OBESITY AND IN-HOSPITAL OUTCOMES AMONG PATIENTS WITH SEVERE COVID-19 IN VIET NAM

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ABSTRACT

Introduction: COVID-19 (Coronavirus disease 2019) is a global pandemic. Overweight and obesity are risk factors related to mortality as well as disease severity. Overweight and obesity are also increasing in Vietnam. Data related to the characteristics of COVID-19 in this vulnerable population was limited in Vietnam. The study was conducted (1) to describe the outcomes of overweight and obese COVID-19 patients, and (2) to investigate factors associated with the outcomes of overweight and obese COVID-19 patients. ***Methods:*** A cross-sectional description was conducted at the Hospital for Tropical Diseases from July 2021 to December 2021. Patients who were (1) ≥ 18 years old (2) diagnosed with COVID-19 with a positive RT-PCR SARS-CoV-2 result and (3) had BMI ≥ 23 kg/m2. Female pregnant women or ascites were excluded from this study. To determine factors associated with mortality and ICU admission, chi-square and Fisher's Exact were used. Variables with $p < 0.05$ were included in the logistic regression model to investigate independent risk factors. Cases directly admitted to the ICU were excluded when analyzing risk factors for ICU admission. ***Results:*** 173 patients were recruited (70 patients (40.46%) were overweight, 74 patients (42.77%) were obesity class I and 29 patients (16.76%) were obesity class II). The overall mortality rate was 28.9%. The ICU admission rate was 46.2% with a median ICU stay of 9 (6 – 15.25) days. The rate of respiratory support was 83.8%, of which 31.8% of patients required invasive mechanical ventilation and the median duration of respiratory support was 12 (6.5 – 16.5) days. Independently factors associated with ICU admission were diabetes (OR = 2.92 (1.27 – 6.67)) and a severe or critical condition at admission (OR = 8.82 (2.51 – 31.08). Independently factors associated with death were vaccination (OR = 0.23 (0.08 – 0.63)), a severe or critical at admission (OR = 15.74 (3.46 – 71.55)) and remdesivir usage (OR = 0.78 (0.16 – 0.87)). ***Recommendation:*** Vaccination against COVID-19 has been shown to be effective in the obese and overweight population.

Key words: *COVID-19, obesity, overweight, vaccine, remdesivir, mortality.*

I. INTRODUCTION

COVID-19 (Coronavirus disease 2019) was first announced in Wuhan, China in December 2019. It soon spread globally and in March 2020, World Health Organization (WHO) declared that COVID-19 was a global pandemic. By now, there are more than 750 million COVID-19 cases have been confirmed with nearly 7 million deaths. From July 2021 to December 2021, with the appearance of the new Omicron variant, Vietnam, especially the southern region, experienced a severe COVID-19 epidemic. Risk factors of death were old age, obesity, and co-morbidities such as hypertension, diabetes, cardiovascular diseases, and chronic obstructive pulmonary diseases.

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Obesity was one of the most common risk factors in some areas [8].

Many studies have investigated the correlation between COVID-19 and obesity. A recent meta-analysis of more than 3 million patients from 170 studies found that obesity was associated with a higher risk of severe disease (RR=1.52, 95% CI 1.41-1, 63) and death (RR = 1.09, 95% CI 1.02-1.16) [4].

Research conducted by Yates et al, 2022 showed that the mortality rate due to COVID-19 recorded in white, black, South Asian, and other minority ethnic groups was 30,067 (0.27%), 1,208 (0.29%), 1,831 (0.29%), and 845 (0.18%), respectively. The estimated risk of death from COVID-19 at a BMI of 40 kg/m2 in white people was equivalent to the observed risk at BMIs of 30.1 kg/m2, 27.0 kg/m2, and 32.2 kg/m2 in black, South Asian, and other minority ethnic groups respectively [5]. Therefore, the study was conducted in Vietnam, a developing country in Southeast Asia (1) to describe the outcomes of overweight and obese COVID-19 patients, and (2) to investigate factors associated with outcomes of overweight and obese COVID-19 patients.

II. METHODS

A descriptive cross-sectional study was conducted from July 2021 to December 2021 at the Hospital for Tropical Diseases. This is the leading infectious disease hospital in the southern region of Vietnam receives and treats severe COVID-19 cases with high-tech testing and patient care facilities such as mechanical ventilation, dialysis, and plasma exchange. Patients who were (1) ≥ 18 years old, (2) diagnosed with COVID-19 with a positive RT-PCR SARS-CoV-2 result, and (3) had BMI ≥ 23 kg/m2. Female pregnant women or ascites were excluded from the study.

Variables collected from medical records included age, gender, address, underlying disease, COVID-19 vaccination, clinical manifestations, and paraclinical results at admission and during the treatment process including drugs (antibiotics, anticoagulants, anti-inflammatories, etc.), and interventions such as respiratory support, mechanical ventilation, and dialysis. Treatment outcome variables included severity at admission; mortality rate, ICU admission rate, respiratory support rate, number of days in hospital, number of days in ICU, number of days requiring respiratory support, and type of respiratory support. In particular, severity at admission was based on the standards of Vietnam's National Guidelines, and the kinds of respiratory support were divided into 4 groups including oxygen ventilation via cannula, HFNC (High-flow nasal cannula), non-invasive ventilation, and invasive mechanical ventilation; The type of respiratory support was recorded according to the highest level of support indicated to patients. Data was analyzed with SPSS software. Patients were divided into 3 groups: overweight (23 kg/m2 ≤ BMI < 25 kg/m2), obesity class I (25 kg/m2 ≤ BMI < 30 kg/m2) and obesity class II (BMI ≥ 30 kg/m2). Epidemiological characteristics, underlying disease, severity at admission, and patient outcomes in the groups were compared by using ANOVA, Kruskal-Wallis tests with quantitative variables, and chi-square tests, Fisher's Exact with qualitative variables. To determine factors associated with mortality and ICU admission, chi-

square and Fisher's Exact were used. Variables with $p < 0.05$ were included in the logistic regression model to investigate independent risk factors. Cases indicated direct ICU admission were excluded when analyzing risk factors for ICU admission.

III. RESULTS

173 patients were recruited. Out of them, 70 patients (40.46%) were overweight, 74 patients (42.77%) had obesity class I and 29 patients (16.76%) had obesity class II.

3.1. Demographic characteristics of COVID-19 obesity patients

Table 1. ***Demographic characteristics of COVID-19 obesity patients***

	All (n=173)		Overweight (n = 70)		Obesity class I (n = 74)		Obesity class II (n = 29)		p
	N	Percent	N	Percent	N	Percent	N	Percent	
Age	55.7 ± 16.3		57.9 ± 17.4		53.7 ± 14.9		55.7 ± 16.4		0.29[a]
18 – 49	59	34.1	33	32.9	27	36.5	19	31.1	0.73
50 – 65	71	41.0	26	37.1	32	43.2	21	44.8	
≥ 65	43	24.9	21	30.0	15	20.3	7	24.1	
Male	84	48.4	37	52.9	34	45.9	13	44.8	0.64
Comorbidity									
0 disease	50	28.9	26	37.1	18	24.3	6	20.7	0.16[b]
1 disease	55	31.8	18	25.7	29	39.2	8	27.6	
≥ 2 diseases	68	39.3	26	37.1	27	36.5	15	51.7	
Hypertension	91	52.6	33	47.1	41	55.4	17	58.6	0.49
Diabetes	53	30.6	19	27.1	26	35.1	8	27.6	0.55
CVD	21	12.1	11	15.7	8	10.8	2	6.9	0.47
COPD or Asthma	14	8.1	6	8.6	6	8.1	2	6.9	0.99
CKD	8	4.6	4	5.7	4	5.4	0	0	0.57[b]
Vaccine									
None	123	71.1	49	70.8	57	77.0	27	58.6	0.40
1 dose	22	12.7	9	12.9	7	9.5	6	20.7	
2 doses	28	16.2	12	17.1	10	13.5	6	20.7	

[a] Krusall-Wallis test, [b]Fisher's Exact test

The average age was 55.7 ± 16.3; 43 patients (24.9%) were ≥ 65 years old. The male proportion was 48.4%. There were 123 patients (71.10%) with at least one underlying disease, of which 68 patients (39.3%) had 2 or more underlying diseases. Among those underlying diseases, hypertension and diabetes accounted for the highest rates with 91 (52.6%) patients and 53 (30.6%) patients, respectively. Only 50 (28.9%) patients were vaccinated with COVID-19 shots, and 28 patients (16.2%) were fully vaccinated with 2 doses at the time of admission.

The epidemiological characteristics of the groups of overweight, obesity class I, and obesity class II were not statistically different. (Table 1).

3.2. Severity of admission and outcome in COVID-19 obesity patients

The proportion of critical, severe, moderate, and mild patients at the time of admission were 14/173 (8.1%), 119/173 (68.8%), 24/173 (13) .9%), and 16/173 (9.2%). In the group of overweight patients, these rates were 4/70 (5.71%), 46/70

(65.7%), 10/70 (14.3%), and 10/70 (14, 3%); In the group of patients with obesity class I, they were 5/74 (6.76%), 50/74 (67.57%), 13/74 (17.52%), 6//74 (8.11%); In the group of patients with obesity class II, they were 5/29 (17.24%), 23/29 (79.31%), 1/29 (3.45%) and 0/29 (0%). The difference between these groups was not statistically significant (p = 0.06). The overall mortality rate in the study was 28.9%, of which the mortality rate within 7 days and 30 days from hospital admission was 8.1% and 26.0%, respectively. The median hospital stay was 14 (11 – 19) days. The ICU admission rate was (46.2%) with a median ICU stay of 9 (6 – 15.25) days. The rate of respiratory support was 83.8%, of which 31.8% of patients required invasive mechanical ventilation and the median duration of respiratory support was 12 (6.5 – 16.5) days.

Table 2. ***Severity of admission and outcome in COVID-19 obesity patients***

	All (n=173)	**Overweight (n = 70)**	**Obesity class I (n = 74)**	**Obesity class II (n = 29)**	**p**
	N (Percent) Median (IQR)	**N (Percent) Median (IQR)**	**N (Percent) Median (IQR)**	**N (Percent) Median (IQR)**	
Severity at admission					
Mild	16 (9.2%)	10 (14.3%)	6 (8.1%)	0 (0%)	0.06[b]
Moderate	24 (13.9%)	10 (14.3%)	13 (17.6%)	1 (3.4%)	
Severe	119 (68.8%)	46 (65.7%)	50 (67.6%)	23 (79.3%)	
Critical	14 (8.1%)	4 (5.7%)	5 (6.8%)	5 (17.2%)	
Outcome					
Mortality	50 (28.9%)	19 (27.1%)	23 (31.1%)	8 (27.6%)	0.86
Mortality at 7 days	14 (8.1%)	6 (8.6%)	5 (6.8%)	3 (10.3%)	0.76[b]
Mortality at 30 days	45 (26.0%)	15 (21.4%)	22 (29.7%)	8 (27.6%)	0.53
Length of hospital (days)	14 (11 – 19)	13.5 (10 – 18)	15 (12 – 19)	17 (11 – 20.5)	0.20[a]
ICU admission	80 (46.2%)	24(34.3%)	38 (51.4%)	18 (62.1%)	**0.02**
Length of ICU (days)	9 (6 – 15.25)	8.5 (5 – 19.5)	10.5 (6 – 17.5)	8.5 (7 – 11)	0.63[a]
Oxygen support	145 (83.8%)	55 (78.6%)	62 (83.8%)	28 (96.6%)	0.07[b]
Length of oxygen support (days)	12 (6.5 – 16.5)	11 (6 – 15)	12.5 (7 – 21.25)	12.5 (6.25 – 16.75)	0.31[a]
Type of Oxygen support					
Conventional oxygen	64 (37.0%)	30 (42.9%)	24 (32.4%)	10 (34.5%)	**0.01[a]**
HFNC	22 (12.7%)	5 (7.1%)	8 (10.8%)	9 (31.0%)	
Non-Invasive ventilation	4 (2.3%)	1 (1.4%)	1 (1.4%)	2 (6.9%)	
Invasive ventilation	55 (31.8%)	19 (27.1%)	29 (39.2%)	7 (24.1%)	

[a] Krusall-Wallis test, [b]Fisher's Exact test

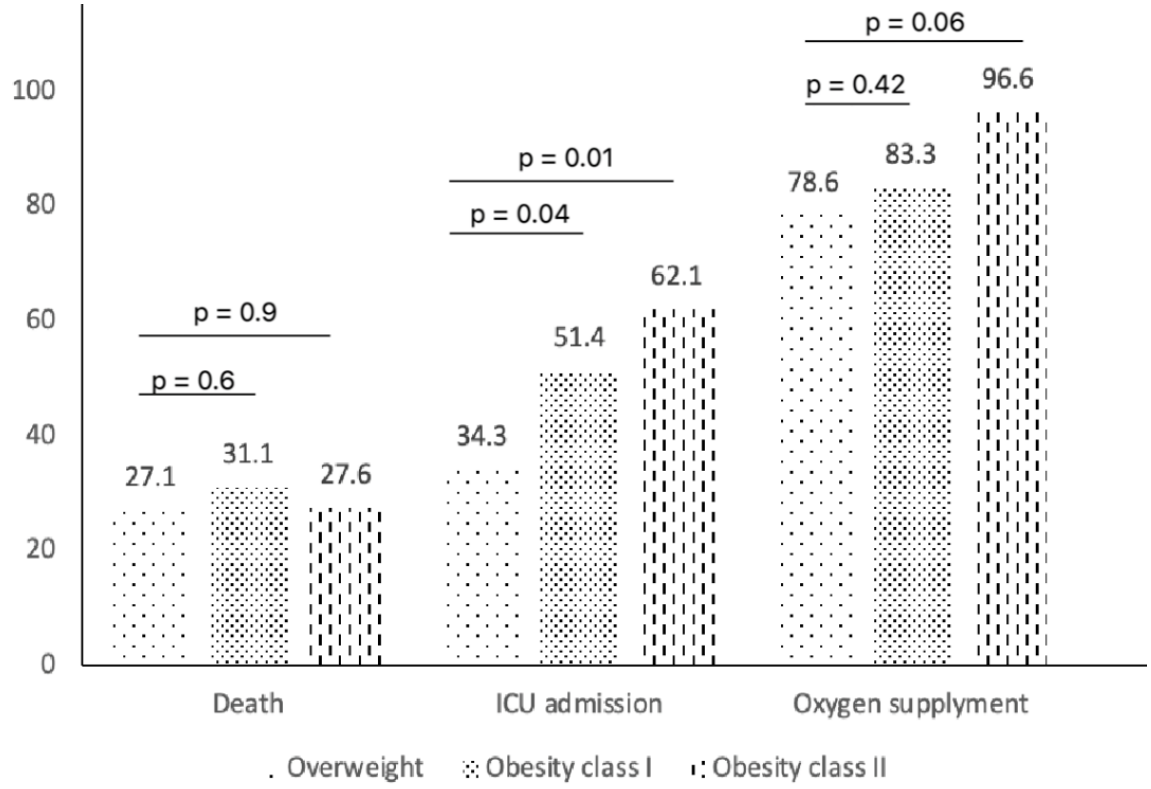

Figure 1. ***Rate of death, ICU admission and oxygen support***

There was no difference in the mortality rate among the three groups of overweight (27.1%), obesity class I (31.1%), and obesity class II (27.6%) (Table 2 and Figure 1). Similarly, the mortality rate within 7 days and 30 days from hospital admission of the 3 groups also had no differences (p = 0.76 and p = 0.53). The hospital stay of the 3 groups was similar with 8.5 (5 - 19.5) days in overweight, 10.5 (6 - 17.5) days in obesity class I, and 17 (11 - 20.5) days in obesity class II, p = 0.2.

The rate of ICU admission increased gradually in the overweight, obesity class I, and obesity class II groups: 34.3%, 51.4%, and 62.1%, respectively. This difference was statistically significant (Table 2 and Figure 1). There was no difference in the length of ICU stay between these 3 groups, p = 0.63. (Table 2)

The rate of respiratory support in the overweight, obesity class I, and obesity class II is 78.6%, 83.8%, and 96.6% respectively. This difference was not statistically significant (Table 2 and Figure 1). There was no difference in the duration of respiratory support among these 3 groups, p = 0.31. Regarding the kinds of respiratory support, the rate of oxygen support via cannula, HFNC, non-invasive ventilation, and invasive ventilation in the overweight group was 42.9%, 7.1%, 1.4%, 27.1%, in the obesity class I was 32.4%, 10.8%, 1.4%, 39.2%, and in the obesity class II was 34.5%, 31%, 6.9%, 24.1%. This difference was statistically significant (p = 0.01).

Table 3. ***Clinical characteristics of the COVID-19 obesity survivors***

	Overweight (n = 51)	Obesity class I (n = 51)	Obesity class II (n = 21)	p
	N (Percent) Median (IQR)	N (Percent) Median (IQR)	N (Percent) Median (IQR)	
Length of hospital (days)	14 (10 – 17)	13 (16 – 19)	17 (13 – 21)	**0.01**[a]
ICU admission	7 (13.7%)	15 (29.4%)	10 (47.6%)	**0.01**
Length of ICU (days)	7 (5 – 10)	9 (6 – 22)	7.5 (7 – 10.5)	0.63[a]
Oxygen support	36 (70.6%)	39 (76.5%)	20 (95.2%)	0.06[b]
Length of oxygen support (days)	9.5 (6.25 – 13)	12 (7 – 21)	13 (6.25 – 16.75)	0.26[a]
Type of Oxygen support				
Conventional oxygen	28 (54.9%)	24 (47.1%)	10 (47.6%)	**0.01**[b]
HFNC	4 (7.8%)	8 (15.7%	8 (38.1%)	
Non-Invasive ventilation	0 (0%)	1 (2.0%)	2 (9.5 %)	
Invasive ventilation	4 (7.8%)	6 (11.8%)	0 (0 %)	

[a] Krusall-Wallis test, [b]Fisher's Exact test

3.3. Risk factors for ICU admission and death

Of the 173 patients participating in the study, 35 patients (20.2%) were admitted to the ICU at the time of admission. Of the remaining 138 patients, 46 were subsequently admitted to the ICU.

Table 4. ***Risk factors for ICU admission by uni- and multi-variable analysis (n = 138)***

	Univariable analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Male	1.08	0.60 – 1.97		
≥ 65 years-old	2.08	0.96 – 4.52		
BMI				
Overweight	1			
Obesity class I	1.76	0.81 – 3.82		
Obesity class II	1.83	0.61 – 5.53		
Hypertension	1.99	0.96 – 4.10		
Diabetes	**3.12**	**1.44 – 6.76**	**2.92**	**1.27 – 6.67**
CVD	1.44	0.48 – 4.32		
COPD or Asthma	0.67	0.17 – 2.59		
Vaccine	0.59	0.26 – 1.31		
Severe or critical at admission	**9.25**	**2.67 – 32.05**	**8.83**	**2.51 – 31.08**
Remdesivir	0.83	0.40 – 1.75		

After univariate and multivariate analysis, we found factors independently associated with ICU admission in overweight and obese COVID-19 patients were diabetes (OR = 2.92 (1.27 – 6.67)) and a severe or critical condition at admission (OR = 8.82 (2.51 – 31.08)).

Table 5. ***Risk factors for death by uni- and multi-variable analysis***

	Univariable analysis			Multivariable analysis	
	OR	95% CI		OR	95% CI
Male	1.29	0.67 – 1.51			
≥ 65 years-old	**2.35**	**1.17 – 4.72**		1.93	0.85 – 4.40
BMI					
Overweight	1				

	Univariable analysis			Multivariable analysis	
	OR	**95% CI**		**OR**	**95% CI**
Obesity class I	1.21	0.59 – 2.49			
Obesity class II	1.02	0.39 – 2.70			
Hypertension	1.93	0.98 – 3.80			
Diabetes	**2.06**	**1.03 – 4.11**		1.84	0.81 – 4.18
CVD	2.03	0.80 – 5.18			
COPD or Asthma	0.98	0.29 – 3.29			
Vaccine	**0.25**	**0.10 – 0.62**		**0.23**	**0.08 – 0.63**
Severe or critical at admission	**10.73**	**2.48 – 46.45**		**15.74**	**3.46 – 71.55**
Remdesivir	**0.45**	**0.21 – 0.94**		**0.78**	**0.16 – 0.87**

After single and multivariate analysis, we found factors independently associated with death in overweight and obese COVID-19 patients were vaccination (OR = 0.23 (0.08 – 0.63)), a severe or critical condition at admission (OR = 15.74 (3.46 – 71.55)) and remdesivir usage (OR = 0.78 (0.16 – 0.87)).

IV. DISCUSSION

The study was conducted at the Hospital for Tropical Diseases where critical Covid-19 patients were received and treated followed by the treatment strategy of the Ministry of Health in Vietnam. This was advantageous in monitoring patients with specialized tests and treatments.

The average age in the study was 55.7 ± 16.3 years. The high average age in the study was also consistent with the studies taking samples from severe and critical patients. The study recorded that the proportion of patients with underlying diseases in this study population sample was 71.1%, of which 39.8% had two or more underlying diseases with the most common comorbidities being hypertension and diabetes. These features were the two most commonly reported comorbidities in the previous studies of COVID-19 in overweight and obese patients [1],[4].

The rates of requirement for respiratory support, invasive mechanical ventilation, ICU hospitalization, and mortality in this study were 83.8%, 31.8%, 56.2%, and 28.9%, respectively. Although the prevalence of requiring respiratory assistance, ICU hospitalization or mechanical ventilation varied significantly owing to changes in demographic characteristics and diagnostic criteria, in general, being overweight or obese increased the risk of severe COVID-19. Rottoli et al also reported greater rates of respiratory failure, ICU hospitalization and mortality in the overweight and obese group. Specifically, the rate of respiratory failure in BMI categories 25 - 29.9 kg/m^2, 30 - 34.9 kg/m^2, and≥ 35 kg/m^2 were 28.4%, 52.4% and 50.0% respectively; the ICU admission rate were 11.9%, 33.3% and 40.0%, while the death rates were 14.2%, 28.6% and 35.0%, respectively [1]. As noted previously, central fat distribution was greater in the group overweight and obese populations, which produced respiratory constraints, coupled with the mechanism of enhanced inflammatory response, which may cause more severe illness, more severe ARDS and greater oxygen demand in this vulnerable population.

Research by Rottoli et al in Italy indicated that all-cause mortality was greater in the obese group by linear regression analysis

with OR 2.18 (95%CI: 1.34 - 3.54).[1] Some multicenter studies in Europe and the Americas showed that the risk of obesity on death from COVID-19 was significant when BMI ≥40 kg/m^2, specifically when compared to the normal weight population (BMI between 18.5 and 24.9 kg/m^2) or after adjusting for co-morbidity factors was 2.68 (95% CI, 1.43-5.04) for the group with BMI 40-44 kg /m^2 and up to 4.18 (95% CI, 2.12-8.26) for the group with BMI of 45 kg/m^2 or more [7]. This may be related to discrepancies in the selection of control groups for comparison. The prior research usually employed a group of patients with normal physical conditions as the control group, but this study examined groups of overweight, obese level I and obese level II, thus the differences between them may be different. Research by Rottoli et al also showed that compared to the group with BMI < 30, the group with BMI from 30 - 35 kg/m^2 had an OR risk of death of only 1.21 (95% CI: 0.64 - 2.27) while groups with BMI ≥ 35 kg/m^2 had an OR risk of death of 1.72 (95% CI: 1.00 – 2.99) [1].

The prevalence of ICU hospitalization and the amount of respiratory support progressively rose with the level of overweight and obesity (Table 2 – Figure 1). This has also been proved by numerous investigations. Research by author Rottoli in Italy recorded the ICU admission rate in BMI groups 25 - 29.9 kg/m^2, 30 - 34.9 kg/m^2, ≥ 35 kg/m^2 as 11.9%, 33.3% and 40.0%%, [1] or Gao et al also showed that for every 1 kg/m^2 increased from 23 kg/m^2, the risk of ICU admission increased by 1.15 (95%CI: 1.10 – 1.20)[2]. From the foregoing data, it could be observed that the amount of overweight and obesity impacted the treatment outcome of patients infected with COVID-19.

In the research, 35 patients were admitted to the ICU at the time of admission. Of the remaining 138 patients, 46 patients were later admitted to the ICU. In univariate and multivariate analysis, two independent risk variables for ICU admission were diabetes mellitus and severity at admission. Diabetes has been demonstrated to be related to the severity of COVID-19 via various research. High blood sugar decreases the immune system's reaction as well as improves the capacity of SARS-CoV-2 to proliferate. Oxidation and pro-inflammatory molecules in diabetics are also greater than in normal persons. This mechanism promotes a cytokine storm in COVID-19 patients, resulting in severe sickness and even death. In addition, greater expression of the ACE-2 receptor in diabetes individuals lets SARS-CoV-2 rapidly enter and proliferate in cells, increasing immunological diseases. Overweight, obesity and diabetes have long been established to have a tight association. Increased amounts of fatty acids, glycerol or pro-inflammatory chemicals such as IL-6 and TNF-α in the blood enhance insulin resistance in obese individuals, resulting in obese patients being more prone to diabetes than normal persons, generally [4]. Therefore, screening and managing diabetes in overweight and obese COVID-19 patients was vitally crucial. Blood sugar management before and during hospitalization lowered ICU admission and death rates in COVID-19 patients.

When examining variables linked with mortality, usage of the vaccination plus the antiviral medicine remdesivir will help minimize the risk of death. Remdesivir therapy lowers the risk of mortality in COVID-19 patients with OR = 0.23 (0.08 – 0.63). This may be an effective weapon for

overweight and obese COVID-19 patients in particular and COVID-19 patients in general. However, the usefulness of remdesivir in COVID-19 patients is still debatable. A meta-study published in the New England Journal in 2020 indicated that medications such as remdesivir, lopinavir, hydroxychloroquine, and interferon therapies had poor efficacy in COVID-19 patients [6]. The studies were gathered mostly in high- or middle-income countries, on "old" and "new" COVID-19 strains, and the recommendations for remdesivir were inconsistent. Therefore, additional study is required in COVID-19 patients, particularly in high-risk participants such as overweight and obesity.

Vaccines helped minimize the mortality risk of overweight and obese hospitalized COVID-19 patients. Clinical investigations on the impact of vaccinations have revealed the vaccine's higher efficacy compared to adverse effects [3]. This is highly solid data highlighting the necessity to conduct vaccination efforts to avoid COVID-19 in specific as well as other infectious illnesses in general. The use of vaccinations, particularly for high-risk individuals such as overweight and obese people, will minimize the number of fatalities as well as the number of hospitalizations. This is a "very effective" weapon to help us battle the COVID-19 epidemic.

The amount of overweight and obesity was not a risk factor for ICU admission or mortality. This was different from several other research. Rottoli's research suggested that BMI and chronic renal disease were strongly associated with ICU admission outcomes ($p < 0.001$) [1], and author Gao's community-based cohort research also indicated an independent connection of BMI value with ICU admission results [2]. The explanation for this may be because the group selected as the standard for comparison was an overweight group, hence the difference identified would be lower than using the group with BMI within the normal range as the standard group as in previous research. Besides, it also revealed that metabolic and immunological diseases may emerge even in the overweight stage, not only in the obese stage.

V. CONCLUSIONS

Obesity increased the risk of COVID-19-related ICU admission and oxygen support. Remdesivir treatment was associated with significant mortality reduction. COVID-19 vaccination needed to be prioritized in this vulnerable population.

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