	1%
		DM2 + HTN + Hypothyroid	1%
		HTN	5%
		Hypothyroid	1%
		NA	45%

(*Continued*)

S No	Question	Possible answers	Replies obtained
16	If pre-existing diabetes, what was the treatment taken? $n = 49$	OHA	35%
		OHA + insulin	3%
		Insulin	1%
		None	10%
		NA	51%
17a	Did you routinely check blood sugars prior to COVID-19 illness, $n = 100$	Yes	28%
		No	72%
17b	If yes, how did you check? $n = 28$	Yes	57%
		No	43%
17c	Did you routinely check blood sugars (in pre-existing diabetics), $n = 49$	Home yes	38%
		Hospital care facility no	62%
18	Was blood sugar controlled? (blood sugar values: 80–140 mg/dL before meals and < 200 mg/dL, 2 hours after meals); $n = 49$	Yes	18.00%
		No	51.00%
		Can't say	31.00%
19	Did you experience any episodes of rapid heart rate, blurry vision, unconsciousness? $n = 49$	Yes	8%
		No	83%
		Can't say	9%
20a	Type of COVID-19 protection mask used? $n = 100$	Cloth	69%
		Surgical	10%
		N-95	9%
		Combination	3%
		No mask	9%
20b	How often was the mask changed/washed? $n = 100$	1-3 days	47%
		4-6 days	24%
		7-14 days	13%
		>14 days	7%
		NA	9%
20c	Was the oxygen mask changed on becoming soiled/wet? $n = 100$	Yes	71%
		No	21%
		NA	8%
21	Did you know about symptoms of black fungus? $n = 100$	Yes	18%
		No	71%
		Incomplete information	11%
22	If yes (complete or incomplete), source of information? $n = 29$	Television/newspaper	62%
		Treating doctor	17.20%
		Internet	13.70%
		Family/Friends	6.89%
23	Were you alerted about the symptoms of mucormycosis before leaving the hospital? $n = 100$	Yes	6%
		No	79%
		NA	15%

(*Continued*)

(*Continued*)

S No	Question	Possible answers	Replies obtained
24	Which symptoms did you notice first? $n = 100$	Face swelling	32%
		Visual disturbances	12%
		SO pain	12%
		Nasal stuffiness	11%
		Vision disturbances + SO pain	10%
		Nasal discharge	7%
		Pain in mandible	6%
		Face numbness	5%
		Blood in cough	2%
		Nasal bleed	1%
		Infraorbital pain	1%
		cough/breathlessness	1%
25	After how many days of diagnosis of mucormycosis was the treatment started? $n = 100$	<5 days	8%
		5–10 days	25%
		10–15 days	25%
		15–20 days	19%
		20–30 days	9%
		30–40 days	7%
		40–50 days	5%
		>50 days	2%
26	What mode of treatment are you being given for black fungus? $n = 100$	Medicine only	23%
		Surgery only	2%
		Both	75%
27	Are you satisfied with the treatment? $n = 100$	Satisfied	84%
		Not satisfied	5%
		Can't say	11%

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COAD, chronic obstructive airway disease; COVID-19, coronavirus disease 2019; CTSS, CT Chest Severity Score; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; HTN, hypertension; NA, not available; OHA, Oral Hypoglycemic Agent; RO, reverse osmosis; RR, relative risk; SPO2, oxygen saturation; SO, supraorbital.

Challenges with Adjuvant Radiation for Intracranial Chondrosarcoma in Pregnancy

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Abstract

Background Managing a brain tumor during pregnancy is a highly confusing and challenging situation, complicated by several technical, medical, ethical, and sociocultural concerns. The interests of the mother and child are often pitted against each other, for which legal opinion may occasionally be needed.

Case Report We present the report of a young lady with intracranial well-differentiated chondrosarcoma who was determined to be pregnant in the immediate postoperative period. We discuss the management of challenges and dilemmas in devising optimum therapy, and the modifications and care required at each step to help safeguard maternal and fetal health. Risks with therapeutic radiation and measures to assess and pre-empt fetal doses that may assist decision-making are also discussed.

Conclusion Radiation therapy during pregnancy is challenging and requires multidisciplinary involvement and psychosocial support for the patient and family.

Keywords
- brain neoplasms
- chondrosarcoma
- radiation therapy
- pregnancy complications
- teratogenesis

Introduction

Surveillance, epidemiology and end results 21 age-adjusted statistics (2013–2017) place the annual incidence of brain neoplasms at 5.4 per 100,000 women; 16% of these occur in the reproductive age group.[1] Nearly 90 women are diagnosed with brain tumors during pregnancy per year in the United States.[2] Depending on histology, extent, and expected prognosis, some of these may merit immediate or early treatment of brain tumor, with special considerations for maternal and fetal safety depending on the period of gestation (POG). The physiological state of pregnancy itself may aggravate symptoms due to increased plasma volume, hypervascularity, and hormonal stimulation, sometimes precipitating pregnancy complications or obstetric emergencies. If the management protocol includes radiation therapy (RT), the risks of teratogenicity, growth retardation, mental retardation, and childhood cancers have to be weighed against the benefits of disease control in the mother creating a mutual conflict of interest.

We discuss the management challenges in a pregnant lady with intracranial chondrosarcoma, referred for adjuvant RT.

Case Presentation

A 27-year-old nulliparous woman presented to the neurosurgeon with headache and vomiting for 6 months and sudden onset right-sided weakness for 2 months. She had memory disturbances, slurred speech, and ptosis left eye. There was no history of trauma, bowel or bladder disturbances, seizures, or loss of consciousness. Clinical examination

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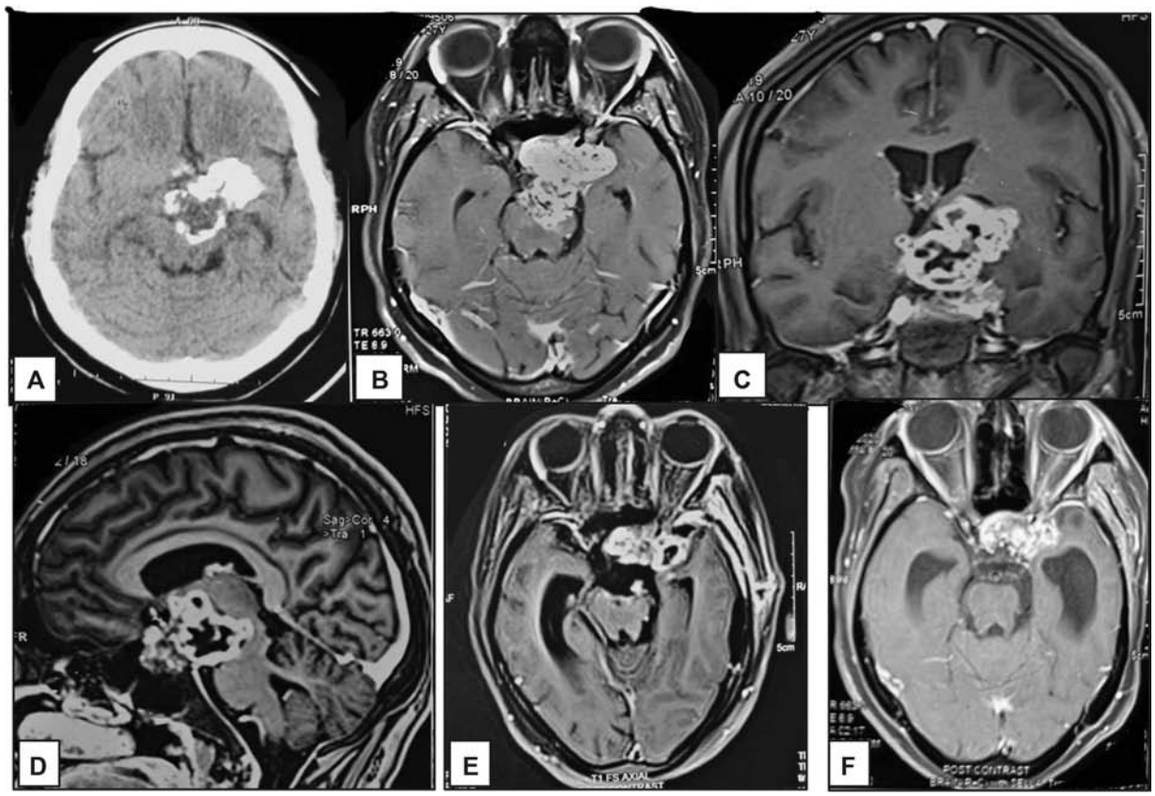


Fig. 1 (A) Baseline computed tomography brain showing a large heterogeneous calcified lobulated swelling in sellar-suprasellar region with extension to left parasellar region and brainstem. Contrast-enhanced magnetic resonance imaging (MRI) in (**B**) axial, (**C**) coronal, and (**D**) sagittal sections show a multilobulated heterogeneously enhancing solid-cystic lesion involving sella, suprasellar and left parasellar region, left internal/external capsules, basal ganglia and frontal periventricular regions. Pituitary gland and optic chiasm are not seen separately. The mass is eroding left lateral wall of sella to extend into left cavernous sinus and extra-axial extradural temporal lobe. Left internal carotid artery is completely encased and narrowed. Posteriorly, the lesion extends into interpeduncular cistern with left posterior midbrain infiltration. Moderate dilatation of right lateral and third ventricle seen. (**E**) Postoperative MRI showing residual disease with reduction in mass effect (**F**) MRI at 30 months postradiotherapy with stable disease.

revealed an average build patient with Glasgow coma scale E4V5M6, right hemiparesis (upper limb 2/5, lower limb 3/5), reduced vision in both eyes (both pupils reacting to light, finger counting at 2 m in right eye and 1 m in left eye), and left oculomotor palsy. She had partial recent memory loss. Contrast-enhanced magnetic resonance imaging (CEMRI) of the brain showed a large sellar-suprasellar lesion with engulfed optic chiasm (►**Fig. 1A–D**). Differential diagnoses considered were clival chordoma, meningioma, and craniopharyngioma.

She underwent craniotomy and subtotal tumor excision. Intraoperatively, it was a rock-hard tumor, with calcification extending from Sylvian fissure involving sella, parasellar region, cavernous sinuses, and ambient cisterns. Postoperative histopathology suggested well-differentiated chondrosarcoma, with S-100 strongly positive.

Postoperative computed tomography (CT) scan showed significant residual disease, hence, a radiation oncology opinion was sought. At this stage, she had a performance status (PS) of Eastern Cooperative Oncology Group 3, right facial palsy, right hemiparesis (upper limb 0/5, lower limb 1/5, decreased vision left eye (finger counting at 0.3 m) and stable right eye vision, psychiatric and memory disturbances, and slurred speech. Postoperative MRI revealed a large ill-defined residual heterogeneous mass with a 10 mm midline shift. Optic chiasm was infiltrated (►**Fig. 1E**). Fundus examination showed bilateral optic atrophy compounded by surgical insult. The patient had developed postoperative panhypopituitarism, including diabetes insipidus and amenorrhea. Details of her last menstrual period seemed unreliable due to psychiatric disturbance. Urine pregnancy test was advised prior to advising adjuvant RT and returned positive. High-risk obstetric clinic evaluation after the positive urine pregnancy test confirmed the pregnancy with POG 23 to 24 weeks.

The following factors were considered while making further management decisions:

- Favoring early RT to delay disease progression: Young patient, good prognosis histology, large residual, multiple cranial nerve involvement, contribution of mass effect to neurologic/psychiatric/hormonal deficits leading to poor PS.
- Favoring delayed RT to allow fetal maturity: RT exposure linked with risk of teratogenesis, mental and growth retardation, fetal carcinogenesis.
- Favoring medical termination of pregnancy (MTP): Low PS, patient dependent and incapable of self-care

(hemiparesis, speech problems, hormonal imbalances, poor vision in left eye, psychiatric and memory disturbances), or taking care of pregnancy on her own, possible prior exposure to multiple teratogens during the first trimester (multiple CT scans and X-rays, drugs including antiepileptics, anesthetic agents, possible fetal hypoxia) and additional risk with RT.
- Against MTP: Primigravida, expected fetal exposure with imaging and cranial radiation within deterministic effects tolerance, medicolegal concerns against termination of pregnancy beyond 20 weeks.

After discussion with the patient's family and deliberation in a special multidisciplinary board highlighting the patient's poor general condition to sustain the pregnancy, a court order was obtained for MTP at 26 to 27 weeks POG, considering a grave risk to the mother with the delay of adjuvant treatment. There was an ethical dilemma of labeling this as MTP (per court orders) or induced delivery because of fetal salvageability. An antenatal scan showed a viable fetus (weight ~1,000 g). The patient underwent induced vaginal delivery with Cerviprime at 27^{+6} weeks POG. A live girl child (birth weight 1 kg, Apgar score of 6,8) was born; she needed neonatal intensive care unit care for the management of respiratory distress, where she stayed till her eventual demise at 2.5 months due to persistent pneumonia. In the postpartum period, the patient's psychiatric problems, speech, and upper limb power (⅖) improved. Within a week of delivery, adjuvant therapy was planned. Since she had a sellar residual calcified tumor with engulfment and distortion of the optic chiasm and left optic canal, which were challenging to delineate even on thin-section CEMRI, we had to limit the deliverable dose to 5,400 centigray (cGy) in 27 fractions over 5.5 weeks. Treatment was delivered using a noncoplanar three-field beam arrangement with three-dimensional conformal radiation therapy (3DCRT) without interruption or significant adverse effects (►**Fig. 2**). She continued medical management for panhypopituitarism and psychiatric disturbances, and physiotherapy for motor weakness, memory and speech. At 2.5 years postradiation, she had significant improvement in lower limb power (⅗), right eye vision (finger counting at 3 m), left facial, and oculomotor nerve function, while left eye vision was unchanged (finger counting at 0.3 m), and CEMRI showed stable disease.

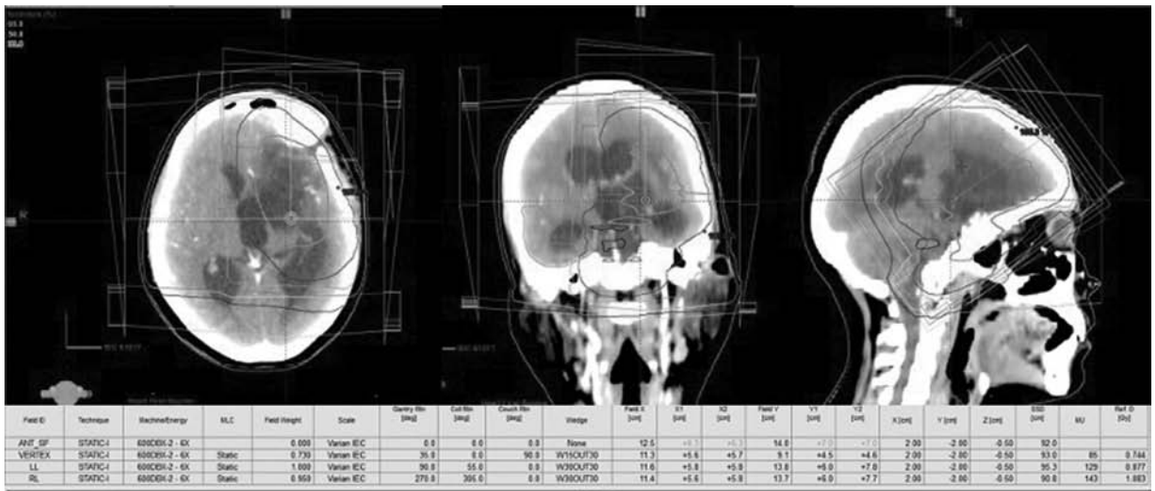
We further evaluated possible fetal doses from therapeutic cranial radiation in vitro to guide decisions on fetal risk in future scenarios. CT images of an anthropometric Atom female phantom (CIRS, Tissue simulation and Phantom Technology, 900 Asbury Ave, Norfolk, Virginia, United States)were acquired on Philips Big Bore 4D-CT and fused with the CT images of the given patient in the Eclipse planning system (Version 11.0, Varian Medical Systems, Palo Alto, California, United States) (►**Fig. 3**). We simulated the treatment plan and delivery conditions, additionally placing three thermoluminescent dosimeters (TLDs) at three different positions on the abdominal surface (5 cm above umbilicus T1, at umbilicus T2, and 5 cm below umbilicus T3 in the midline) to measure the absorbed dose. At 26 to 28 weeks, the estimated position of the proximal part of the fetus was approximately 50 cm from the lower border of the treatment field.

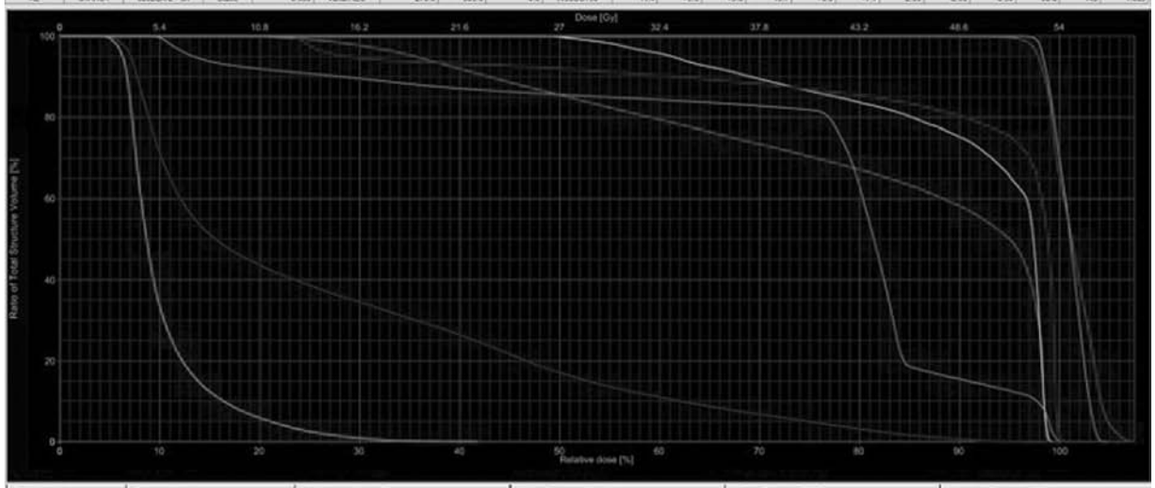
All the TLDs, LiF: Mg, Ti (TLD 100, Rexon TLD Systems and Components, Ohio, United States) with cuboid shape (dimension: 1mm × 1mm × 6 mm) were annealed pre-RT to eliminate the previous history of residual information left by the procedure involving heating at 400°C for 1 hour followed by 105°C for 2 hours in a microprocessor-based heating oven.[3] TLD sorting and element correction coefficient for each TLD were determined.[4] RT doses delivered using 6 megavolts (MV) photon beam from a medical linear accelerator (Clinac DBX 1160, Varian, California, United States) were measured by A19 Exradin ion chamber with active volume 0.6cc (ref. 92734, Standard Imaging, Middleton, Wisconsin, United States), Supermax Electrometer (ref. no. 90018, Standard Imaging, Middleton, Wisconsin, United States) and RW3 solid water phantom with density 1.04 g/cm^3 (area 30×30 cm^2, thickness range 0.1–1 cm) at 5 cm depth, 10×10 cm^2 field size, and 100 cm source to surface distance. The monitor units required to deliver dose range 0.4 to 1,000 cGy were recorded, and a dose calibration curve for the given dose range for TLDs was obtained.[5] Recording and analysis of thermoluminescence (TL) spectra from TLDs after RT were performed on Rexon UL-300 readout system (Model UL 300, Rexon TLD Systems and Components, Ohio, United States).

Post-RT annealing for TLDs was performed at 105°C for 15 minutes in the heating oven. The nonlinear curve fitting method already installed in graphical computer software Origin Pro (Version 8.5, OriginLab Corporation, Northampton, United States) was used for dose–TL response curve fitting for low dose range, that is, 0.4 to 30 cGy. Different models for nonlinear curve fitting (linear, exponential, sine, logistic, Gaussian) were used. Although the chi-squared values were very small for all mentioned models, the minimum value of chi-square ($\chi^2 = 0.00654$) was obtained for fitting with amplitude version of Gaussian peak function. The total dose recorded by these TLDs (T1, T2, and T3) for the entire planned dose of 5,400 cGy with the 3DCRT plan were 3.0599, 0.7135, and 1.9619 cGy, respectively. The possible lower dose of T2 versus T3 could be due to the placement of TLD nearly 1 cm dorsal (deep) in the umbilical region compared with the other TLDs placed on the abdominal surface.

Discussion

Intracranial chondrosarcomas are rare but carry an excellent prognosis (5-year survival 77% overall and 90% for well-differentiated).[6] Adjuvant RT after incomplete resection dramatically reduces 5-year recurrence rates from 44 (after surgery alone) to 9% (after combined surgery and RT).[6] Management involves multiple imaging studies (CT and MRI), surgical resection under general anesthesia, and adjuvant therapy based on grade and extent of resection. Before proceeding with investigations, it is crucial to test for possible pregnancy in any sexually active patient in the reproductive age group. In the setting of pregnancy, there is a need for modifications such as omission of CT scanning or other





DVH Line	Structure	Volume [cm³]	Min Dose [%]	Max Dose [%]	Mean Dose [%]
	RT TEMPORAL	49.6	9.1	100.1	74.7
	RT OPTIC NERVE	0.6	19.0	98.9	81.6
	RT EYE	8.6	3.7	42.0	10.3
	PTV	437.2	78.7	107.5	101.3
	LT OPTIC NERVE	0.4	48.3	99.2	91.1
	LT EYE	8.6	3.4	96.3	26.8
	GTV	86.1	96.2	104.8	101.0
	BRAIN STEM	17.7	23.0	100.6	90.3

Fig. 2 Three-dimensional conformal radiotherapy plan images showing the planning target volume (PTV) (red outline) and the isodose levels 95% (green), 50% (yellow), and 30% (blue) in axial, coronal, and sagittal planes, for a planned dose of 54 gray (Gy) in 27 fractions to the target, delivering 357 monitor units. A noncoplanar vertex beam (~11 cm × 9 cm) with couch rotation was used in addition to two parallel opposed collimated beams (~12 cm × 14 cm). Dose volume histogram depicts doses received by PTV and organs at risk.

kilovoltage X-ray exposure, MRI studies without gadolinium, choice of antiepileptic agents (if presenting with seizures), and timing and type of anesthesia, patient positioning during surgery, as well as the need for fetal-maternal monitoring in the perioperative period. Although surgery is deemed safe during any trimester, it is preferable to delay it to the second trimester or later for asymptomatic patients with a stable disease course.[7] Our patient had an undiagnosed pregnancy when she underwent investigations and surgery for her brain tumor; the disease adversely affected her PS and quality of life (QOL), while the investigations, medications, surgery under anesthesia without fetal monitoring, and need for RT risked fetal viability and normalcy.

Fetal risks from therapeutic radiation during pregnancy may either be stochastic (childhood malignancy, sterility) and independent of dose and POG, or deterministic and dependent on dose and POG at exposure. Doses of 10 to 20 cGy may cause fetal death, mental retardation, congenital defects, and growth retardation. The risk is highest in the first trimester and decreases considerably in subsequent trimesters.[8–10] Unless there is an urgent need, RT should be postponed to the postpartum period. MTP is justifiable only if fetal dose estimates exceed 10 cGy. Cranial RT during pregnancy usually entails fetal exposures within the deterministic threshold due to large separation between treatment isocenter and fetus, and may be necessary, especially in

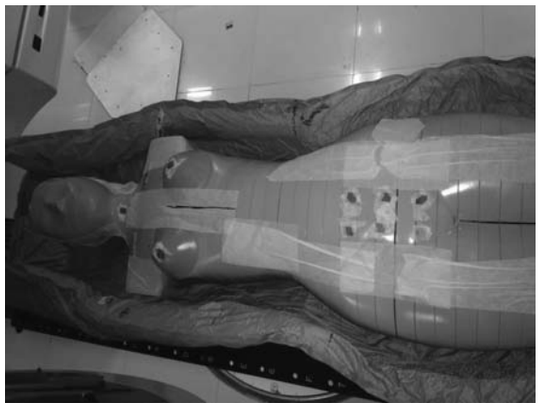


Fig. 3 Photograph with female Atom phantom with pelvic thermoluminescent dosimeters in situ.

aggressive malignancies. For situations where RT contributes significantly to disease control and QOL, RT may be planned in later pregnancy with necessary precautions, such as pretreatment phantom-based dose simulations, abdominal lead shielding to reduce fetal exposure, treatment plan modifications (linear accelerator with beam energy <10 MV preferred over cobalt-60, 3DCRT with minimal beam modifying devices preferred over intensity modulated RT, flattening filter-free beams).[11] During cranial RT in the second trimester, the fetal position is at a distance of 40 to 50 cm from the cranial field edge. At this distance, the contribution from external scatter exceeds that from internal scatter.[12] The major contributors to fetal dose include leakage from machine head (nearly 50%), wedge scatter, collimator scatter, and internal scatter; hence, shielding near machine head/patient neck may help curtail fetal exposure.[13]

Conclusion

In our patient, the surrogate fetal dose estimates during postpartum RT for the patient's disease were within acceptable limits (<10 cGy) and would have further reduced if reduction due to shielding was incorporated.[14] The decision to terminate pregnancy/induce early delivery was taken after considering her poor general health and social support. In a fit patient with good PS and minimal neurologic symptoms, a well considered decision to continue the pregnancy would be justifiable with minimal fetal risk; decisions on the timing of RT would depend on the volume of residual disease and its rate of progression. In situations where the pregnancy was known earlier and due precautions taken during assessments and surgery to safeguard the fetus, if the patient had better PS with minimal sequelae from disease and surgery or if a near-complete resection was feasible, adjuvant RT could be delayed till delivery; a possible induction after 34 to 36 weeks after fetal lung maturity would ensure optimum maternal–fetal and oncologic outcomes. The patient and family must be counselled about the risks and gains, and their informed consent (high risk) is mandatory. Following delivery, the patient can be treated as any nonpregnant patient, and advice on breastfeeding, contraceptive use, and modification of antiepileptics given. Follow-up imaging such as CEMRI poses no hindrance to breastfeeding. Even with favorable maternal and fetal health at delivery, long-term follow-up for both the mother (disease control, QOL, mental health, future pregnancies) and the child (structural and neurocognitive development, cancers, fertility) is recommended.[15]

Ethical Approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions

A.K.Y. contributed to concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, and manuscript review. S.G. and R.M. were involved in concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. R.S., A.C., and D.K. helped in definition of intellectual content, data acquisition, and manuscript review.

Conflict of Interest

None declared.

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Granulomatosis with Polyangiitis Presenting as a Renal Mass: A Scarce Case Report with a Review of the Literature

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Abstract

Wegener granulomatosis (WG) now known as granulomatosis with polyangiitis (GPA) is an uncommon autoimmune disorder of undivulged etiology affecting the respiratory tract including paranasal sinuses, nasal cavity, lungs, and kidneys predominantly. GPA presenting as a solitary renal mass is rarely seen. We present a case report of a 27-year-old female presenting with a right renal mass along with pain, low-grade fever, and arthralgia. Computed tomography scan of the abdomen revealed a hypodense low attenuated renal mass with indistinct margins. Ultrasound-guided biopsy revealed features typical of GPA. She was started on oral steroids (prednisolone 40 mg) and azathioprine. She developed pain, vomiting, and diarrhea after starting treatment with azathioprine. Azathioprine was stopped and rituximab 1 g weekly was started for 4 weeks followed by 500 mg 6 monthly injections. She got symptomatic relief at 4 weeks with a diminution of renal mass at 6 months follow-up. We report this rare entity of WG presenting as renal mass. Suspecting and diagnosing renal mass as a part of GPA prevented us from undertaking unnecessary surgical treatment in this patient. Medical treatment with steroids and rituximab is effective in inducing remission and maintenance.

Keywords

- Wegener granulomatosis
- granulomatosis with polyangiitis
- immunosuppressive therapy

Introduction

Wegener granulomatosis (WG) now known as granulomatosis with polyangiitis (GPA) was first described by Friedrich Wegener in 1936. It has characteristics of necrotizing granulomatous inflammation and pauci-immune vasculitis in small- to medium-sized blood vessels. Involvement of the kidney is common, which presents as proteinuria, hematuria (microscopic), and hypertension.[1,2] A very rare presentation of GPA is solitary renal mass or multiple renal masses. Differential diagnoses are renal tumors, abscesses, and lymphomas. Solitary renal mass is rarely a presenting feature of GPA and is reported in only eight cases to date. Treatment is cyclophosphamide, azathioprine, rituximab, and glucocorticoids. Most patients were diagnosed after nephrectomy; however, we suspected GPA and managed conservatively

Granulomatosis with polyangitis is uncommon autoimmune small to medium vessel disease affecting kidney frequently. GPA presenting as solitary renal mass is very rarely seen. Early diagnosis of GPA on basis of clinical features and radiological study like CT scan is crucial. Imaging guided biopsy is paramount for making a diagnosis of GPA. Diagnosing GPA could prevent surgery as medical treatment is effective. We highlight our rare presentation of GPA with renal mass and its medical management.

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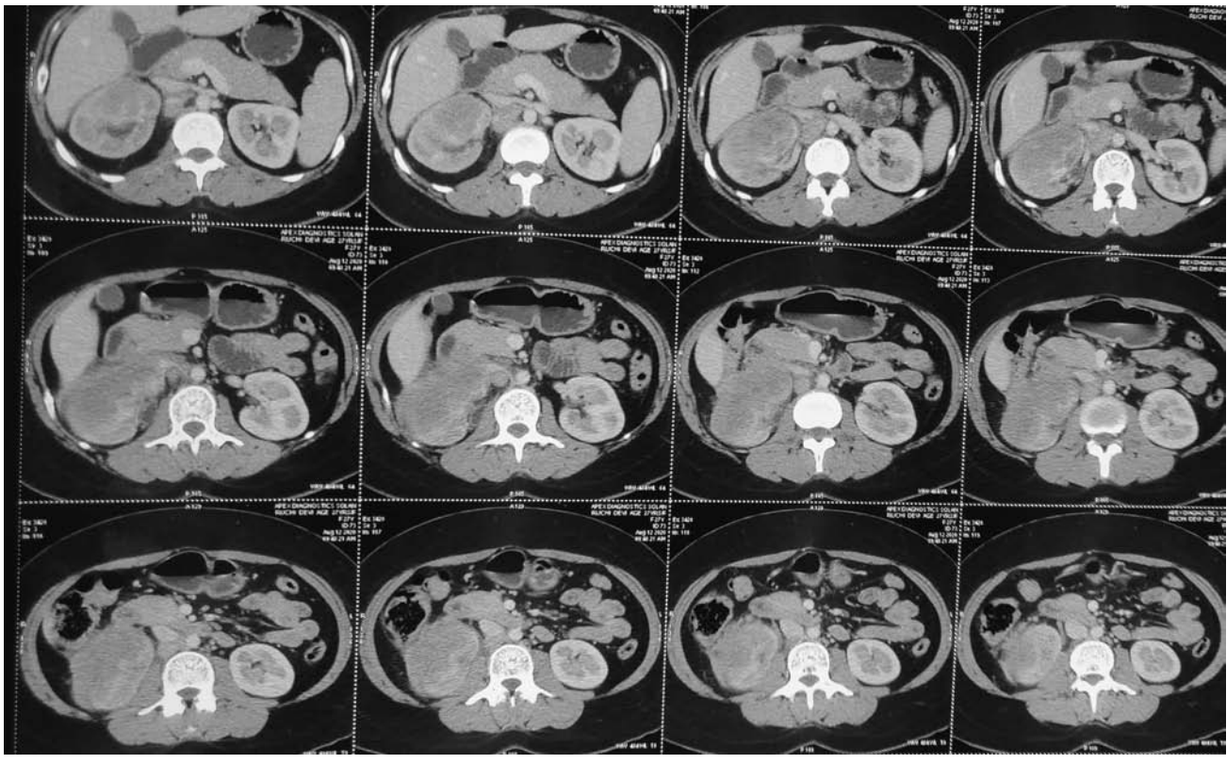

Fig. 1 Axial contrast-enhanced computed tomography scan showing ill-defined heterogeneous mass occupying in mid and lower pole of the right kidney with perinephric stranding.

with rituximab, and steroids after diagnosing with ultrasound-guided biopsy. This article aims to present this rare entity and review the literature.

Case Summary

A 27-year-old female presented with mild flank pain, loss of appetite, and low-grade fever for 3 months. On examination, her vitals were as follows: pulse was 84/min, blood pressure 108/70, and a lump was palpable in the right lumbar region extending into the right hypochondrium and umbilical regions. Investigations revealed hemoglobin 9.5 g/dL, urea 25 mg/dL, creatinine 0.8 mg/dL, total leucocyte count 10,300, C-reactive protein (CRP) 127 mg/L, and erythrocyte sedimentation rate 57 mm, and urine culture was sterile.

Ultrasound kidney, ureter, and bladder showed a heterogeneous hypoechoic mass of size $8.6 \times 7.8 \times 5.2$ involving the lower and mid pole of the right kidney that was displacing the pelvic calyceal system. Contrast-enhanced computed tomography (CT) scan was suggestive of an ill-defined mass $8.6 \times 7.8 \times 5.2$ cm in the lower and mid pole displacing the pelvicalyceal system toward the upper pole, with minimal internal vascularity. Mass had unclear borders and was infiltrating perinephric fat and duodenum. Contrast enhancement of mass was 50 to 60 Hounsfield unit, which was as low compared to normal kidney parenchyma. The heterogeneous perinephric fat stranding was seen. Multiple lymph nodes were enlarged predominantly paraaortic, and aortocaval, the largest measuring 28×32 mm (►**Figs. 1–3**).

Since the radiological features were unlikely of renal cell carcinoma (RCC), an ultrasound-guided biopsy was planned to rule out RCC, renal abscess, lymphomas, or tuberculosis. Biopsy revealed inflammatory infiltrate with foci of neutrophilic micro-abscess, epithelioid cells granuloma, and multinucleated giant cells spread among lymphocytes and plasma cells along with neutrophils. The inflammatory infiltrates comprised patchy foci of neutrophilic microabscesses, occasionally scattered epithelioid cells with epithelioid cell granuloma (►**Figs. 4** and **5**).

Cytoplasmic–antineutrophil cytoplasmic antibody was 1:290 with strongly positive anti-PR3, suggesting WG. On systemic examination, she had sinusitis with no involvement of respiratory tract, lungs, eyes, ear, and skin. She was prescribed azathioprine and steroids (prednisolone 60 mg). She was counselled regarding the disease and prednisolone 60 mg was started with weekly tapering of steroids (5mg/week till the 5 mg dose was achieved. Prednisolone 5 mg continued for 1 year. Azathioprine 50 mg twice daily was started; however, she developed abdominal pain, diarrhea, and vomiting after 2 weeks. Azathioprine was stopped and rituximab was started 1 g weekly for 4 weeks then 500 mg every 6 months. On follow-up, symptomatic resolution was seen with a resolution of renal mass at 6 months, and her full blood count, renal function, and CRP returned to normal.

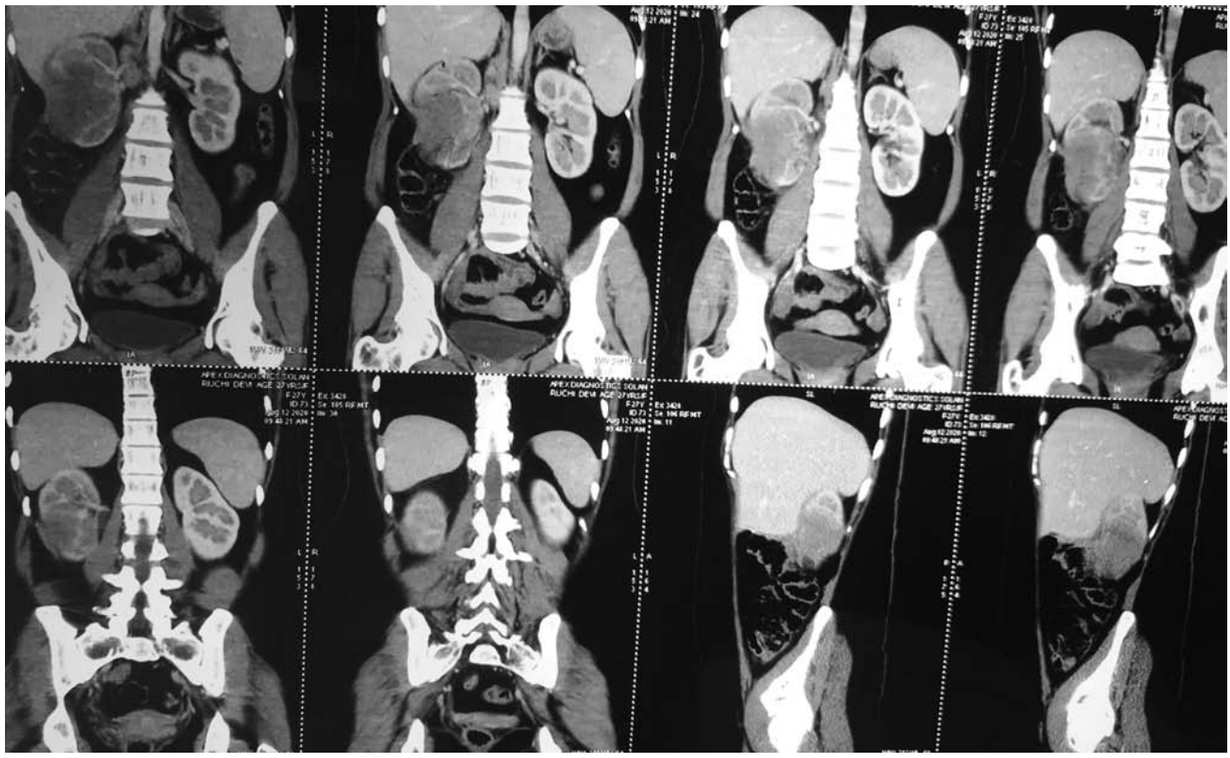

Fig. 2 Coronal sections of the contrast-enhanced computed tomography abdomen show heterogenous mass mid and lower pole with ill-defined margins, perinephric stranding, and involving duodenum.

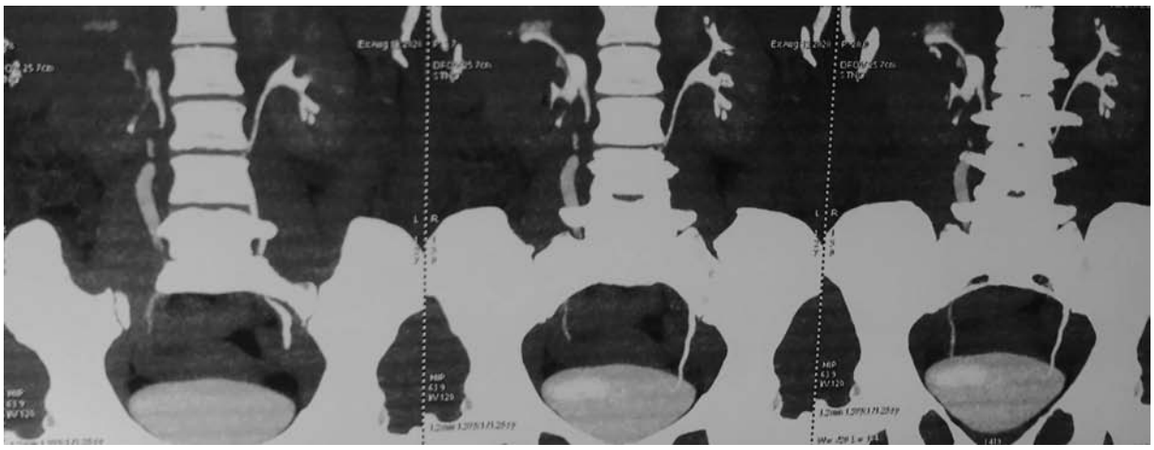

Fig. 3 Urography films of contrast-enhanced computed tomography abdomen showing heterogenous mass mid and lower pole with ill-defined margins. For Peer Review pushing calyces away without involving them.

Discussion

WG is necrotizing granulomatous vasculitis of unknown etiology involving the respiratory tract, lungs, skin, eyes, kidneys, etc. It has varied presentations ranging from mild-to-severe illness. It is small-to-medium vessel vasculitis with necrotizing granulomatous inflammatory nodules involving the respiratory tract, and kidneys. GPA initially involves the kidney in 20% of cases, although subsequent involvement is seen in 80% of cases. Ocular manifestations of WG are seen in 50 to 60 % of cases. It may occur secondary to granulomatous sinusitis or due to focal vasculitis in the form of nasolacrimal duct obstruction, proptosis, conjunctivitis, episcleritis, scleritis, corneoscleral ulceration, uveitis, and optic neuritis. Kidney involvement is seen as microhematuria, proteinuria, and renal failure. Microscopically, it is seen as patchy necrotizing glomerulonephritis.[1,2]

Renal mass is a rare presentation of GPA and its clinical and radiologic manifestations are similar to a renal abscess, tumor, or an inflammatory process.[3]

Maguire et al reported one patient had renal mass out of 31 patients presenting with GPA.[4]

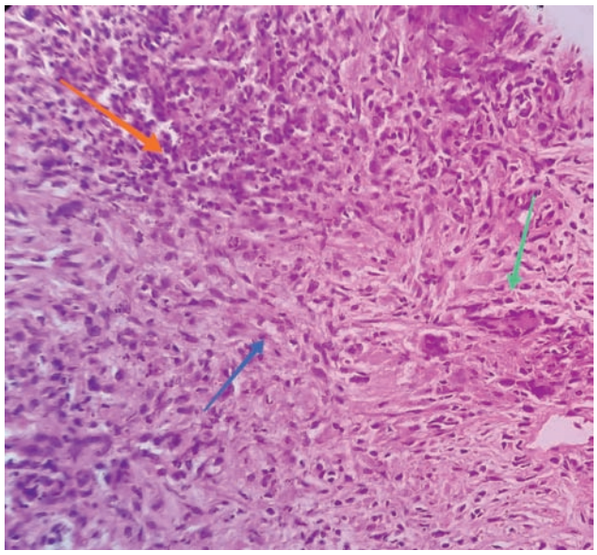

Fig. 4 Histopathology showing areas of necrosis with a collection of neutrophils (orange arrow), few epithelioid cell granulomas (blue arrow), and occasional giant cells (green arrow) (400X, hematoxylin and eosin).

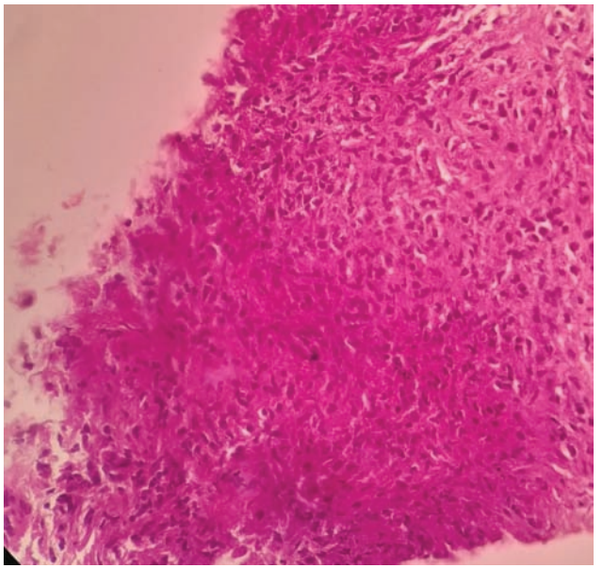

Fig. 5 Histopathology showing areas of necrosis with a collection of neutrophils, few epithelioid cell granulomas, and occasional giant cells (400X, hematoxylin and eosin).

Frigui et al[5] et al in a review of literature reported renal involvement as renal mass in 13 patients. He concluded that imaging alone cannot differentiate between renal tumors and mass due to WG. Villa-Forte et al[6] reported a case of simultaneous development of RCC and GPA renal lesions and proposed renal biopsy to confirm the diagnosis of suspected GPA and repetition of imaging studies to determine the resolution of mass lesions after appropriate treatment. He reported renal lesions in a WG along with RCC.

GPA presenting with solitary renal mass is seen in only eight case reports. Three patients were diagnosed with GPA after nephrectomy for renal mass and one after partial nephrectomy for renal mass. Four patients were diagnosed with percutaneous biopsy and managed conservatively.[7–15]

Pathologic analysis of the masses in these cases revealed them to be inflammatory masses or pseudo tumors or RCC. It is prudent to differentiate RCC from the inflammatory mass. Taking a meticulous history and physical examination and high clinical suspicion is of great importance to prevent unnecessary interventions and delay treatment.

Yamamoto et al reported 24 cases of renal mass in GPA with solitary lesions seen in 62%, (13/21), both kidneys having multiple masses in 28.5% (6/21), and unilateral kidneys having multiple masses. The finding was confirmed with a CT scan in 15 patients. The most common finding was hypovascular mass with undemarcated margins. Other investigations that can help differentiate could be magnetic resonance imaging and positron emission tomography scans. Other sites involved were seen in 50 % of cases including the upper respiratory tract, ears, and lungs.

Immunosuppressive therapy, that is, primarily azathioprine, cyclophosphamide, rituximab, and steroids, has markedly improved survival and remission rates in GPA patients. However, the therapy with cyclophosphamide is associated with significantly increased side effects and risk of urinary bladder cancer development. Rituximab and azathioprine are fewer toxic alternatives to cyclophosphamide.

In our case, a history of fever, arthralgia, flank pain, and atypical features on CT scan like hypovascular mass with indistinct borders, peritumoral stranding, and lymphadenopathy were crucial for diagnosis. Ultrasound-guided biopsy clinched the diagnosis. In addition, antineutrophil cytoplasmic antibodies and anti-PR3 antibodies were positive. She was prescribed steroids and rituximab and she responded dramatically. Renal biopsy, although paramount, should not delay treatment if other features suggest GPA. Diagnosis of WG is critical as surgery could be detrimental in these patients with delay in treatment.

Conclusions

In case of hypovascular renal mass in young patients with suggestive history, a clinician should keep GPA in mind as early diagnosis can make a difference. Medical treatment with steroids and rituximab is effective in inducing remission and maintenance.

Conflict of Interest
None declared.

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Emerging Syndemic: Black Fungus—A Post-COVID-19 Mucormycosis

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Novel coronavirus has created a havoc in India; about 30 million cases have been reported and 0.4 million deaths are recorded till now due to coronavirus disease 2019 (COVID-19). But nowadays, some patients of COVID-19 in India are battling a very rare but fatal disease, that is, mucormycosis or "black fungus" disease. The consciousness about the black fungus disease in many people of India is due to its rising cases of COVID-19-associated mucormycosis (CAM) mostly among the people who have recovered from COVID-19. Following recovery from COVID-19, thousands of cases of several complications of patients regarding CAM are reported especially during the second wave of COVID-19 in India. Mucormycosis or "black fungus" is a rare disease caused by fungi belonging to the order Mucorales. It is a disease observed following infection with the novel coronavirus in India and has already taken the form of a pandemic in many states.[1,2] Therefore, scientists have chosen to name the disease as a syndemic since this is synergistically created with the pandemic. The ubiquitous molds of mucormycosis having a worldwide dispersal, including the *Rhizopus*, *Apophysomyces, Mucor,* and *Lichtheimia* species, are found in plants, soil, decaying fruits and vegetables, and even in air. If contact occurs with airborne spore, then it germinates into hyphae and is regarded a very rare occurrence. This preferentially takes place inside the bucconasal cavity. After germination, it can invade the neighboring tissue and blood vessels that results in characteristic hemorrhage followed by black color development. The visualization of these dark necrotic tissues on skin and blood vessels of the affected person is termed as black fungus disease. Till now five major forms of mucormycosis have been identified, for example, rhinocerebral (44–49%), cutaneous (10–16%), pulmonary (10–11%), disseminated (6–11.6%), and gastrointestinal (2–11%) forms. Among these, the most common rhinocerebral form usually occurs in immunocompromised individuals. It exhibited a "pattern paranasal infection" with a porch into the oral cavity often. It is a quickly emerging angioinvasive infection, with rhinoorbital-cerebral and pulmonary manifestations. According to the Indian government, there are over 11,700 reported cases and over 126 casualties as of May 2021.[3] There is a surge in terms of infection rates. Though mucormycosis is generally regarded as harmless to an immunocompetent host, it may be fatal in some cases in its combination form with factors like indiscriminate use of steroids or other immunosuppressants, even in subjects presenting with mild symptoms of COVID-19. Immunocompromised patients like people with hematological malignancies, damaged mucosal layer, uncontrolled diabetes, ketoacidosis, and viral induced lymphopenia are the prime victims of this deadly fungus.[4] It is a fatal disease if unnoticed as it is invasive to blood vessels, distant organs, nose, mouth, eyes, sinus, and even brain. If untreated, the infection usually develops speedily, and leads to death within a few days of contamination.

Till the time this disease of public health importance remains under-explored along with the scarcity of literature available with regard to various perspectives on mucormycosis, medical professionals remain devoid of all the necessary information collated together for tackling the syndemic of mucormycosis. Mortality rate is as high as 80% for this fatal disease.[5] General diagnosis relies on tissue culture and histology that are very time consuming as there are no serological tests for early diagnosis. Thus, after recovery from COVID-19, patients should maintain a tough vigilance in their health and if they find either of the following symptoms, they should seek medical help as

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soon as possible. Some symptoms of black fungus disease are as follows:

a. Face swelling
b. Eye swelling
c. Unusual bloody or black-brown discharge from the nose
d. Pain and numbness
e. Nasal or sinus congestion
f. Black lesions on nasal bridge or upper inside of the mouth

It is the need of the hour to prevent this syndemic to spread in patients by limiting the usage of steroids (glucocorticoid mainly) to people with mild COVID-19 infections. Beside this, only medical grade oxygen should be used for all the patients after proper sanitization of the cylinders. Wearing a mask post-COVID-19 can minimize the infection of CAM, but reuse of the same mask for 2 to 3 weeks can increase the chances of infection of CAM. As previously stated, one combination factor of CAM is ketoacidosis; it can enhance proton-mediated displacement of ferric form and accumulate serum-free irons that in turn impair phagocytic activity which aids in the growth of fungal pathogen.[6] Similarly, the extensive use of iron-laden multivitamins as "immunity boosters" might lead to augmented free-iron levels as well. Some other precautions should be taken by all the medical professionals to beat the mucormycosis are as follows:

i. Proper decontamination of hospital environment. Fungal pathogens can live up to hours to month in hospital beds, bed bars, table, tap, etc.
ii. Use of disposable oxygen humidifiers and clean distilled water in humidifiers and in oxygen concentrators.
iii. Limit the use of iron and zinc supplements for the management of COVID-19.
iv. Avoid the use of broad-spectrum antibiotics unless required.
v. Maintain the personal hygiene strictly even after recovery from COVID-19.
vi. Avoid staying in a damp environment.
vii. Avoid the overuse of steam inhalation and nonhumidified oxygen. Steam inhalation may result in destruction of the mucous layer that may lead to easy penetration of Mucorales.
viii. Maintain strict metabolic control including the blood sugar levels.
ix. Educate the patients suffering from COVID-19 about the early signs and symptoms of mucormycosis during hospital discharge.
x. Use the amphotericin B (antifungal drug) to treat mucormycosis followed by surgical debridement.

Presently the incidence of CAM is as high as 70% in India than global average. Therefore, we must be very cautious about the secondary fungal infections in COVID-19 patients. This is the time to bring awareness of fungal diseases in India as India needs better consensus for fungal diseases.

Conflict of Interest
None declared.

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Reforming the Culture of Medical Faculty Promotion and Appointment

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A fairly recent paper published in the *Annals of the National Academy of Medical Sciences* attempted to provide improved and refined suggestions, based on a survey with a limited number of respondents ($n = 182$), on how to improve the faculty promotion criteria as suggested by the Medical Council of India (MCI).[1] The objectives of that paper were noble, providing a finer-scale "reward" scale for different manuscript types, and attempting to provide greater equity to additional authors, thereby giving them a fairer chance of more equal promotion opportunities. This letter encourages reflection on additional issues that the erstwhile MCI and Indian medical practitioners could consider to better or additionally assess faculty promotion.

The first suggestion may be controversial. In Table 4 of the article by Patra et al, only positive scores are assigned to each manuscript category, but no attention is paid to corrective measures or misconduct. Consequently, an additional fractional positive score (e.g., +0.1) could be awarded for select corrective measures in the literature that correct errors,[2] while a punitive score (–1) be assigned to any paper category that has been retracted due to misconduct such as guest authorship, plagiarism, data fabrication, or other forms of fraud. This supplemental set of scores would encourage the correction of erroneous literature and would also send a clear message that misconduct would have a negative impact on career prospects and employment security, allowing medical practitioners to reflect more carefully before engaging in any nefarious or unethical activity.

The MCI promotion criteria focus heavily on a scientist's achievements. I propose a wider focus on science, society, and scientists, in a balanced or equal proportions (the "triple-S" approach). In this approach, research and research papers that collectively display a responsible attitude toward the integrity of science, such as through principles of open science and reproducibility,[3] are rewarded a bonus +1 point per paper. Similarly, research that tangibly benefits either local or international communities,[4] or that accommodates robust and ethical international collaboration, could also be rewarded. Finally, a bonus for research and publication practices, including authorship attribution, that take into consideration a fair (i.e., considering qualifications) and balanced approach to gender equity[5] would endow the research institute and country with additional reputational benefit.

Some of these suggestions might be considered liberal or progressive, but ultimately a reflection on them is to make medical faculty promotion and appointment fair, balanced, equitable, and based on more realistic principles and criteria.

Authors Contribution

The author contributed entirely to the intellectual discussion underlying this paper, literature exploration, writing, reviews and editing, and accepts responsibility for the content of the paper.

Conflicts of Interest

None declared.

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