Original

The Risk of Refeeding Syndrome in ICU COVID-19 Patients and Some Association Factors in the COVID-19 Hospital in Vietnam

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ABSTRACT: *Background and purpose*: Many COVID-19 patients in ICU suffer from acute respiratory distress syndrome (ARDS), which requires urgent respiratory and hemodynamic support. In these patients, nutrition support plays a pivotal role and should be combined with comprehensive treatment as early as possible. Also, there are several nutrition-specific issues in ICU COVID-19 patients that need to be taken into consideration and one of them was the risk of refeeding syndrome (RFS). In this study, we aimed to describe the risk of refeeding syndrome in severe and critically ill COVID-19 patients at The COVID-19 Patients Treatment Hospital (COVID-19 hospital) in 2021-2022. *Methods:* A cross-sectional study was conducted among 460 patients with moderate and severe conditions admitted to the COVID-19 hospital from September 2021 to May 2022. The risk of refeeding syndrome was evaluated by ASPEN 2020 criteria. *Results*: The percentage of patients who had the risk of refeeding syndrome was 55.3%, of which the moderate risk was 43%, and 12.3% for severe risk; 16.9% of patients were diagnosed with the refeeding syndrome. The most common comorbidities were hypertension and diabetes, which occurred in 56.6 and 38.5 percent of patients respectively. There was a statistically significant association between age, oxygen therapy, feeding method (EN and no EN), nutrition status, COVID-19 condition of patients, propofol usage, and the risk of refeeding syndrome with $p < 0.05$. *Conclusion*: RFS is a severe complication of nutritional intervention, therefore, early diagnosis and preventive treatment of refeeding syndrome will help prevent feeding complications in severe and critically ill patients.
Keywords: COVID-19 patients, malnutrition, Refeeding syndrome, COVID-19 Patients Treatment Hospital

INTRODUCTION

The COVID-19 pandemic is an ongoing global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). This pandemic has been responsible for millions of deaths all over the world. Researches show that up to 30% of COVID-19 patients presenting with acute respiratory distress syndrome (ARDS) require urgent respiratory and other life support in the intensive care unit (ICU) (2). In these patients, nutrition support plays a pivotal role and should be combined with comprehensive treatment as early as possible. Regarding nutritional management, there are several nutrition-specific issues in COVID-19 patients in the ICU that need to be taken into consideration and one of them was refeeding syndrome (RFS). The refeeding syndrome is defined by the disturbance of vital electrolytes and minerals like potassium, magnesium, and phosphorus,..and its clinical sequelae that happened when moderate and severely malnourished patients, often in ICU, responded to nutritional re-introduction (3). If treated inappropriately, RFS can cause serious complications to patients, including seizures, heart failure, and comas (4).

RFS is closely related to the critical condition of ICU patients (5). In the context of COVID-19 patients in the ICU, the management of RFS play an important role in the overall treatment of these patients. COVID-19 patients in ICU are often vulnerable (old and weak) and with comorbidities such as diabetes, hypertension, or other chronic diseases (6). Patients are also staying in ICU for long periods, ranging from 6-15 days, and are ventilated for most of their time (6-7). Therefore, it is expected that COVID-19 patients who survived ICU would present severe malnutrition and muscle mass loss. As a consequence, COVID-19 patients in ICU were susceptible to RFS and can suffer from its complications.

Although there were many researches about refeeding syndrome in ICU patients (5, 8-9), there were few studies in the field of COVID-19 patients in ICU. In this study, we aim to evaluate the risk of RFS in these patients with two objectives:

1. Describe the risk of RFS in severe and critically ill COVID-19 patients in the ICU at COVID-19 Patients Treatment Hospital 2021-2022.
2. Identify some associated factors that can contribute to the risk of RFS in these COVID-19 patients in the ICU.

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MATERIAL AND METHODS

Settings and Sample

The study was designed as a cross-sectional study that involved the convenience sampling of a total of 342 patients in the ICU at the COVID-19 Patients Treatment Hospital from September 2021 to May 2022. The inclusion criteria were patients diagnosed with, severe and critical COVID-19 status. The study excluded patients who could not get enough anthropometric measurements.

Data collection

We collected data on a convenience sample in two ICU departments in the COVID-19 Hospital for six months from September 2021 to May 2022.

Variables

Demographic characteristics: age, gender, comorbidities, the ability for self-feeding skills and method (independent, partial support, complete support), oral feeding, enteral nutrition (EN), parental nutrition (PN), oxygen therapy (invasive mechanical ventilation (IMV), Noninvasive positive pressure ventilation (NIV), high flow nasal cannula (HFNC), oxy mask, nasal cannula, room air). The data were collected from electronic medical records, medical staff (nurses, doctors, dietitians), and subjects.

Non-volitional weight loss: we asked patients or caregivers by mobile-phone or previous medical staff to know patients' weight loss status.

Reduced muscle mass: nurses or doctors or dietitians would examine or observe some positions on patients' bodies. These are the temples, clavicle, shoulder, scapula, thenar, thigh/knee, and calf. In terms of Subcutaneous fat loss, we examine or observe some body's locations such as orbital fat pads, buccal fat pads, and triceps.

Reduced food intake or assimilation: we asked patients or caregivers or previous medical staff to know patients' intake status or observed patients' eating during the initial 24 hours of entering the hospital if we could not obtain any information from patients or caregivers or previous medical staff.

COVID-19 patients stay in an inflammation condition.

Screening refeeding syndrome according to ASPEN guideline 2020

Screening refeeding syndrome: we based on the ASPEN 2020 recommendation for screening refeeding syndrome. There are two levels of refeeding syndrome, which have moderate and severe levels.

Statistical Analysis

The data were entered by using Microsoft Access (Microsoft Corporation, Hanoi, Vietnam) and Stata 14.0 statistical software (Stata Corp LLC, California) for analysis. The intergroup comparisons were performed using the Chi-squared test, Fisher's exact test, and the Mann-Whitney U test. Statistical differences were considered significant at $p < 0.05$.

Ethics Approval

The study has been approved by the research review board of Hanoi Medical University. The study was approved by the Board of Directors of Hanoi Medical University Hospital and the Board of Directors of Hanoi Medical University under Decision No. 1469/QD-ĐHYHN dated May 20, 2022.

RESULTS

Table 1 showed that the total participants of the study were 342 patients at age of 18 to 103 years old, and the mean of age was 72.3 ±16.1. Elderly patients who were more than 65 years old accounted for 70.3% of the total patients. In terms of gender, males accounted for 53.2% and females accounted for 46.8%. For the COVID-19 condition in the first 24-48h of ICU admission, 39.8% of patients were in severe condition and 60.2% in critically ill condition. Regarding comorbidity, only 9.4% of ICU patients did not have any comorbidity disease. On the contrary, the percentage of patients who suffered from ≥3 comorbidities was the highest, at 39.2%. Hypertension accounted for the highest percentage with more than 70 percent of ICU patients having this comorbidity. The percentage of patients who had Diabetes or Obesity was lower, at approximately 50.8 and 14 percent respectively. When assessing the nutritional assessment of these COVID-19 patients in the ICU based on GLIM criteria, about 78.4 percent of these patients suffered from malnutrition, of which 47.7 percent were moderate and 30.7 percent for severe malnutrition. In the first 24 to 48 hours of hospital admission, only 7% of patients did not need any kind of oxygen support. The percentage of patients who needed oxygen through masks was the highest, at 38.9%. The figure for invasive mechanical ventilation (IMV) was the second highest, at 30.6%.

Table 1: The characteristics of COVID-19 patients in ICU (n=342)

n=342	X ± SD	Min	Max
Age	71.3 ± 16.06	18	103
Height	159.8 ± 7.60	140	185
Weight	57.2 ± 11.4	35	100
BMI	22.3 ± 3.5	14.8	38.1
Time from COVID-19 detection to ICU admission	4.1 ± 3.6	1	25

		n	%
Gender	**Male**	182	53.2
	Female	160	46.8
Condition of patients in ICU	**Severe**	135	39.8
	Critical ill	204	60.2

Oxygen support	**Room air**	24	7
	Oxy mask	133	38.9
	Nasal-cannula	46	13.5
	HFNC	18	5.3
	NIPPV	16	4.7
	IMV	105	30.6
	None	32	9.4
Comorbidity	**1**	69	20.2
	2	107	31.2
	>=3	134	39.2
Most common comorbidity	**Hypertension**	252	73.7
	Diabetes	177	51.8
	Obesity	48	14
Propofol usage	**Yes**	109	31.9
	No	233	68.1
Malnutrition diagnosis based on GLIM criteria	**Normal condition**	74	21.6
	Moderate malnutrition	163	47.7
	Severe malnutrition	105	30.7

Table 2. The risk of refeeding syndrome

Assessment criteria (ASPEN) (n=342)		**n**	**Rate (%)**
Low BMI (kg/m^2) (n= 342)	**< 16.0**	6	1.8
	16-18.5. kg/m^2	40	11.7
Weight loss (n= 342)	**Moderate loss**	120	26.1
	Severe loss	6	1.3
Loss of muscle mass/loss of subcutaneous fat (n= 342)	**Mild to moderate loss**	135	39
	Severe loss	25	7.2
Caloric intake (n= 342)	**< 75% estimated energy requirement**	132	38.2
	< 50% estimated energy requirement	24	7
Low potassium levels (n = 57)	**> 30%**	6	1.8
	≤ 30%	40	11.7
Low phosphorus levels (n = 14)	**> 30%**	5	35.7
	≤ 30%	9	64.3

Table 2 showed the ASPEN evaluation of COVID-19 patients in the ICU. Nearly half of ICU patients suffered from losing muscle mass and subcutaneous fat, of which about 40 percent had a moderate loss and 7 percent had a severe loss. Similarly, more than 40 percent of patients had reduced caloric intake, mostly lower than the 75% estimated energy requirement.

Based on figure 1, the risk of refeeding syndrome in COVID-19 patients was 55.3% overall. Of these, 42.3% of patients had a moderate risk of RFS, and 12.3% with severe risk. Of these patients who had the risk of RFS, 16.9% of patients were diagnosed with the refeeding syndrome, of which 43.7 percent for severe RFS and 37.5 percent for moderate RFS.

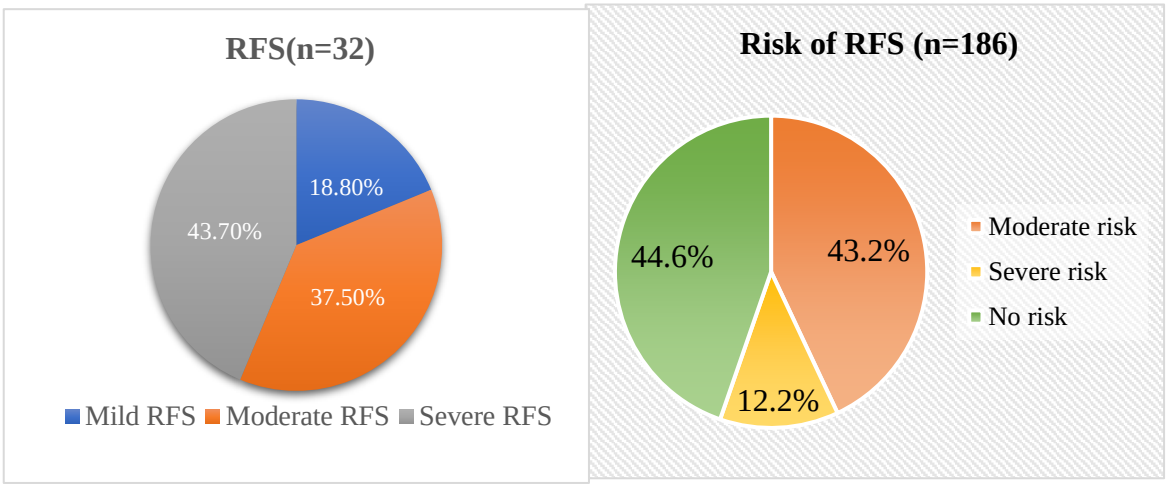

Figure 1. Patients at risk of refeeding syndrome and RFS diagnosis

Table 3: The risk of RFS in different aged groups and comorbidities

		Risk of RFS n (%)	No risk of RFS n (%)	p	OR (95% CI)
Sex	**Male**	99 (54.4)	83 (45.6)	0.73*	1.07 (0.70 – 1.65)
	Female	90 (56.3)	70 (43.8)		
Age		72.4 ±16.6	69.8±15.4	**0.04** ♀	
	<65	43 (22.75)	47 (30.7)	0.096*	1.51 (0.93 – 2.45)
	≥65	146 (77.25)	106 (69.3)		
Comorbidities	**≥ 3**	69 (51.5)	65 (48.5)	0.26*	0.77 (0.50 – 1.21)
	< 3	120 (57.7)	88 (42.3)		
Common comorbidity	**Hypertension**	102 (56)	89 (61.2)	0.29*	0.79 (0.50 – 1.23)
	Diabetes	74 (41.8)	67 (47.2)	0.34*	0.80 (0.51 – 1.26)
	Obesity	14 (7.4)	34 (22.2)	**0.000***	0.28 (0.14 – 0.55)

*: Chi-square test

♀: Mann Whitney test

Table 3 shows that sex, hypertension, and diabetes comorbidities are not associated with the risk of RFS while age and obesity comorbidity are associated with the risk of RFS.

Table 4: The risk of refeeding syndrome and clinical condition of patients

	Variables	Risk of RFS	No risk of RFS	p	OR (95%CI)
Oxygen support	**IMV**	90 (74.4)	31 (25.6)	**0.000***	3.58 (2.15 – 5.95)
	Oxy mask	99 (44.8)	122 (55.2)		
Condition of COVID patients	**Critical ill**	131 (64.2)	73 (35.8)	**0.000***	2.53 (1.60 – 4.00)
	Severe	56 (41.5)	79 (58.5)		
GLIM	**Malnutrition**	188 (70.2)	80 (29.9)	**0.000***	171.55 (15.17 – 1940000)
	Normal	1 (1.4)	73 (98.7)		
ICU time	**≥ 7 days**	42 (53.9)	36 (46.2)	0.775*	0.93

	< 7 days	147 (55.7)	117 (44.3)		(0.56 – 1.54)
Propofol usage	**Yes**	75 (68.8)	34 (31.2)	**0.001***	2.30 (1.41 – 3.76)
	No	114 (48.9)	119 (51.1)		
Nutrition feeding route	**No EN**	97 (45.5)	116 (54.5)	**0.000***	0.34 (0.21 – 0.55)
	EN (bolus)	92 (71.3)	37 (28.7)		
	PN	7 (87.5)	1 (12.5)	0.085**	6.13 (0.59 – 63.68)
	EN + PN	16 (53.3)	14 (46.7)		

*: Chi-square test

**: Fisher‘s exact test

Table 4 showed that the types of oxygen support, condition inpatients, malnutrition condition, propofol usage, and nutrition feeding route are associated factors with the risk of RFS, and these associations are significant ($p<0.05$).

DISCUSSION

The research was carried out on 342 severe and critically ill COVID-19 patients at COVID-19 Hospital 2021 of Hanoi Medical University Hospital. The median age was 71.3 years old (ranging from 18-103 years old). A total of 182 males and 160 females participated in the research. The mean age was higher than that of a similar Korean study (57.5 years) (10). The severity of COVID-19 was classified as pneumonia without oxygen treatment (7%), pneumonia with oxygen treatment by nasal cannula (13.5%), oxy mask (38.9%), and HFNC (18%). Additionally, 35.3% of patients needed mechanical ventilation support (both NIPPV and IMV). In terms of comorbidity, the most common comorbidities were hypertension (73.7%), diabetes mellitus (51.8%), and obesity (14%). These figures were different in composition of comorbidities than that of Ye Minn Htun’s study In Myanmar in 2021 (58.3% for hypertension, 29.8% for diabetes mellitus) (11). These comorbidities cause the COVID-19 disease more severe and increase the risk of death in patients.

In terms of RFS, RFS is historically described as a range of metabolic and electrolyte alterations occurring as a result of the reintroduction and/or increased provision of calories after a period of decreased or absent caloric intake. In patients experiencing refeeding syndrome, a dangerous shift in fluids and electrolytes occurs within the body, resulting in compromised cardiovascular status, respiratory failure, seizures, and even death. RS diagnostic criteria are outlined as the following: A decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%–20% (mild RFS), 20%–30% (moderate RFS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamin deficiency (severe RFS). And occurring within 5 days of reinitiating or substantially increasing energy provision. Overall, in our research, 55.3 percent of patients in the ICU had the risk of RFS. This percentage was higher than that of the Boot R study (36.8%) and lower than the Zahra study in 2022(82%) (7, 12). This can be explained by that we had taken a wider patient spectrum (severe and critically ill patients) than that of the Zahra study (only critically ill patients). More specifically, 18.8% of patients suffered from severe RFS, of which 5 of them had reduced blood phosphorus of more than 30%; 37.5% of patients suffering from moderate RFS with 9 patients had reduced blood phosphorus under 30%. Reduced blood phosphorus can lead to disorientation, encephalopathy, areflexic paralysis, seizures, coma, tetany, cardiac, hypotension, shock, decreased stroke volume, and hematologic. In addition, the condition of diaphragmatic weakness, and respiratory failure leads to patients having difficulty weaning off the ventilator support. Consequently, the prevention and treatment of RFS play an important role in the overall therapeutic strategy of COVID-19 patients.

Regarding the exploration of associated factors, we assessed the association between demographic variables, medical history, and clinical indicators with RFS risk. There are some similarities and complementarities in the results when compared with Zahra's study (12). As for the similarities, both studies showed that gender was not an associated factor, while malnutrition was strongly associated with RFs risk. This is because while malnutrition happened when a patient had been malnourished for a long period of time, the action of reintroduction of food to them can lead to RFS. Similarly, both studies found a correlation between age and the risk of RFS. As a complement to Zahra's study, there were differences in results when assessing associations with comorbidity, and feeding routes. While Zahra reported that comorbidity was a risk factor for the occurrence of RFS, our study found no association, with the exception of Obesity. The reason for these differences is that the classification of the variables is different. In terms of comorbidity, Zahra concluded that having one or more comorbidities was a risk factor, and our results add to the information that patients with 3 or more diseases had no difference in the risk of RFS compared with patients with 1 or 2 diseases. Our study also found that there is a correlation between patients who also had obesity and the risk of RFS. Regarding the feeding route, when only comparing the risk of RFS between the two groups of PN and PN+EN routes, no association was found. However, we further compared the EN group with the no EN group showing that no EN group is a risk factor for RFS. In addition, mechanical ventilation was a risk factor for RFS compared with oxygen with an OR = 1.83. Our study also found that the propofol usage of patients is also related to the risk of RFS with an OR = 2.30.

CONCLUSION

In conclusion, this study investigated the refeeding syndrome and some of its associated

factors in severe and critically ill COVID-19 patients in the ICU. The results showed that nearly half of these patients with COVID-19 had the risk of RFS and some of the patients were diagnosed with RFS. We also found that while sex, type of oxygen support, and the feeding route of patients required in ICU, the COVID-19 condition of inpatients is associated with the risk of RFS, the difference in sex and comorbidity showed no association. Therefore, we suggest that malnutrition and RFS may favor the onset of COVID-19 and increase the severity of COVID-19 disease. Recognizing the risk and identifying, stratifying, avoiding, and managing RFS should be included in the overall treatment of COVID-19. Further research is needed on the impact of malnutrition and refeeding syndrome in COVID-19.

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