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SARS-CoV-2-host dynamics: Increased risk of adverse outcomes of COVID-19 in obesity

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A B S T R A C T

Background and aim: The pandemic of COVID-19 has put forward the public health system across countries to prepare themselves for the unprecedented outbreak of the present time. Recognition of the associated risks of morbidity and mortality becomes not only imperative but also fundamental to determine the prevention strategies as well as targeting the high-risk populations for appropriate therapies.
Methods: We reviewed, collated and analysed the online database i.e. Pubmed, Google scholar, Researchgate to highlight the demographic and mechanistic link between obesity and associated risks of severity in COVID-19.
Results: We observed a changing dynamic in the reporting from the time of initial pandemic in China to currently reported research. While, initially body mass index (BMI) did not find a mention in the data, it is now clearly emerging that obesity is one of the profound risk factors for complications of COVID-19.
Conclusion: Our review will help clinicians and health policy makers in considering the importance of obesity in making the prevention and therapeutic strategies of COVID-19. An extra attention and precaution for patients with obesity in COVID-19 pandemic is recommended.

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1. Background

On December 31, 2019 several cases of pneumonia with an unidentified origin emerged from Wuhan, China which were reported to World Health Organisation (WHO) [1].The cause of these cases was confirmed to be severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after a week [2]. Considering its spread; the outbreak was declared a Public Health Emergency of International Concern on January 30, 2020 and later WHO announced a name for the new coronavirus disease as COVID-19 [3].

As of July 14, 2020 there have been 1,29,64,809cases and 45,70,288 deaths globally due to COVID-19 spanning across all countries with USA, Brazil and Europe reporting the maximum load [4].

While most people with COVID-19 develop no symptoms or have only mild illnesses, the evidence from China indicate that approximately 14% develop severe disease that requires hospitalisation and oxygen support, while 5% require admission to an Intensive Care Unit (ICU) [5].

Due to the mounting public health concerns about COVID 19 worldwide, scientists have been poring over data about the spectrum of clinical manifestations of COVID-19. Certain factors such as age and co-morbidities like hypertension, diabetes and cardiovascular disorders have mostly been found to be associated with severe illnesses requiring robust measures and support from health care system [6]. Such an association with obesity and high BMI has been insufficiently reported and considering it as the forerunner of many of these co-morbidities, it becomes inevitable to investigate an association of obesity with severe outcomes of COVID-19.

Nonetheless, the exact mortality rate varies greatly between regions and countries which can partly be due to the varying extent of testing and also possibly be due to differing trajectories based on population demographics and quality of health care availability.

Keeping in mind that there is lack of herd immunity and absence of an effective vaccine and antiviral therapy, countries are bound to take stringent measures to flatten the transmission curve in order to cope with the demands of health care systems. Thus, taking into account evidence and lessons from the ongoing situation of COVID-19 from different parts of the world, it becomes imperative to identify which patients are most at risk for hospitalisation. It can

assist emergency care providers in making triage decisions. Further, it can help inform policymakers about highest risk populations, who may need particular protection through policy decisions. Finally, it can help epidemiologists to improve the accuracy of projections about the likely need for hospital beds and staffing in a region by knowing its demographic characteristics. Hence, we put forth the detailed evidence and changing clinical demographics related to obesity being an important risk factor for complicated outcomes in COVID-19, thereby also ascertaining the putative reasons behind it.

2. Early data on COVID-19 in obesity: evidence from China

After a scrutiny of published literature, we found a paucity of information about the BMI of cases of COVID-19 because majority of the studies from China [7] which have reported co-morbidities, did not provide data on BMI of such patients. However, the findings from a retrospective analysis on 112 patients with COVID-19 infection admitted in a Hospital in Wuhan, between 20 January 2020 to 15 February 2020 are noteworthy. In this study, the BMI of the critical group was significantly higher than that of the general group. Patients were further divided into two groups, survivors (84.8%) and non-survivors (15.18%). Among the non-survivors, 88.2% of patients had a BMI >25 kg/m^2, which was in a significantly higher proportion ($P < 0.001$) than in survivors (18.8%) [8]. The authors concluded that a higher BMI was more often seen in critical cases and non-survivors.

In another study from Wenzhou, China; it was found that the presence of obesity in metabolic associated fatty liver disease (MAFLD) patients was associated with a ~6 -fold increased risk of severe COVID-19 illness (unadjusted −OR 5.77, 95% CI 1.19—27.91, p = 0.029). This association with obesity and COVID-19 severity remained significant (adjusted −OR 6.32, 95% CI 1.16—34.54, p = 0.033) even after adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidaemia [9]. Moreover, Qingxian Cai et al. examined an association between obesity and severity of COVID-19 using data from only the referral hospitals in Shenzhen, China [10]. They found that overweight group showed 86% of higher odds, and obesity group showed 2·42-fold higher odds of developing severe pneumonia.

As the COVID-19 continues to spread worldwide, such an evidence from China is sufficient to provide an insight to clinicians to maintain a high level of attention for obese patients. Persons with severe obesity who become ill and require intensive care (5% of infections) present challenges in patient management like difficult intubations, difficulty in obtaining an imaging diagnosis (there are weight limits on imaging machines) and a requirement of special beds and positioning/transport equipment which might not be widely available in a majority of hospital set ups.

3. Emerging data from Europe and USA: Change in trend for risk factors of severe outcomes in COVID-19

A close survey of the available data on co-morbidity and mortality for COVID-19 across the world (Later March and April 2020); points towards the emergence of obesity as one of the major risks for complications apart from older age [12—18].

A descriptive study of a small sample of 24 critically ill patients diagnosed with COVID-19 in the Seattle region (USA) was among the first to report BMI data (3 patients with a BMI in the normal category, 7 with overweight, 13 with obesity and 1 with missing data). Although the numbers were too small for meaningful statistical analyses but 85% of the patients with obesity required mechanical ventilation and 62% of the patients with obesity died was a noteworthy finding. These proportions were greater than

those in the patients without obesity, in which 64% required mechanical ventilation and 36% died [11].

Many recent studies are now reporting obesity as one of the risk factors for severity of COVID-19 in USA, Brazil, UK, Italy, Spain and France [12–18,67] (summarised in Table no 1).

In the current scenario, since USA has become the epi-centre of the COVID-19 pandemic; the dynamics of patient characteristics in terms of associated complications is showing a difference from the initial data put out by China. This might be attributed, on one hand, to the paucity of reported BMI related information of the positive and critical cases from the data of China during the initial stages, and on the other hand, to the higher incidence and prevalence of obesity in USA as compared to other nations in the world. The prevalence of obesity in US has been 42.4% in 2017−2018 with a high burden of class III obesity i.e. 9.2% of the population with BMI>40 kg/m^2 [20]. In fact, it is also listed as a risk factor for COVID-19 by the USA Centres for Disease Control and Prevention [21].

4. Obesity in Indian population

In India, the prevalence of obesity varies due to age, gender, geographical environment and socio-economic status. According to ICMR-INDIAB study 2015, prevalence rate of obesity and central obesity varies from 11.8% to 31.3% and 16.9%−36.3% respectively.[22] Infact more than 135 million individuals are affected by obesity [22] and the prevalence is rising fast amounting to a huge burden on healthcare infrastructure in our country, particularly, abdominal obesity which is considered to be one of the leading causes of cardiovascular diseases.

Moreover, Asians often display lower cardiorespiratory fitness and carry proportionally more fat percentage for any BMI as compared to their counterparts from the western world [23].

5. Experiences from history: Influenza pandemics and obesity

The influenza of 1956−1960 (*Asian*) and of 1968 (*Honk Kong*) have confirmed that obesity and diabetes had led to a higher mortality and a prolonged duration of illness even in the absence of other chronic conditions which increased the risk of influenza-related complications [24]. During the 2009 H1N1 pandemic, obesity was recognized as an independent risk factor for complications from influenza [25]. Moreover, it had been well established that obesity increased the duration of viral shedding in H1N1 pandemic by 42% as compared to adults who did not have obesity [25]. Worldwide, diabetes and obesity were the most frequently identified underlying conditions in fatal cases who were older than 20 years of age. However, anecdotal observations of high prevalence of obesity in severe and fatal cases were also reported from Chile, Manitoba and Mexico [25].

Several reports from around the world identified obesity and severe obesity as risk factors for hospitalisation and mechanical ventilation [26]. The distribution of obesity among hospitalized patients in California and New Mexico exceeded the 35% prevalence of obesity in US adults in 2009−2010 [25,27].

Moreover, it's a matter of concern knowing the fact that persons with obesity have diminished protection from influenza immunization with a study showing that adult recipients of Influenza vaccine (IIV3) with obesity had two times greater incidence of influenza and/or influenza like illness despite being vaccinated [28].

Thus, prior experience of the impact of obesity on morbidity and mortality from previous influenza pandemics should definitely sensitise the clinicians in caring for patients with obesity and COVID-19 towards a need for their aggressive management. Moreover, strict precautionary measures must be advised to this

Table 1
A summary of prevalence of obesity as well as co-morbidities in Covid-19 from review of the current literature.

First Author	City/Country	No of subjects	Obesity (%)	Adverse clinical outcomes in obese
Goyal P et al. [12]	New York City	393	35.8	Majority needed invasive mechanical ventilation
Petrilli CM et al. [13]	New York City	4103	26.8	BMI$\geq$ 40 kg/m^2 was second strongest independent predictor of hospitalisation after old age.
Richardson S et al. [14]	12 Hospitals in New York City area, long Island, Westchester County.	5700	41.7	Obesity was second major co-morbidity after hypertension
Lighter J et al. [15]	New York City	3615	BMI: 30–34 kg/m^2 (21%) and BMI$\geq$35 kg/m^2 (16%)	patients with BMI$\geq$35 were 3.6 times more likely to be admitted for critical care as compared to normal BMI.
Garg S et al. [16]	COVID-NET USA	–	48.3	–
Simmonet A et al. [17]	Lille, France	124	BMI >30 kg/m^2 (47.6%) and BMI >35 kg/m^2 (28.2%)	Need for mechanical ventilation was associated with BMI$\geq$35 kg/m^2, independently of other comorbidities.
Intensive Care National Audit and Research Centre (ICNARC) report [18]	UK	3383	72% were overweight or obese	38% of patients admitted to critical care with a diagnosis of SARS-CoV-2 were obese.Out of these 57.6% died in critical care, as opposed to approximately 45% of those with a BMI<30 kg/m^2
Bello-Chavalla OY [19]	Mexico	51,633	20.7	Obesity mediated 49.5% of the effect of diabetes on COVID-19 lethality. Obesity also conferred an increased risk for ICU admission and intubation with five-fold increased risk of mortality in COVID-19 patients.
Suleyman G et al. [67]	Detroit	463	57.6% obese with 19.2% severely obese	Severe obesity was significantly associated with need for mechanical ventilation (OR 3.2; 95%CI, 1.7–6.0)

group of individuals in the present pandemic. These include mandatory social distancing and home quarantine considerations with a close watch on the quality and quantity of food being consumed.

6. SARS-CoV-2- Host dynamics in obesity

6.1. Presence of other co-morbidities is common

Obesity potentiates multiple cardiovascular risk factors with premature development of cardiovascular disease and adverse cardiorenal outcomes. In individuals with diabetes, obesity and excess ectopic fat leads to impairment of insulin sensitivity and a reduced beta-cell function. Both limit the ability to evoke an appropriate metabolic response upon immunologic challenge. Overall, there is a loss of integrated regulation of metabolism required for the complex cellular interactions and for an effective host defence, further leading to the functional immunologic deficit. There is a significant worsening of the clinical profile and influenza disease severity whenever there is presence of multiple co-morbidities associated with obesity [23].

Furthermore, obesity enhances thrombosis, which is evident by the association between severe COVID-19 and pro-thrombotic disseminated intravascular coagulation and high rates of venous thromboembolism. Beyond cardiometabolic and thrombotic consequences, obesity has detrimental effects on lung function, diminishing forced expiratory volume and forced vital capacity [23]. Obesity has a well-known impact on Pulmonary functions. It is associated with decreased expiratory reserve volume, functional capacity, and respiratory system compliance. Pulmonary function is further compromised by decreased diaphragmatic excursion, making ventilation even more difficult [29].

All these are possible determinants of worst clinical outcomes in COVID-19 with obesity and associated metabolic co-morbidities. During the present pandemic, till now, it has been well established that cardiovascular diseases and diabetes are the major risk factors for poor outcomes but considering a higher BMI to be a forerunner for both these co-morbidities, the inclusion of obesity and overweight individuals as candidates for poor COVID-19 outcomes becomes very important. However due to paucity of reported anthropometric characteristics from the initial outbreak in China, it is difficult to comment on obesity being independent risk factor for complicated COVID-19. But changing demographic dynamics has now pointed towards importance of noting the important anthropometric data for all the affected individuals.

6.2. Perturbations in the immune system

Obesity is considered as a chronic inflammatory state. Such individuals have a higher concentration of several pro-inflammatory cytokines like TNF-α, MCP-1 and IL-6, mainly produced by visceral and subcutaneous adipose tissue leading to a defect in the innate immunity [30]. When an antigen is presented in such an environment, a reduced macrophage activation and a blunted pro-inflammatory cytokine production occurs [31]. This microenvironment explains the emergence of antiviral-resistant and vaccine escape variants in the obese population [32,33].

Studies of cytokine dynamics in human "cytokine storm" models shows that IL6 sustains activation of multiple cytokine pathways for many days post initial immune insult [34]. Interestingly, in early COVID-19 studies IL6 was a strong independent predictor of mortality [35]. Human adipose tissue is a major source of IL6 and its receptor IL6R [36] and, thus, adipose tissue may provide a reservoir for IL6 activation and cascade signalling in viral infection. Viral spread from affected organs to adjacent adipose tissue may take days, with subsequent prolonged viral shedding contributing to the delayed cytokine storm and consequences for tissue injury in patients with COVID-19. In line with this, IL6 inhibition has already been proposed as a treatment in COVID-19 and the results of trials of Tocilizumab are awaited [37].

B and T cell responses are impaired in obese patients, and this causes an increased susceptibility and a delay of resolution of the viral infection [38,39]. The hormonal milieu is such that in obesity; that there is an adipokine dysregulation with higher leptin (pro-inflammatory adipokine) and lower adiponectin (anti-inflammatory adipokine) levels. Leptin resistance was also found to be an important factor associated with severe lung injury in 2009 H1H1 pandemic [38]. Not only this, studies in obese mouse models have suggested that both innate and adaptive immune responses to Influenza A virus and its vaccine antigens like type I interferon response, Natural Killer cell functions, antigen presentation by dendritic cells and antigen specific memory of CD8$^+$ lymphocytes

PULMONARY COMPLICATIONS IN OBESITY:

- Impaired respiratory mechanics[30](↓FEV, ↓FVC, ↑airway resistance, ↓diaphragmatic excursion)
- Obstructive Sleep Apnea (OSA)
- Increased viral shedding[25]

PERTURBATIONS OF IMMUNE SYSTEM IN OBESITY:

- ↑ pro-inflammatory cytokines (TNFα, IL-6, CRP, MCP-1)[31]
- Cytokine storm[35]
- Complement activation[44]
- Adipokine dysregulation (↑leptin, ↓adiponectin)[39]
- Chronic low-grade inflammation
- Altered innate & adaptive immune response[33,34]

CARDIOVASCULAR AND METABOLIC CO-MORBIDITIES:

- Dyslipidemia, hypertriglyceridemia
- Fatty Liver
- Insulin Resistance, Diabetes Mellitus[23]
- Hypertension
- ↑risk of thrombo-embolic complications[23]

EMERGING MECHANISMS:

- Ectopic fat depositions in various organs
- ACE-2 receptors expressions in adipose tissue[56]
- Lipofibroblasts as postulated cells involved with pulmonary fibrosis in obesity[66]

Problems/Burden on health care system:

- *Longer duration of infectivity*
- *↑ ICU bed requirement; Difficulty in intubation*
- *Difficulty in imaging (there are weight limits on imaging machines)*
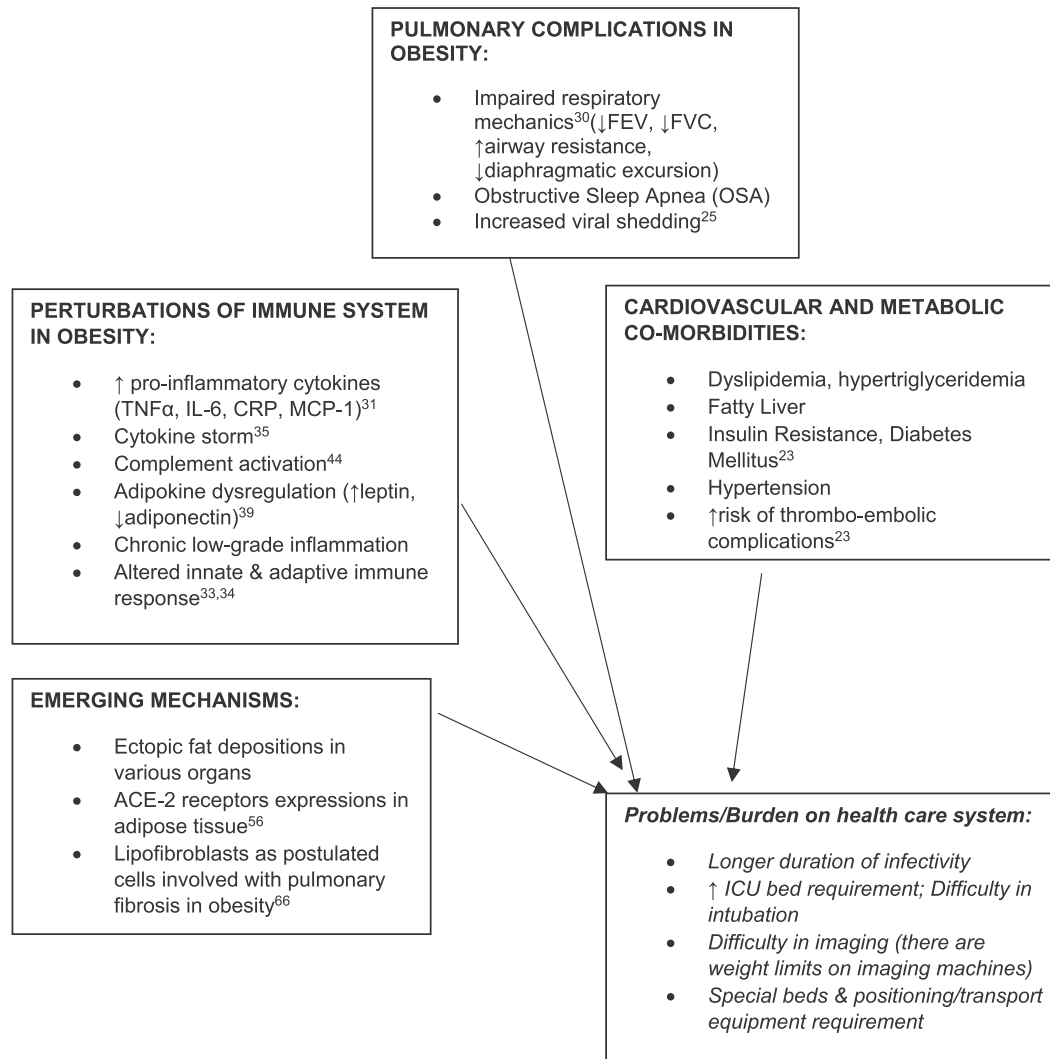- *Special beds & positioning/transport equipment requirement*

Fig. 1. Schematic summary of the possible mechanisms and challenging problems which could complicate COVID-19 course in obesity.

were defective [38].

Additionally, a diminished interferon response and an increased influenza virus replication were found in normal bronchial epithelial cells derived from obese subjects [40–42]. Shared viral tropism for lung epithelium and adipose tissue has already been shown for H5N1 virus infection [44].

Gralinski and collaborators identified the complement system as an important host mediator of SARSCoV-induced disease [43]. Notably, Eculizumab, an antibody with complement system modulatory activity, is now being studied in an FDA expanded type of trial (ClinicalTrials.gov Identifier: NCT04288713) to assess its effect on COVID-19 infected patients relative to duration of intensive care treatment and mechanical ventilation, together with mortality outcomes [45].

Currently there is no evidence for direct SARS-CoV-2 infection of adipose tissue, although ACE2 receptor expression represents a basis for viral tropism in several cells within this tissue [46] including adipocytes, smooth muscle cells and endothelial cells [47].

If we look into the past influenza pandemics also, it has been found that many Adipose tissue resident cells are proven targets for multiple viruses like adipocytes (H1N1, Type A influenza and adenovirus 36) [48–50], adipo-stromal cells (Adenovirus 36, [51] CMV [52]), endothelial cells (SARS-CoV) [53], macrophages

(influenza A, SARS-CoV, adenovirus36, HIV) [53,54] and lymphocytes (SARS-CoV, HIV) [52,53]. Considering, large extent of adipose tissue mass in obesity and its immune dysfunctions; its role in augmenting the prolongation and consequent complications of COVID-19 seems inevitable.

6.3. Angiotensin converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP-4) in adipose tissue

Severe acute respiratory syndrome coronavirus (SARS-CoV) binds with the angiotensin converting enzyme 2 (ACE2) receptor for intracellular invasion, and the mechanism for acute lung injury during infection has been postulated to be mediated through the activation of the renin-angiotensin- system (RAS) [55]. RAS blockade has been proposed as a potential treatment for COVID-19 [56]. Remarkably, ACE2 is expressed in the human adipose tissue. Individuals with obesity have more adipose tissue and therefore an increased number of ACE2 expressing cells [57]The overall angiotensin converting enzyme (ACE)/angiotensin II (Ang II)/type 1 angiotensin 2 receptor (AT1R) RAS axis activation plays an important role in the pathophysiology of obesity and visceral adiposity-related cardiac risk [58]. Thus, the interaction between ACE2-RAS system, adipose tissue and the SARS-CoV-2 could, at least

partially, explain the higher morbidity and mortality risk of COVID-19 in obese patients. Additionally, it can be stated that treatment with specific anti-hypertensive medications (ACE inhibitors and angiotensin receptor blockers, ARBs) will increase expression of ACE2 and increase patient susceptibility to viral host cell entry and propagation [59]. Thus a layer of complexity is added while managing COVID-19 infected persons who have more than one co-morbidity.

Secondly, human dipeptidyl peptidase 4 (DPP4) was also identified as a functional receptor for the spike protein of the Middle East coronavirus (MERS-Co-V) [60]. MERS-CoV binds to the receptor-binding domain and interacts with T cells and nuclear factors such as NF-kβ, involved in the pathogenesis of inflammatory disorders. DPP4 a transmembrane protein, has been found to be highly expressed in human visceral adipose tissue and is associated with insulin resistance and adipocyte inflammation. DPP-4 inhibition increases glucagon like peptide -1 (GLP-1) secretion leading to an improved insulin sensitivity and glucose metabolism within the adipocyte [61]. DPP4 inhibitors are commonly prescribed in Type 2 diabetes with obesity.Considering the immune modulatory effects of DPP4 inhibitors like suppression of T-cell proliferation and the secretion of pro inflammatory cytokines, such as IL-6 and 10,[62] it becomes logical to translate such findings in context to COVID-19 in obesity. Thus DPP4 may represent a potential target for preventing and reducing the risk and progression of the acute respiratory complications that type 2 diabetes may add to COVID-19 in obesity.

6.4. Postulated role of pulmonary lipofibroblasts

Progressive consolidation of the lung leading to severe acute respiratory syndrome is recognized as the most common complication of SARS-CoV virus [63]. This virus shares a high degree of genetic homology with SARS-CoV-2. One of the main reasons for this pulmonary consolidation is an extensive pulmonary fibrosis which was evident from CT scan and autopsy findings in SARS-CoV infections [11,63]. The pathophysiology of pulmonary fibrosis is not fully elucidated but role of myofibroblasts in modifying the lung structure and functions have been established in such conditions [64]. Such cells have also been found to be connected with adipocyte —myofibroblasts trans-differentiation in certain fibrotic lesions of skin [65]. Moreover, pathophysiological pathways have been linked with adipogenic-myogenic transition in lungs in pulmonary fibrosis where pulmonary lipofibroblasts have been proposed to be playing a central role. This population of cells carry characteristic lipid droplets and express high levels of perilipin-2 and are found adjacent to the ACE2 expressing alveolar epithelial cells [66]. Thus its logical to explore whether SARS-CoV/CoV-2 can directly influence these cells and thereby promote enhanced Lipofibroblast-myofibroblast transition [66]. It has also been postulated that adipose tissue can serve as a viral reservoir, whereas trans-differentiation of pulmonary lipofibroblasts into myofibroblasts can contribute to the development of pulmonary fibrosis and thus is likely to influence the clinical severity of COVID-19 [66]. Further, this population of cell has been proposed to increase the severity of the local response to COVID-19 in the lung [66]. This could be explored to avert the pulmonary complications of COVID-19 in obesity.

7. Conclusion

The pandemic of COVID-19 has put the public health system under immense strain to tackle the load of its high transmission and critical complications with the available limitations of the present health-care infrastructure. Putting together, our data has brought up some important insights towards considering BMI and

obesity as one of the risk factors for severity and critical admissions for COVID-19 (as summarised in Fig. 1). However, whether obesity, over and above its cardio-metabolic co-morbidities might independently contribute to COVID-19 risk; needs more robust and detailed prospective survey.

Declaration of competing interest

Rakhee Yadav: Conceptualization, Data curation, Formal analysis, Writing - original draft, review & editing, Design, Literature search, Data acquisition, Data analysis, Manuscript Preparation, Manuscript editing, Manuscript review, Guarantor, Sandeep Aggarwal: Conceptualization, Writing - review & editing, Concepts, Contribution to intellectual content, Literature search, Manuscript editing, Manuscript review, Archna Singh: Formal analysis, Writing - review & editing, Contribution to intellectual content, Data analysis, Manuscript editing, Manuscript review.

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