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Understanding the Prevalence and Mortality of Acute Right Ventricular Strain in Covid-19 Patients, an Observational Analysis

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ABSTRACT

Coronavirus disease 2019 or COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a virus that has impacted nations and caused a global pandemic. Although COVID-19 is known to initially manifest as a pulmonary disease, we now understand it affects many major organ systems in the body, including the heart. Case reports have been published showing evidence of right ventricular (RV) strain as a result of contracting the COVID-19. However, the overall prevalence of RV strain secondary to the virus has not been well established. In this multicenter, observational analysis, we studied the prevalence of RV strain in hospitalized patients with COVID-19. We found the prevalence of RV strain to be small, ~1.5%. The average length of stay in patients with RV strain was 7 days compared to 8.63 days in non-RV strain patients. Those with RV strain were witness to have a 50% mortality rate.

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Introduction

COVID-19 is traditionally known to cause an upper and/or lower respiratory tract infection in most individuals. Initial symptoms of the virus include fever, cough, and dyspnea but can lead to hypoxemic respiratory failure and even death [1]. While the virus predominantly affects the pulmonary system, evidence has demonstrated that it also affects different organs including the gastrointestinal tract, kidneys, and even the cardiac system. Regarding the heart, numerous case reports have been published that describe the virus' ability to damage the heart directly, through inflammatory myocarditis, and indirectly, via hypoxia or electrolyte imbalances from renal dysfunction [2]. Unfortunately, limited data demonstrates the virus's potential to cause RV strain. In this study, we will observe the prevalence of RV strain in hospitalized patients infected with COVID-19.

RV strain is caused by failure of the right heart to pump efficiently in the setting of a high-pressure system further in circulation [3]. Some common diagnoses causing RV strain include pulmonary embolism (PE), acute respiratory distress syndrome (ARDS), severe pulmonary hypertension, and more. Infection with COVID-19 has been documented to cause a hypercoagulable state, which can predispose patients to develop a PE leading to strain [4,5]. This form of obstruction leads to volume overload due to poor forward flow from the right ventricle, leading to RV strain. ARDS is caused by the body's recruitment of inflammatory markers into the lungs that can cause an influx of fluid leading to increase in afterload on the right heart [6]. Pulmonary hypertension also incorporates this same notion of increased afterload causing strain [7]. RV dysfunction can also result from "pump failure", secondary to ischemia and infarction of inferior myocardial [8]. The ischemic tissue develops contractile dysfunction, leading to diminished peak-systolic pressure, increased residual diastolic volume leading to poor cardiac output into the pulmonary system [9]. All these phenomena have been seen in hospitalized COVID-19 patients.

Methods

This observational study was approved by the Institutional Review Board at Saint Michaels Medical Center in Newark, New Jersey. The initial population consisted of subjects who were admitted to an inpatient hospital service from two academic community-based institutions from April 30th, 2020 through April 29th, 2021. One hospital is in Bucks County, PA, and the other in Philadelphia County, PA. The demographics of these two areas were relatively diverse with a mixture of white-Caucasian and African American individuals according to census.gov. Endpoints recorded are listed below:

Primary endpoints: Prevalence of RV strain, mortality and length of hospital stay
Secondary endpoints: Prevalence of PE, mortality and length of hospital stay

Tertiary endpoints: Prevalence of preexisting comorbidities, mortality and length of stay

To determine if a patient has RV strain, we used three modalities: echocardiogram, Computed Tomographic Angiogram (CTA) imaging and cardiac catheterization.

1. Echocardiogram via Tricuspid Annular Plane Systolic Excursion (TAPSE)
2. CTA chest via RV volume (RVV) / left ventricular volume (LVV) end-diastolic area ratio
3. Cardiac catheterization via direct measurement of heart chamber pressures

Echocardiogram has a sensitivity and specificity of 56% and 42%, respectively, for detecting RV strain while CT has sensitivity and specificity of 81% and 47% respectively. These are the current modalities to detect strain therefore both were used [10]. According to Nakamura et al., a TAPSE value of less than 16mm is considered abnormal and thus we used 16mm to determine the presence of RV strain [11]. According to Mansencal et al., RV strain on CTA imaging can be determined by calculating the RV volume (RVV) / left ventricular volume (LVV) end-diastolic area ratio [12]. An RVV/LVV area ratio > 1 has a sensitivity and specificity of 88% and 88%, respectively, and so we used RVV/LVV area ratio > 1 to be positive for RV strain. Cardiac catheterization can detect RV satrain by noting elevated filling pressures in cardiac chambers. While prohormone of Brain Natriuretic Peptide, or proBNP, can be a marker for cardiac wall stress, the marker is nonspecific and can be skewed in patients with renal dysfunction, variations in muscle mass, gender and age. Therefore, proBNP was not incorporated as an indication for RV strain [13]. However, if these nonspecific markers were elevated with symptoms suggestive of cardiac failure, echocardiogram was performed as ventricular stress causes the release of ANP and BNP which then can warrant imaging [14]. Similarly, if patients showed symptoms of pulmonary embolism, a CTA would be warranted. To protect hospital members from contracting the virus, tests were not done for the sole purpose of the study but instead, on a clinically "as needed" basis.

Table 1 shows the inclusion criteria while Table 2 shows the exclusion criteria for the study.

Table 1: Demonstrates the inclusion criteria for the study

Inclusion Criteria: 1. Age >18 years old 2. Admitted to an inpatient service 3. Diagnosis of COVID-19 via positive polymerase chain reaction for COVID-19 4. Echocardiogram, CTA chest or cardiac catheterization performed while acutely infected with COVID-19

Table 2: Demonstrates the exclusion criteria for the study

Exclusion Criteria: 1. Age <18 years old admitted to the hospital 2. Negative for COVID-19 3. No echocardiogram, CTA chest or cardiac catheterization performed

Figure 1 displays the total n population before and after the inclusion and exclusion criteria. Total n sample size = 130.

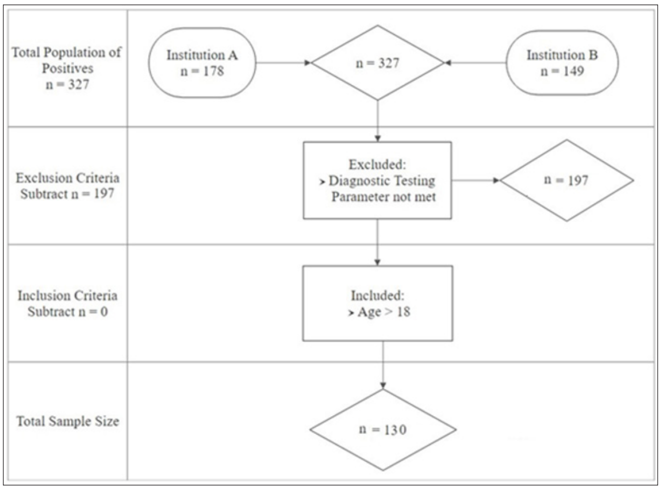

Figure 1: Institution A consisted of 178 patients while Institution B consist of 149 making the total of inpatient COVID-19 positive subjects 327. Of those patients, n = 197 subjects were excluded. Of the remaining, all patients were > 18 years of age to participate in the study, leaving the final sample size of n = 130.

Results:
Table 3 illustrates the number of subjects for the entire sample population in each age bracket associated with each bracket's own Mean LOS (days), Mortality (n), and mortality rate (%).

Age subsets	n	Mean LOS	Mortality	Mortality rate*
20-29	3	7.33	0	0
30-39	3	5	0	0
40-49	9	7.13	2	0.22
50-59	23	7.87	3	0.13
60-69	31	9.70	10	0.32
70-79	33	10.12	10	0.30
80+	28	7.21	11	0.39
Mean Age	67.09	Mean LOS 8.6	Total Mortality 36	

*Mortality rate is expressed as a ratio of mortality in an age subset (mortality n / age subset n)

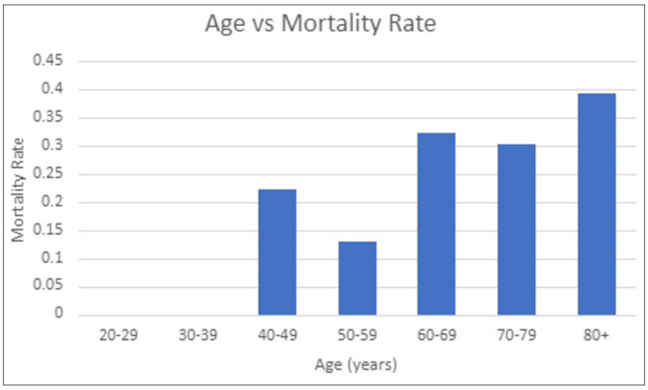

Figure 2: Age versus Mortality Rate for entire sample population

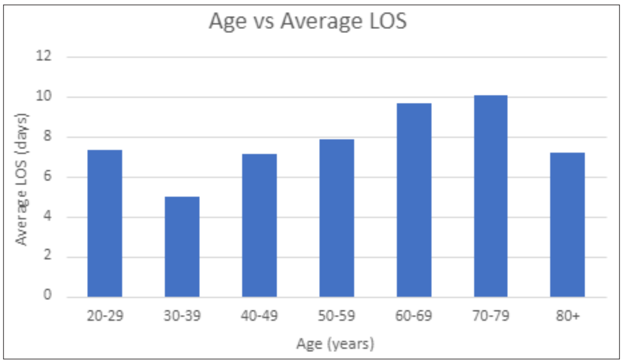

Figure 3: Age versus Mean LOS for entire sample population

Table 4: Gender Distribution of sample population

Gender:	
Male	62
Female	68

Table 5: compares PE group with rest of population

	Non-RV strain	**RV strain**
Population	128	2
Mean LOS (days)	8.63	7
Mortality (# of subjects)	35	1
Mortality rate	0.27	0.50
Mean age	67.09	77
Mean Initial D-dimer (mg FEU/L):	>2.95*	2.36
Mean Peak D-dimer (mg FEU/L):	>4.29**	3.38

*5 subjects had D-Dimer values too high to record therefore were not included in mean
**10 subjects had D-Dimer values too high to record therefore were not included in mean

Table 6 compares PE group with rest of population

	Non-PE	**PE**
Population	121	9
Mean LOS (days)	8.69	7.44
Mortality (# of subjects)	32	3
Mortality rate	0.26	0.33
Mean age	67.25	67.22
Mean Initial D-dimer (mg FEU/L):	>3.0*	>8.17**
Mean Peak D-dimer (mg FEU/L):	>4.0***	>8.45****

*1 subjects had D-Dimer values too high to record therefore were not included in mean
**4 subjects had D-Dimer values too high to record therefore were not included in mean
*** 6 subjects had D-Dimer values too high to record therefore were not included in mean
****4 subjects had D-Dimer values too high to record therefore were not included in mean

Table 7: demonstrates all major risk factors set forth by the Center of Disease Control (CDC) and shows number of subjects with each risk factor, Mortality (n), and LOS (days). Other major risk factors indicated by the CDC not included in this analysis are Interstitial Lung Disease, Cystic Fibrosis, Down Syndrome, Pregnancy, Transplant patients or Immunocompromised patients on chemotherapy or chronic steroids. These risk factors were not present in patient population

	No RV strain / no PE			PE			RV strain			Total		
Risk Factors:	**n**	**Mortality**	**Mean LOS**	**n**	**Mortality**	**Mean LOS**	**n**	**Mortality**	**Mean LOS**	**n**	**Mortality**	**Mean LOS**
Active or Hx of Cancer	15	1	7.40	0	0	0	0	0	0	15	1	7.40
Chronic Kidney Disease	19	8	13.05	3	3	11	0	0	0	22	11	12.77
COPD	20	5	8.15	0	0	0	2	1	7	22	6	8.05
Asthma	11	1	6.64	1	0	3	0	0	0	12	1	6.33
Pulmonary Hypertension	20	8	10.15	3	2	11.67	1	0	2	24	10	10
Dementia/ Alzheimer	14	6	7.21	0	0	0	0	0	0	14	6	7.21
Diabetes Mellitus I or II	49	16	9.37	3	2	13.67	0	0	0	52	18	9.62
Systolic Heart Failure	14	5	8.36	0	0	0	1	0	2	15	5	7.93
Abnormal Diastolic Dysfunction	32	11	10.75	2	1	15.50	1	0	2	35	12	10.77
Coronary Artery Disease	25	10	7.28	1	0	6	1	0	2	27	10	7.04
Hypertension	67	21	8.40	5	2	8.20	1	0	2	73	23	8.30
Atrial Fibrillation	12	4	6.17	0	0	0	0	0	0	12	4	6.17
HIV	3	1	14	0	0	0	0	0	0	3	1	14
Liver disease	4	1	9	0	0	0	0	0	0	4	1	9
Obesity	45	10	8.11	2	0	4.50	0	0	0	47	10	7.96
Thalassemia	1	0	39	0	0	0	0	0	0	1	0	39
Current or history of smoking	27	7	8.56	1	1	26	0	0	0	28	8	9.18
CVA	6	2	5.33	0	0	0	1	1	12	7	3	6.29
Substance use	2	0	9.50	0	0	0	0	0	0	2	0	9.50
Ventilated:	26	19	16.42	2	1	14	1	1	12	29	21	16.10

PE = Pulmonary Embolism, RV = Right Ventricular, COPD = Chronic Obstructive Pulmonary Disease, CVA = Cerebral Vascular Accident

Table 8: Mean LOS (days) & Mortality (n) per Risk Factor (see table7) depicts the Mean LOS (days) and mortality (n) per quantity of risk factors (*x*)

Number of Risk Factors	*n*	Mean LOS	Mortality	Mortality rate
0	11	9.73	1	0.09
1	13	7.85	4	0.31
2	28	6.29	7	0.25
3	27	8.89	6	0.22
4	23	10.52	9	0.39
5	16	8.94	4	0.25
6	7	9.71	3	0.43
7	4	7.50	2	0.5
8	1	10.00	0	0
Total:	130	8.6	36	

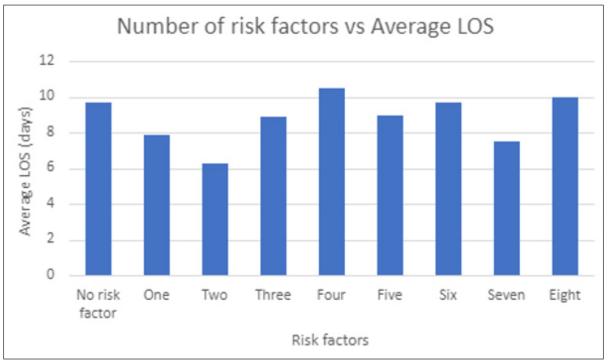

Figure 4: Risk factors versus Average LOS bar graph

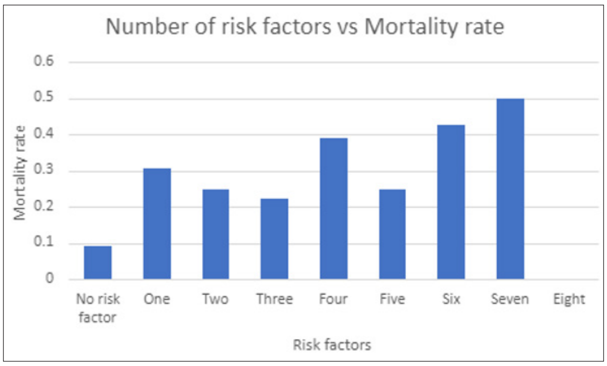

Figure 5: Number of risk factors versus mortality rate

Discussion

Looking at our primary outcomes, of our 130 subjects, 81 echocardiograms, 1 cardiac catheterization and 79 CTA chests were done in our sample population. This showed only two subjects to have RV strain. These RV dysfunctions stemmed secondary to severe ARDS and pulmonary HTN. Only 1 patient with RV strain survived making the mortality rate 50%. Interestingly, none of the 9 PE subjects were witnessed to have RV strain. Some characteristics of these two patients included a past medical history of COPD, heart failure (both systolic and diastolic), coronary artery disease, and hypertension. The major risk factors for mortality in RV strain appear to be more cardiac dependent compared to pulmonary, however with only two subjects, this is difficult to decipher. According to table 5, the mortality rate for RV strain is higher (50%) than those who did not have RV strain (27%). The LOS for RV strain was 7 days while that of non-RV strain was 8.63. This comparison may be skewed as the early mortality for RV strain lowers hospital LOS.

In our secondary outcomes, we looked for a sample within our data who was found to have a PE. Of the 130 subjects, 9 subjects were found to have a PE on CTA chest making the prevalence of PE in our COVID-19 population to be ~6.9%. In a prospective study, Alonso-Fernández et al., demonstrated that the prevalence of a PE in a COVID-19 population can be as high as 50% [15]. The indication for undergoing imagining was based on standard guidelines such as clinical evidence (shortness of breath, chest pain, tachycardia, Wells' criteria, Pulmonary embolism rule out criteria [PERC] score and laboratory (D-dimer) to suggest an embolism. Lastly, according to table 6, the mean LOS for patients with PE was shorter (7.44 vs 8.69), this may be attributed to the higher mortality rate (0.33 for PE patients vs 0.26 for non-PE patients) as a higher mortality rate can lower LOS.

According to Table 3, our sample population showed an older population, 70% of those hospitalized for this study were greater than 60 years of age with a mean age of 67.09. Similar to our study, Mueller et al. found that 80% of patients with COVID-19 who require hospitalization are greater than 65 years old [16]. Both hospitalization and mortality are higher amongst the elderly population. The gender distribution amongst our population was relatively similar; males ~47% and females ~53%. Next, we interpret the overall mean LOS as a function of number of risk factors (risk factors detailed in table 7). According to Figure 4, there is no positive or negative trend relating to number of risk factors and length of stay. Figure 5 shows that there is a positive trend between the number of risk factors and mortality.

Some notable key risk factors are worth mentioning. Unfortunately, because only two patients developed RV strain, it would be difficult to compare risk factors for this group, but we can look at the PE group to make some interesting points. For example, patients with chronic kidney disease overall had a 50% mortality rate. Among patients who had diagnosed PE with a risk factor of CKD, we noticed higher mortality compared to patients with CKD without diagnosed PE (100% vs 42%). Our study corroborates the result from Gansevoort and Hilbrands analysis that chronic kidney disease does have a worse prognosis in patients who contract COVID-19, compared to other chronic organ diseases [17]. We also witnessed the complication of diabetes mellitus I or II in patients with a PE and compared them to those without witness embolism. Patient with diabetes mellitus I or II were witnessed to have worse outcomes in the setting of PE with a mortality rate of ~32% in the non-PE group compared to 66% in the PE group. Diabetic patients with PE were noted to have a longer length of stay (13.67 LOS with PE vs 9.37 LOS without PE).

Some shortcomings of our project include that our final sample population who met the inclusion criteria was only n = 130. The barrier to this was limited resources and money in a community hospital setting. Preservation of hospital staff members was also of high priority. Another short coming is the population demographics; the study was limited to only the state of Pennsylvania and only the eastern half within two nearby counties. Given that our sample is a small subset of the population, it does not reflect the true population. A similar multicenter study conducted on a larger scale can help minimize any confounding variables. Lastly, the time of which a patient received the imaging modality or a cardiac catheterization when indicated was variable. Some patients received it early during their COVID-19 hospitalization which may underrepresent RV strain as more time may be necessary to develop these features.

Conclusion

In conclusion, the prevalence of RV strain among our sample size of 130 hospitalized COVID-19 patients between two institutions, was ~1.5%. They did experience a high mortality rate of 50% compared to non-RV stain developing patients. Furthermore, we also found that only 9 subjects (or ~6.9%) were found to have PE without any significant. The mortality rate was noted to be higher in patients with PE than those without PE. Lastly, we did notice that patients with chronic kidney disease had the highest mortality rate (50%) compared to other comorbidities.

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