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Abstract:

Purpose: Coronavirus disease 2019 (COVID-19) has affected millions of people all over the world with worse proven outcomes in those with certain comorbid conditions, such as diabetes, cardiovascular disease, and pulmonary complications. The Rio Grande Valley located in South Texas with a largely Hispanic population has been hit especially hard during this pandemic with over 3,200 virus-related deaths. This region's high population of diabetic and obese patients is likely correlated with the especially high mortality rate. While it is understood the impact that obesity has on worsening health outcomes, further research is needed to better understand whether more adverse COVID-19 outcomes are correlated with an underdiagnosis of Obesity Hypoventilation Syndrome (OHS) amongst obese patients.

Patients and Methods: Using an observational database from Valley Baptist Medical Center (VBMC) in Harlingen, TX, we gathered a list of COVID+ patients admitted between March 19, 2020 and September 25, 2020. COVID-19 was diagnosed based on World Health Organization (WHO) guidance. The official database is still a work-in-progress, as we are still working on manual data-entry for co-existing conditions and lab values for these patients. Once the database is completed, evaluation guidelines as listed in the American Journal of Respiratory and Critical Care Medicine will be used as a screening method to identify OHS in COVID+ patients. COVID-19 outcomes including hospitalization length, ICU transfer/admission, intubation count, in-hospital death will then be evaluated.

Results: Of the 1114 patients with COVID-19+ included in our database, we have completed chart review on 112 patients. Once the database is completed, statistical analysis will be performed using Python to see if there is a higher percentage of adverse COVID-19+ outcomes in OHS-suspected patients compared to obese patients who don't meet the criteria for OHS. Further analysis will also be done to compare these outcomes to the remaining admitted COVID+ patients.

Conclusion: Database still in progress and no conclusion can be drawn at this time.

1. Introduction:

Obesity is correlated with multiple health conditions such as metabolic syndrome, hypertension, cardiovascular diseases, pulmonary complications, renal disease, and various other obesity-associated comorbidities. These comorbidities place patients in a hypercoagulable state and have been shown to correlate with the increased risk of death related to COVID-19 (1). While there have been a lot of knowledge gained on clinical features of COVID-19 and risk factors that places individuals at higher risk for COVID-19 hospitalization, the data is limited regarding obesity hypoventilation syndrome (OHS) amongst obese patients and mortality in COVID-19. Obesity causes compression of the diaphragm, lungs and chest cavity, which increases pulmonary resistance and impairs lung function (2). These patients are at a higher risk for a number of pulmonary diseases, such as COPD, asthma, and sleep apnea. Obese individuals are also more prone to developing OHS, which presents with additional daytime hypoventilation and sleep-disordered breathing (2). Due to the restriction of chest wall expansion caused by excessive mass of thoracic tissue present in patients with OHS, these patients present with severe upper airway obstruction and restrictive lung damage leading to central hypoventilation and impaired compensatory response to acute hypercapnia (2). Underdiagnosed and thus untreated OHS could potentially be correlated with worsening hypoxemia and cytokine storm in obese patients. Thus, we hypothesize that worse COVID+ prognosis in obese patients may be correlated with an underdiagnosis of OHS in this population, leading to COVID-19 complications such as acute respiratory distress syndrome (ARDS) and multiorgan failure (3).

Human angiotensin-converting enzyme 2 (ACE2) is the receptor that allows for entry of SARS-CoV-2 into target cells (4, 5). The interaction of SARS-CoV-2 with ACE2 receptor, which is expressed on several organs including lung, heart, kidney, has been hypothesized to cause endothelial damage, leading to tissue damage and cytokine release (6). Furthermore, it is found that there is a higher level of ACE2 expression in adipose tissue is much higher than even that of lung tissue (4). Obese patients are found to have higher number of ACE2 receptors due to increased amount of adipose tissue in these patients (4, 7). This finding coupled with the inflammatory disease process, lung injury, and immobility secondary to ICU admission may predispose obese individuals to have worse complications with COVID-19 (6). Patients with obesity are already in a pro-inflammatory state with an already lower than adequate ventilation at baseline. These physiologic disadvantages may facilitate the development of a 'cytokine storm' when faced with the need to mount off a viral infection. Studies have shown that obesity impairs immunity by decreasing the cytotoxic response, reducing the anti-viral role of immunocompetent cells (5, 8). The ineffective ability to mount a cellular immune response against an infection is likely to be associated with more severe disease outcomes and increased mortality in this population of patients with COVID-19 (5).

Patients with obesity often suffer from a wide variety of other metabolic disorders and co-morbidities. The high population of diabetic and obese patients in the Rio Grande Valley is likely to be correlated with the high mortality rates of patients with COVID-19 in this region of Texas. Thus, in our study we would like to examine further whether there is an underdiagnosis of OHS in obese patients and whether those patients suspected of having OHS have more severe outcomes of COVID-19. Furthermore, looking at the treatments that these COVID+ and OHS-suspected patients have received, we can see whether there are certain treatment regimens that fare better than others. This could help us better understand how to approach patients who present to the ER with typical symptoms of COVID-19 and high suspicion for OHS.

2. Materials/Methods:

2.1. Data Source

Our study design was guided by a retrospective cohort study on ACEi/ARBs use and COVID-19 outcomes (9). We analyzed deidentified data using an automated extraction of data from inpatient and outpatient electronic health records at Valley Baptist Medical Center (VBMC) in Harlingen, TX. A manual data-entry process was then conducted for verification and continued extrapolation of values and risk factors that could not be automatically extrapolated. All protected health information was stripped from each record before continuing with manual data collection. The collection and analysis of data in the registry have been deemed exempt from IRB oversight.

2.2 Patients and eligibility

Our dataset initially included a total of 1566 patients that were automatically extracted based on our inclusion criteria of all patients who tested positive with either COVID-19 antigen or COVID-19 PCR who presented to Valley Baptist Medical Center between March 19, 2020 and September 25, 2020. Patients who were still hospitalized past this time frame were still included in our study, as the purpose of our study is primarily focused on patient clinical characteristics presented at the time of admission. The discharge dates will be edited accordingly throughout our manual data-entry process.

Patients who were admitted to the hospital and were discharged under 24 hours were eliminated from our database, as well as patients who passed away from non-COVID related health complications. Patients who were infants and under 2 years of age were also excluded

from our study. After exclusion criteria were met, we were left with 1114 patients to begin our manual data-entry process.

2.3. Data Collection

Using COVID reports available from inpatient and outpatient electronic health records at VBMC, all patients with COVID-19 antigen (+) or COVID-19 polymerase-chain-reaction (PCR) (+) who presented to the hospital between March 19, 2020 and September 15, 2020 were recorded. COVID-19 was diagnosed on the basis of the World Health Organization guidance. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on nucleic acid amplification (NAA) or real-time reverse-transcriptase-PCR (RT-PCR) assay of nasal or pharyngeal swab specimens. Patients with a negative test were not included in this study. Only one positive test was necessary for the patient to be included in the analysis.

Patient demographics and clinical information including age, sex, BMI, ethnicity, admit date, discharge date were automatically extracted as noted in either inpatient or outpatient electronic health record. Coexisting conditions, ACEi/ARBs medications, vital signs, lab values, and COVID-19 treatments were manually collected from patient charts. Vital signs and lab values are collected within 24-48 hours of presentation to the ER. Vital signs consist of systolic BP, diastolic BP, pulse, respiratory rate, temperature, and O2 saturation upon presentation. Lab values consist of CO2, CRP, LDH, D-dimer, Ferritin, and CPK from BMP. From the ABG, we will also be collecting pCO2, pO2, HCO3-, and pH. Coexisting conditions included history of hypertension (HTN), diabetes, smoking history, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), heart failure (HF), hypothyroidism, and chronic kidney disease (CKD). Coexisting conditions were recorded based on patient admission H&P notes, as well as under discharge notes for a discharge diagnosis. Use of ACEi/ARBs medication were only recorded if they have prescription documented in the EMR and not if they were given the medication while in the hospital. If the patient's EMR did not include information on use of ACEi/ARBs or if the patient did not remember medications, this was recorded as not present. This was also the case if the EMR designated an unknown smoking history or did not include specific coexisting conditions (e.g., hypertension, diabetes, COPD, etc), these were similarly recorded as not present. COVID-19 treatment, including administration of steroids, anticoagulants, antivirals, or plasma were manually recorded.

Patient outcomes of this study include total length of hospitalization, admission/transfer to ICU during hospitalization, death, endotracheal intubation count, and mechanical ventilation count was automatically extracted as well. Of these, only admission/transfer to ICU during hospitalization was manually collected.

2.4 Statistical Analysis

The goal of the study is to evaluate whether there is an underdiagnosis of OHS amongst patients who are admitted to the hospital and the effect this has on the end point of length of hospitalization, ICU admission, need for endotracheal intubation, and hospital death. We plan on confounding for demographic characteristics (e.g., age, ethnicity, BMI) as well as coexisting conditions. Categorical variables will be shown as frequencies and percentages, and continuous variables as means and standard deviations. Independent sample t-tests were completed for all comparisons between various categorical and continuous variables. These variables were grouped by death, which is one of the outcomes of our study. Further grouping by other outcomes including total length of hospitalization, admission/transfer to ICU, endotracheal intubation count, and mechanical ventilation count will be included in the future once the database is complete. Statistical analysis of this project is still work in progress, as we are still

waiting to obtain more ABG values in order to see which values are more consistently reported so that we could use that to predict OHS. All statistical analyses will be performed using Python.

3. Results:

We began manual chart review starting from patients admitted June 1st, as this month was when the Rio Grande Valley was hit the hardest with the pandemic. Of the 1114 patients with COVID-19+ included in our database, we have completed chart review on 112 patients. We decided to run a preliminary statistical analysis on these patients to assess our data collection methods before we proceed further. The complete database is still work-in-progress. Demographic information is summarized in Table 1.

From the 112 patients that have been charted so far, our population is shown to be predominately Hispanic (88.4%) with a disproportionately higher percentage of female patients (95.5%) (Table 1). Patient's BMI and ethnicity were not significantly correlated with COVID-related mortality (*p-value*: 0.25 and 0.83, respectively). There was a significant correlation with patient's age in their COVID prognosis with p-value of 0.002. Mean age of COVID-related death was 66.6, whereas those that survived had a mean age of 55.6.

Statistical analysis was then conducted on these patients to find potential correlations with co-existing medical conditions on COVID-related mortality. There was a significantly higher prevalence of HTN in patients who died from COVID than in patients who survived (80% vs. 50.6%, *p-value:* 0.01). Amongst those that passed away from COVID, 70% of these patients had history of diabetes, whereas amongst those that survived, 56.8% of those patients had history of diabetes. While there is a slight difference amongst these groups, the difference is not statistically significant (*p-value:* 0.30). Furthermore, there was also no significant correlation in COVID outcomes amongst patients taking ACEi/ARBs with p-value of 0.23. Statistical analysis on the lab values gathered from patient charts were also grouped by death. However, as indicated in the third column, there is a significant number of values missing from certain patients' chart. Thus, we will need to continue working on the database to have a larger sample size and analysis should be re-conducted on these variables.

Table 1. Patient Demographics Grouped by Death

		Grouped by DEATH				
		Missing	**Overall**	**0.0**	**1.0**	**P-Value**
n			112	81	31	
GENDER, n (%)	**Female**	0	107 (95.5)	78 (96.3)	29 (93.5)	0.616
	Male		5 (4.5)	3 (3.7)	2 (6.5)	
age, mean (SD)		0	58.7 (17.8)	55.6 (17.6)	66.6 (15.9)	0.002
ETHNICITY, n (%)	**Hispanic**	0	99 (88.4)	73 (90.1)	26 (83.9)	0.254
	Non-Hispanic		8 (7.1)	6 (7.4)	2 (6.5)	
	Unknown		5 (4.5)	2 (2.5)	3 (9.7)	
BMI, mean (SD)		0	32.8 (10.0)	32.9 (11.2)	32.5 (5.9)	0.826

Table 1. Our preliminary patient demographics (n= 112) showed a disproportionately higher percentage of female patients (95.5%), as well as a largely Hispanic population (88.4%).

Table 2. Co-existing Conditions Grouped by Death

		Grouped by DEATH				
		Missing	**Overall**	**0.0**	**1.0**	**P-Value**
n			112	81	31	
ACEi/ARBs, n (%)	**0.0**	1	78 (70.3)	60 (74.1)	18 (60.0)	0.227
	1.0		33 (29.7)	21 (25.9)	12 (40.0)	
HTN, n (%)	**0.0**	1	46 (41.4)	40 (49.4)	6 (20.0)	0.010
	1.0		65 (58.6)	41 (50.6)	24 (80.0)	
Diabetes, n (%)	**0.0**	1	44 (39.6)	35 (43.2)	9 (30.0)	0.296
	1.0		67 (60.4)	46 (56.8)	21 (70.0)	
Smoking, n (%)	**0.0**	1	98 (88.3)	71 (87.7)	27 (90.0)	1.000
	1.0		13 (11.7)	10 (12.3)	3 (10.0)	
COPD, n (%)	**0.0**	1	104 (93.7)	76 (93.8)	28 (93.3)	1.000
	1.0		7 (6.3)	5 (6.2)	2 (6.7)	
CAD, n (%)	**0.0**	1	97 (87.4)	71 (87.7)	26 (86.7)	1.000
	1.0		14 (12.6)	10 (12.3)	4 (13.3)	
HF, n (%)	**0.0**	1	103 (92.8)	76 (93.8)	27 (90.0)	0.444
	1.0		8 (7.2)	5 (6.2)	3 (10.0)	
Hypothyroidism, n (%)	**0.0**	1	102 (91.9)	73 (90.1)	29 (96.7)	0.440
	1.0		9 (8.1)	8 (9.9)	1 (3.3)	
CKD, n (%)	**0.0**	1	102 (91.9)	74 (91.4)	28 (93.3)	1.000
	1.0		9 (8.1)	7 (8.6)	2 (6.7)	

Table 2. Patients with history of HTN seemed to be significantly correlated with worse COVID outcomes (p-value 0.01). No significant correlation noted between use of ACEi/ARBs, history of diabetes, smoking, COPD, CAD, HF, hypothyroidism, and CKD on COVID-related mortality. ACEi/ARBs: angiotensin converting enzyme inhibitor/angiotensinogen receptor blockers, HTN: hypertension, COPD: chronic obstructive pulmonary disorder, CAD: coronary artery disease, HF: heart failure, CKD: chronic kidney disease.

Table 3. Lab Values Grouped by Death

		Grouped by DEATH				
		Missing	**Overall**	**0.0**	**1.0**	**P-Value**
n			112	81	31	
Serum CO2, mean (SD)		3	23.4 (5.7)	23.8 (5.0)	22.3 (7.1)	0.295
CRP, mean (SD)		73	11.4 (8.3)	10.5 (7.8)	14.0 (9.7)	0.316
LDH, mean (SD)		72	339.8 (191.8)	333.5 (204.6)	361.2 (147.2)	0.657
D-dimer, mean (SD)		53	102.9 (502.5)	54.3 (190.8)	233.6 (921.7)	0.452
Ferritin, mean (SD)		73	34131.5 (209515.9)	609.2 (823.5)	164030.1 (462637.9)	0.351
CPK, mean (SD)		80	281.1 (487.5)	184.5 (338.1)	493.6 (692.1)	0.207
pCO2 (from ABG), mean (SD)		70	33.0 (8.1)	32.9 (8.2)	33.3 (8.2)	0.876
pCO2 <12.5 (from ABG), n (%)	**1.0**	110	2 (100.0)	1 (100.0)	1 (100.0)	1.000
pO2 (from ABG), mean (SD)		68	80.1 (41.7)	67.4 (29.6)	102.3 (50.9)	0.020
HCO3- (from ABG), mean (SD)		68	19.4 (7.1)	19.5 (6.7)	19.1 (8.0)	0.852
pH (from ABG), mean (SD)		68	7.4 (0.1)	7.4 (0.1)	7.3 (0.2)	0.434

Table 3. Higher pO2 from Arterial Blood Gas (ABG) correlated with higher COVID-related mortality (p-value: 0.02). However, many lab values were missing as ABG was not ordered in multiple patients. Thus, we will need to perform this statistical analysis again after an adequate sample size is obtained.

4. Discussion:

The database for this project is still under works and more patients will need to be reviewed before we can decide the most consistent variables to look at in order to predict OHS. Potentially, we will base our clinical suspicion for OHS from the evaluation guidelines as listed in American Journal of Respiratory and Critical Care Medicine (10). As listed in their summary of recommendations on the evaluation and management of OHS, they recommend to measure PaCO2 rather than serum bicarbonate or SpO2 to diagnose OHS in obese patients (BMI ≥30 kg/m^2) with sleep-disordered breathing, most likely obstructive sleep apnea (OSA). An elevated serum bicarbonate >27 mEq/L could also increase the likelihood of OHS; however, serum HCO3- was not found from manual data extraction from any patients. After looking at these recommendations, it would retrospectively also be helpful to begin recording history of OSA along with our other co-existing clinical conditions. Again, this project thus far is only creating a database of COVID+ patients upon admission and an official clinical question is still under discussion based on the end result of the database of 1114 patients. The topic on OHS and hypothesis that I have based this paper on is one of the discussed hypotheses that could be studied once the database is completed. This project that I am hoping to look more into is not diagnosing patients with OHS, but instead to find those patients that we have high suspicion for

OHS in order to see if there is a high underdiagnosis of obesity hypoventilation syndrome in patients with worse prognosis of COVID-19

From the statistical analysis completed on our preliminary dataset, there has been a significant correlation shown between patients having history of HTN and COVID-related mortality. This finding is consistent with another retrospective study that consisted of 487 COVID-19 patients in Zhejiang Province of China that showed a higher prevalence of HTN in the 49 severe cases of COVID compared to the remaining 439 cases (53.1% vs. 16.7%, *p-value* < 0.0001) (11, 12). Another study in Wuhan, China where the first COVID outbreak began also saw a higher prevalence of hypertension amongst patients with more severe COVID-19 cases (*p-value* < 0.001) (13). There is also significant evidence showing multiple other comorbid conditions, such as diabetes and coronary artery disease, that are risk factors for more severe prognosis of COVID-19. A case series of 5700 patients hospitalized with COVID-19 in the New York City area found that patients with diabetes were more likely to have received invasive mechanical ventilation or care in the ICU compared to those who did not have diabetes (14). The percentage of patients that later developed acute kidney injury as a complication of COVID-19 was also higher amongst patients with diabetes compared to those without (14). To the contrary, our findings as indicated in Table 2 did not show a significant correlation between patients having a co-existing condition of diabetes and COVID-related mortality. However, since we only grouped these variables by death, we need to also perform statistical analysis grouping these co-existing variables by other COVID outcomes, including days of hospitalization, ICU admission, endotracheal intubation, and mechanical ventilation. Furthermore, our data may also be limited given our smaller sample size. According to Table 2, there also seemed to be no correlation found amongst those taking ACEi/ARBs on COVID-related mortality. While initially it was thought that these antihypertensive drugs might increase expression of ACE2 and thus increase the chance for virus entry into organs, multiple studies have found that ACEi/ARBs do not increase risk of COVID-19 requiring ICU admission or fatal cases (11, 15). These studies are consistent with our findings thus far. Table 3 in our results showed that there are multiple patients that are missing lab values, specifically values gathered from ABG since this was not part of COVID protocol when a patient presented to the hospital with a positive COVID test. Thus, continued data collection will need to be performed in order to have a higher sample size of patients from which we can use the variables to assess for clinical suspicion of OHS.

The limitations of this study include that this is an observational design, the possibility of human manual data-entry error, and the coverage of a short term admission range of ~ 6 months (March 19, 2020 – September 25, 2020). Another limitation to this study that we noticed upon looking at our demographics table is that a majority of our population thus far is female. There will need to be a further look into the possible cause for this. Our database also only included record of patients who were currently smoking. If there was no documented history of smoking or were former smokers, this was recorded as no tobacco use. Current smokers were not specified how many pack-years, as this could not be located in the EMR. Since former smokers were not reported, this could present many confounding variables, as patients who recently smoked >15 pack-years and who recently quit, for example, are likely to carry many of the cardiovascular and pulmonary risk factors as current smokers. This flaw in data collection may affect the reliability of this variable. Another confounding variable is if patients were on anti-coagulation for other chronic conditions prior to their presentation to the ER. These patients may have better COVID-19 outcomes, regardless if they met our criteria for high suspicion for OHS. This is based on COVID-19 being a hypercoagulable state and studies showing promising evidence in the use of anticoagulation with better prognosis in severe COVID-19 cases as well as offer beneficial anti-inflammatory effects to minimize lung damage (16).

Another limitation of our data collection process is the inclusion of patients who presented to the ER with non-COVID related symptoms but rather symptoms of another co-existing clinical condition. These patients may have been tested prior to undergoing procedure

for another condition and incidentally tested positive for COVID; however, their initial presentation to the ER was not for COVID-related symptoms. Inclusion of these patients may bias our population towards less severe COVID-19 prognosis as these patients may be asymptomatic for COVID. Furthermore, while we attempted to exclude patients who received endotracheal intubation as part of surgery unrelated to COVID-19 related symptoms, there is still the possibility of human data-entry error.

During our data-collection process, we also noticed that some patients who were excluded from our study due to being admitted for < 24 hours often times present back to the hospital a few days later and were admitted the second time. These patients were excluded from our study, but further continuation of this study should include assessment of what percentage of COVID+ patients got discharged without admission and presented back again with similar or worsening COVID-19 symptoms. Of these patients that presented back a second time, we could perform further analysis to see many of these second presentations resulted in an admission. As of now, we are still in the process of creating a database for COVID+ admitted patients. Thus, future studies will need to take into consideration the data collection limitations listed above. Once the database is complete, we hope to further expand our study towards better understanding not only the impact of obesity on COVID-19 outcomes, but also look into which treatment regimens have better outcomes in this subset of population. More studies need to be done to see whether these patients should have a lower threshold for advanced respiratory support, intubation or placed on tailored doses of anticoagulation, steroid, or viral medications to decrease the risk for severe COVID-19 complications down the line.

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