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Covid-19 pandemic in Brazil

Clinical manifestation and effect of comorbidities on outcomes of hospitalized SARI cases

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Covid 19 Pandemic

- Covid-19 refers to the Severe Acute Respiratory Infection (SARI), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS – CoV -2) [1]. The virus emerged in Wuhan, China in early December 2019 [1].
- As of December 15th, there are reported 70,476,836 cases and 1,599,922 deaths globally [2].
- When considering the statistics by WHO defined regional groupings, Americas Region has 30,116,395 reported cases and 776,708 deaths [2].
- Of those, 6,836,227 cases and 180,437 deaths are reported by Brazil [2].

Covid -19 Clinical signs and symptoms

- Most common clinical manifestations: fever, cough, dyspnea, expectoration, headache, and myalgia or fatigue [3].
- Less Common: diarrhea, hemoptysis, and shortness of breath [3].

- The presence of comorbidities, like high blood pressure and diabetes is associated with a worse prognosis, especially in older patients [3].

SIVEP GRIPE Surveillance System

- An existing Surveillance system is used in Brazil to report hospitalized Severe Acute Respiratory Infection cases (SIVEP GRIPE).
- This system has been utilized to report Severe Acute Respiratory Infection cases before the 2020 Pandemic.
- The data are publicly available from the Ministry of Health of Brazil [4].
- The data are published online, and the one used for this presentation come from the latest being on 13th of October 2020 [4].
- Also, for the purposes of analysis, the dataset containing SARI cases from 2019 is used and it is lastly updated on 24th April 2020 [4].

Case definition from individual register file

Case of Severe Acure Respiratory Syndrome (SARI-hospitalized):

-Individuals of any age hospitalized with [fever and (cough or throat pain)] and who have [dyspnea or O2 blood saturation <95% or respiratory discomfort) [5].
- Cases of death caused by SARI independent of hospitalization status [5].

Data preparation

- There were 777,088 cases in the downloaded data.
- SAS 9.4 software was used to prepare and analyze the data, while R version 4.0.3 was used to produce the graphs.
- After removing cases for whom the final classification of disease was not known and cases having non-plausible observations there were 617,020 cases eligible for analysis.
- Based on whether SARS – CoV -2 was the etiologic agent two groups were created: Covid and non-Covid.
- Duration of Hospitalization and ICU stay was calculated.
- Clinical signs and symptoms were used to classify the severity of SARI following the guidelines from National Institutes of Health (NIH) [6] as below:

Fever	Cough	Throat Pain	Diarrhea	Vomiting	Dyspnea	Resp. discomf .	Sat. <95	Chest X-Ray	Severity
✘	✘	✘	✘	✘	✘	✘	✘	✘	Asymptomatic
✔	✔	✔	✔	✔	✘	✘	✘	✘	Mild
					✔	✔	✔	✔	Severe

Models considered to estimate the effect of predictors

- It is of interest to explore the effect of comorbidities, clinical characteristics and etiologic agent of SARI on the clinical outcomes and length of stay while adjusting for the effect of sociodemographic factors (age, gender, race).
- (binary and multinomial) Logistic regression models are considered for the effect on ICU admission, type of VS, PCR* result and end outcome of SARI, following the methodology from Agresti [6].

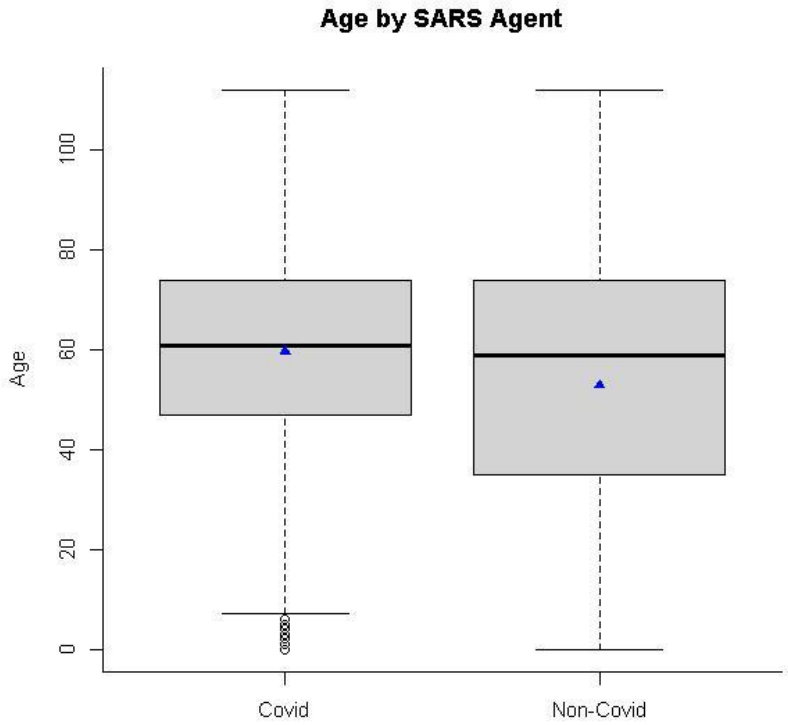
- Poisson regression is used to model the effect on length of hospitalization and ICU stay, following the methodology from Agresti [7].

*PCR here refers to PCR test of another test using mocelucular biology technology.

Demographics by etiologic agent of SARI

In total there are 617,020 eligible cases for analysis.
364,904 (59.1%) have Covid-19 as etiologic agent.
252,116 (40.9%) are reported to not have Covid-19 as etiologic agent of SARI.

Variable	Covid (%)	Non-Covid (%)
Sex		
Male	206,836 (56.7)	132,783 (52.7)
Female	157,984 (43.3)	119,219 (47.3)
Missing	*84*	*114*
Race		
Black	17,771 (6.5)	13,024 (6.6)
White	124,863 (45.8)	98,909 (50.3)
Other	129,858 (47.7)	84,559 (43)
Missing	*92,412*	*55,624*
Education		
No education	10,194 (8.1)	10,203 (12.1)
1st cycle	35,244 (28.0)	28,773 (34.0)
2nd cycle	23,557 (18.7)	15,649 (18.5)
High school	39,030 (31.0)	21,615 (25.6)
University	18,111 (14.36)	8,335 (9.86)
Missing	*238,768*	*167,541*



Comorbidities

Comorbidity	Covid (%)	Non-Covid (%)	Comorbidity	Covid (%)	Non-Covid (%)
Heart Disease			**Immunodepression**		
Yes	12,1835 (33.4)	74,041 (29.4)	Yes	9,395 (2.6)	11,381 (4.5)
No	243,069 (66.6)	178,075 (70.6)	No	355,509 (97.4)	240,735 (95.5)
Lung Disease			**Renal Disease**		
Yes	13,263 (3.6)	18,569 (7.4)	Yes	152,23 (4.2)	11,799 (4.7)
No	351,641 (96.4)	233,547 (92.6)	No	349,681 (95.8)	240,317 (95.3)
Diabetes			**Liver Disease**		
Yes	91900 (25.2)	47,618 (18.9)	Yes	3,166 (0.9)	3,206 (1.3)
No	273004 (74.8)	204,498 (81.1)	No	361,738 (99.1)	24,8910 (98.7)
Asthma			**Obesity**		
Yes	9485 (2.6)	14,277 (5.7)	Yes	17,182 (4.7)	6,554 (2.6)
No	355419 (97.4)	237,839 (94.34	No	347,722 (95.3)	24,5562 (97.4)

51.6% (n=188377) of Covid cases and
49.7% (n=125356) of Non- Covid
have at least one Comorbidity

*Assumption about filling the form.

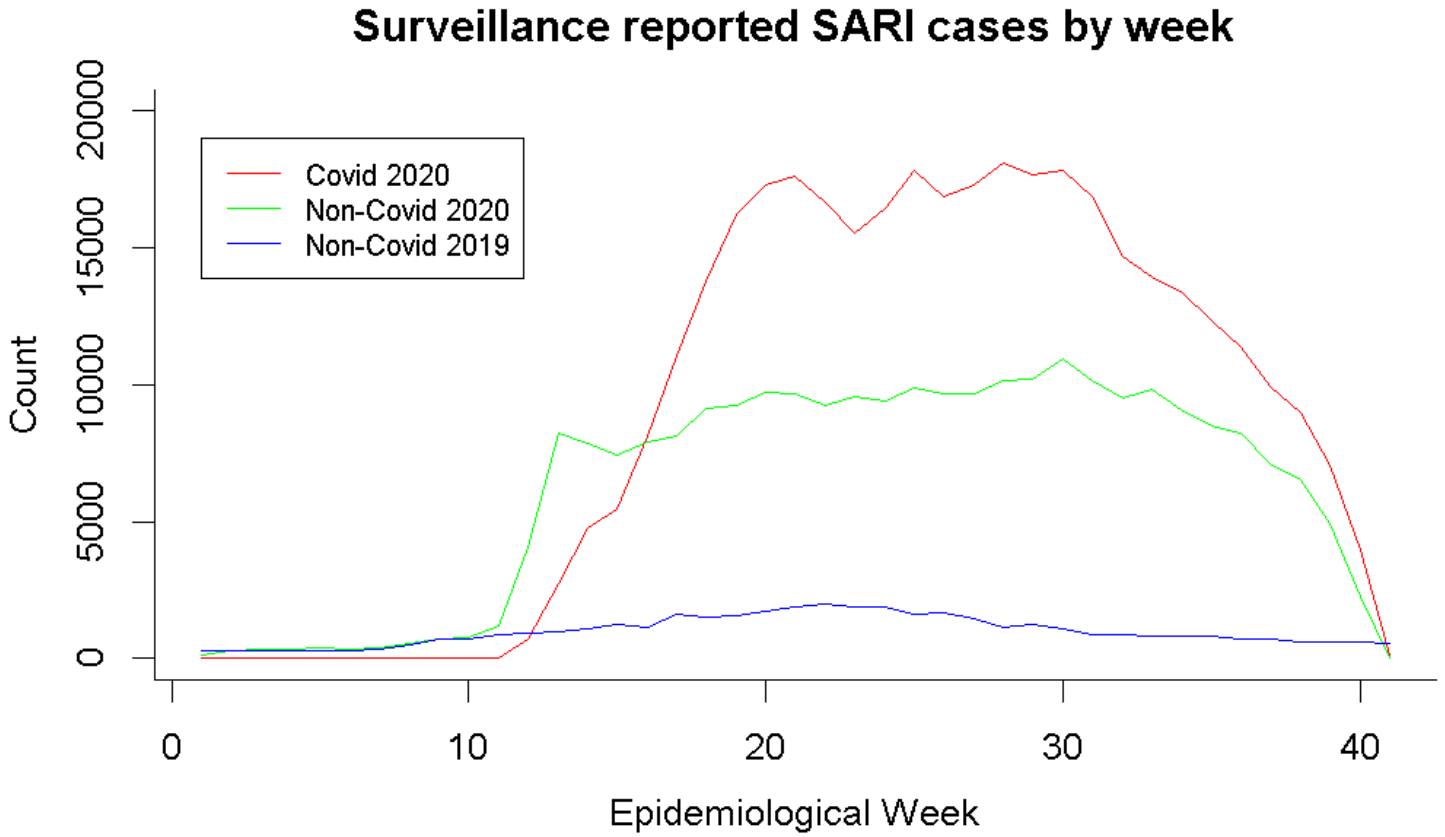
Clinical signs and symptoms by etiologic agent of SARI

Variable	Covid (%)	Non-Covid (%)	Variable	Covid (%)	Non-Covid (%)
Fever			**Cough**		
Yes	235,006 (73.8)	136,492 (62.3)	Yes	261,048 (80.6)	166,794 (74.2)
No	83,349 (26.2)	82,701 (37.7)	No	62,818 (19.4)	57,897 (25.8)
Missing	*46,549*	*32,923*	*Missing*	*41,038*	*27,425*
Throat Pain			**Diarrhea**		
Yes	66,165 (25.0)	39,776 (20.6)	Yes	47,706 (18.3)	25,316 (13.2)
No	198,385 (75.0)	15,3111 (79.4)	No	212,273 (81.7)	165,910 (86.8)
Missing	*100,354*	*59,229*	*Missing*	*104,925*	*60,890*
Vomiting					
Yes	28121 (11.1)	25105 (13.2)			
No	226356 (88.9)	165525 (86.8)			
Missing	*110,427*	*61,486*			
Dyspnea			**Respiratory discomfort**		
Yes	258,046 (79.8)	175,275 (77.3)	Yes	210,190 (70)	151,257 (69.9)
No	65,202 (20.2)	513,65 (22.7)	No	89,952 (30)	65,005 (30.1)
Missing	*41,656*	*25,476*	*Missing*	*64,762*	*35,854*
			Chest X-Ray results		
O_2 blood saturation <95%			Normal	8,307 (6.2)	15,423 (14.4)
Yes	209,253 (69.3)	134,962 (63.5)	Interstitial Infiltrate	60,865 (45.8)	47,302 (44.3)
No	92,525 (30.7)	77,679 (36.5)	Consolidation	8,265 (6.2)	8,968 (8.4)
Missing	*63,126*	*39,475*	Mixed	10,307 (7.8)	8,648 (8.1)
			Other	45,243 (34)	26,474 (24.8)
			Missing	*23,1917*	*14,5301*

Severity, ICU admission, VS, evolution, length of hospitalization and ICU stay by group

Variable	Covid (%)	Non-Covid (%)
Severity		
Asymptomatic	187 (0.05)	351 (0.14)
Mild	28,891 (8.22)	21,873 (9.02)
Severe	322,481 (91.73)	220,371 (90.84)
Missing	*13,532*	*9,872*
ICU admission		
Yes	113,894 (36.6)	65,091(29.8)
No	197,539 (63.4)	153,491 (70.2)
Missing	*53,471*	*33,534*
VS		
No	84,861 (28.2)	77,579 (36.8)
nonIVS	151,943 (50.5)	97,765 (46.4)
IVS	63,834 (21.2)	35,286 (16.8)
Missing	*64,266*	*41,486*
Case Evolution		
Cured	191,277 (60.0)	158,610 (74.8)
Dead	127,430 (40.0)	53,316 (25.2)
Missing	*46,197*	*40,190*

Variable	Covid	Non-Covid
Length Hospitalization (days)		
Mean (sd)	10.8 (11.7)	8.6 (11.1)
Median (IQR)	7.0 (10.0)	5.0 (7.0)
Length ICU stay (days)		
Mean (sd)	10.2 (10.8)	7.3 (9.9)
Median (IQR)	7.0 (11.0)	4.0 (7.0)

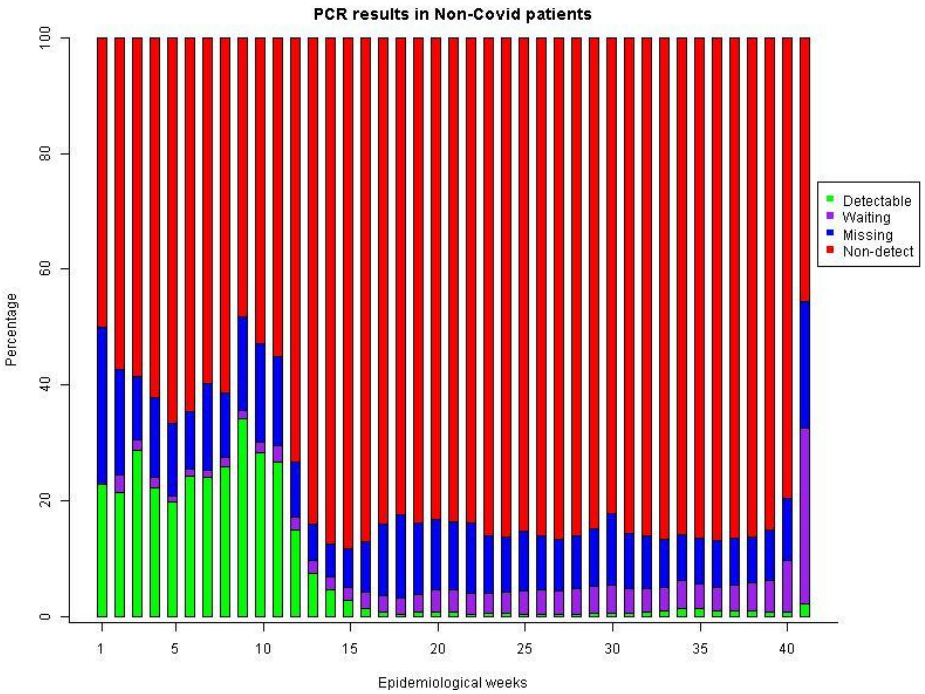


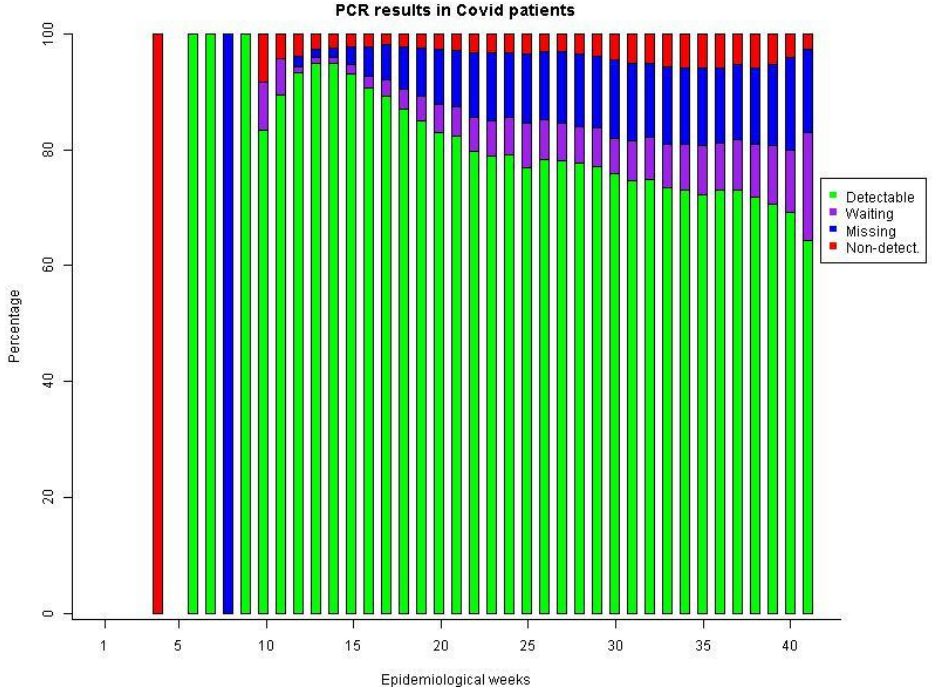
Epidemiological Week: Epidemiological week of the date the case was reported

Criteria for case determination and PCR result

	Case determination Criteria	Detectable	Not detectable/ Inconclusive	Waiting result	Missing	Total
Covid cases	**Laboratory**	282,206 (83.1)	8,731 (2.6)	17,593 (5.2)	31,040 (9.1)	339,570 (93.1)
	Epidemiological linking	178 (7.8)	272 (11.8)	651 (28.3)	1,196 (52.1)	2,297 (0.6)
	Clinical	407 (5.5)	1,004 (13.6)	1,596 (21.6)	4,398 (59.4)	7,405 (2.0)
	Other	162 (2.3)	3,576 (51.6)	1,004 (14.5)	2,185 (31.5)	6,927 (1.9)
	Missing	4,474 (51.4)	432 (5.0)	1,868 (21.5)	1,931 (22.2)	8,705 (2.4)
Non-Covid cases	**Laboratory**	4,771 (2.2)	203,640 (91.9)	5,721 (2.6)	7,404 (3.3)	221,536 (87.9)
	Epidemiological linking	0 (0.0)	498 (20.9)	332 (13.9)	1,553 (65.2)	2,383 (0.9)
	Clinical	13 (0.1)	2,432 (13.6)	2,025 (11.3)	13,452 (75.1)	17,922 (7.1)
	Other	0 (0.0)	354 (50.4)	77 (11.0)	271 (38.6)	702 (0.3)
	Missing	105 (1.1)	6,082 (63.5)	1,424 (14.9)	1,962 (20.5)	9,573 (3.8)

PCR results over time





Effect of education on PCR result

The odds of having a nondetect./incon. result vs detectable are:
- 2.89 times higher [2.77, 3.01] in no education category
- 2.32 times higher [2.24, 2.40] in fundamental 1st cycle
- 1.67 times higher [1.61, 1.73] in fundamental 2nd cycle
- 1.25 times higher [1.21, 1.29] in high school

as compared to university (reference).

The odds of having a waiting result vs detectable are:
- 3.30 times higher [3.05, 3.64] in no education category
- 2.02 times higher [1.88, 2.18] in fundamental 1st cycle
- 1.57 times higher [1.44, 1.70] in fundamental 2nd cycle
- 1.30 times higher [1.20, 1.40] in high school

as compared to university (reference).

PCR is crucial in prevention of the virus [8]. Does it have an effect on outcomes?

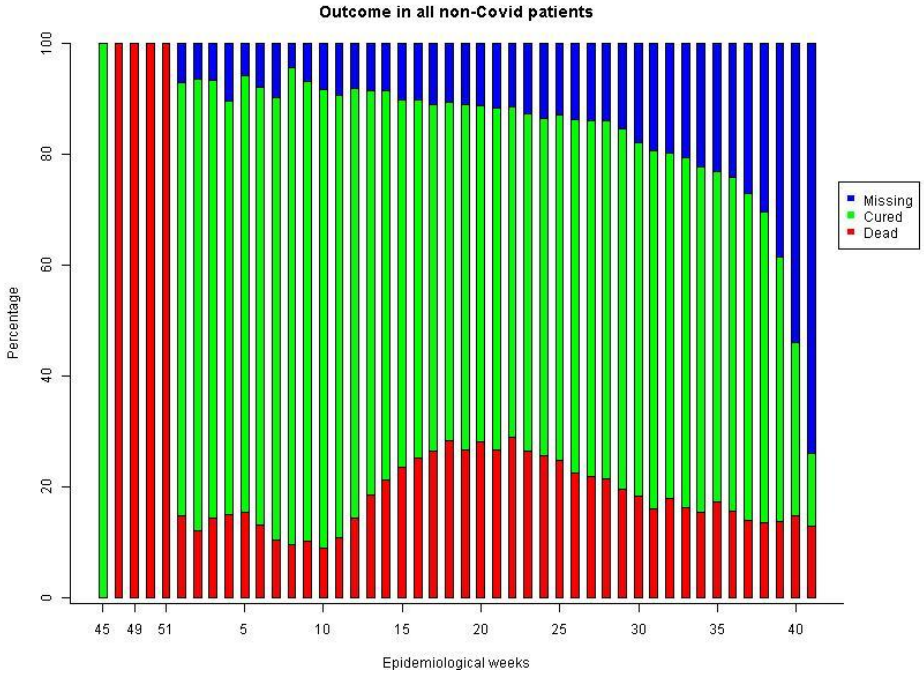
Effect of PCR result on death

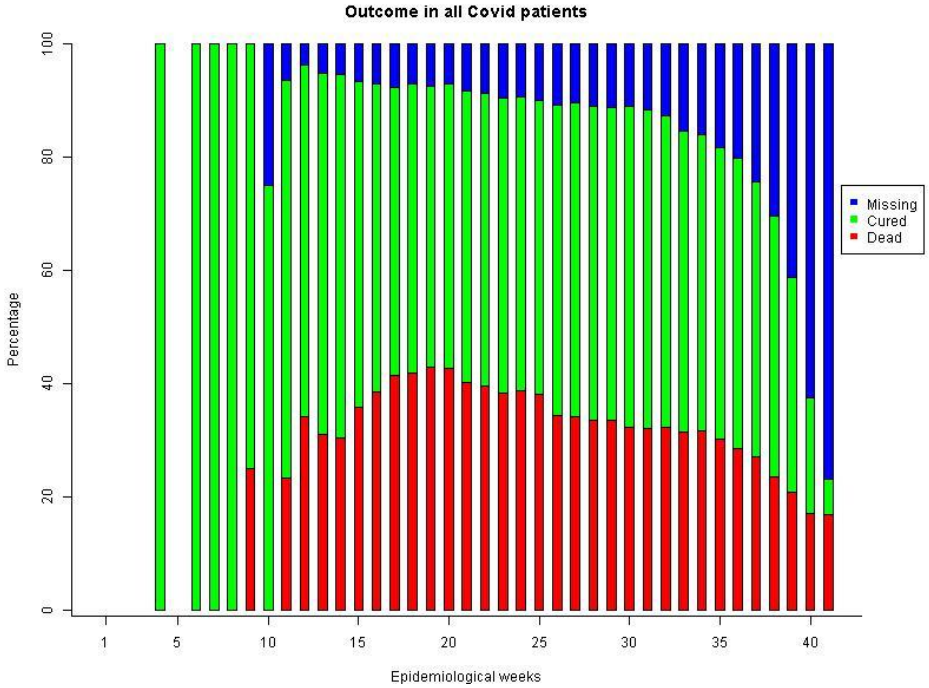
Variable	β	SE	P value	OR
		In nonCovid		
Intercept	-3.1	0.05	<.0001	
PCR *				
Nondetectab./incon.	0.25	0.05	<.0001	1.28 (1.16; 1.41)
Waiting	0.50	0.06	<.0001	1.65 (1.47; 1.75)
Severity ‡				
Asymptomatic	-0.04	0.20	0.84	0.96 (0.66, 1.40)
Severe	0.70	0.02	<.0001	2.02 (1.92; 2.12)
Age	0.03	0.002	<.0001	1.03 (1.03; 1.03)
Sex†	-0.19	0.01	<.0001	0.83 (0.81; 0.84)
		In Covid		
Intercept	-4.07	0.05	<.0001	
PCR *				
Nondetectab./incon.	-0.05	0.02	<.0001	0.95 (0.91; 0.99)
Waiting	0.05	0.02	<.0001	1.05 (1.01; 1.08)
Severity ‡				
Asymptomatic	-0.37	0.24	0.13	0.69 (0.43, 1.12)
Severe	0.65	0.02	<.0001	1.92 (1.86; 1.99)
Age	0.05	0.002	<.0001	1.05 (1.05; 1.05)
Sex†	-0.20	0.01	<.0001	0.82 (0.80; 0.83)

The model is contrasting outcome of death vs reference 'Cured')

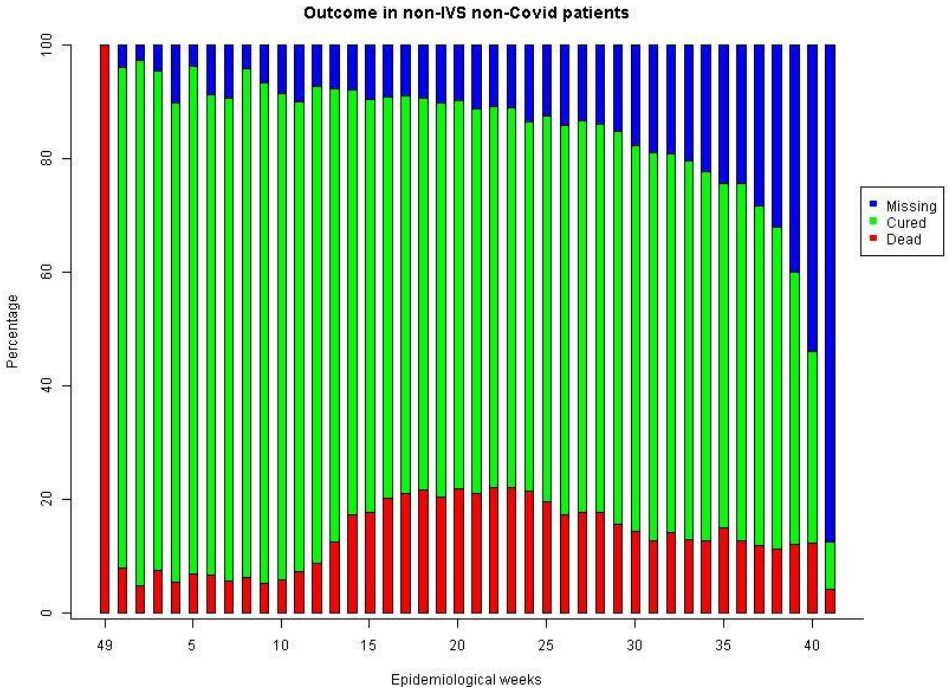
*Reference category is 'detectable'
‡ Reference category is 'Mild'
† Reference category is 'Male'

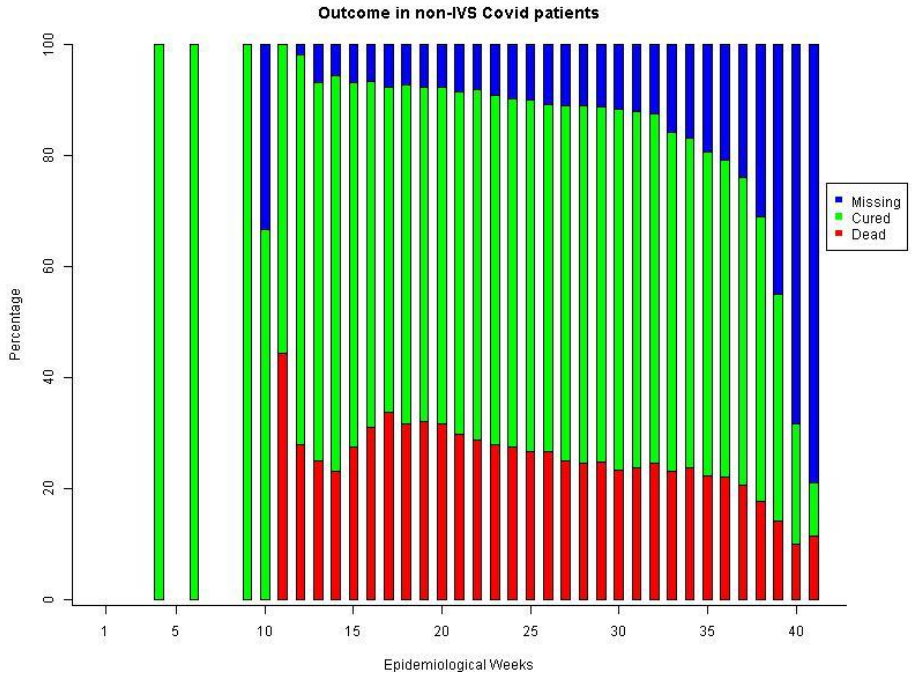
Outcome evolvement over time – All the patients



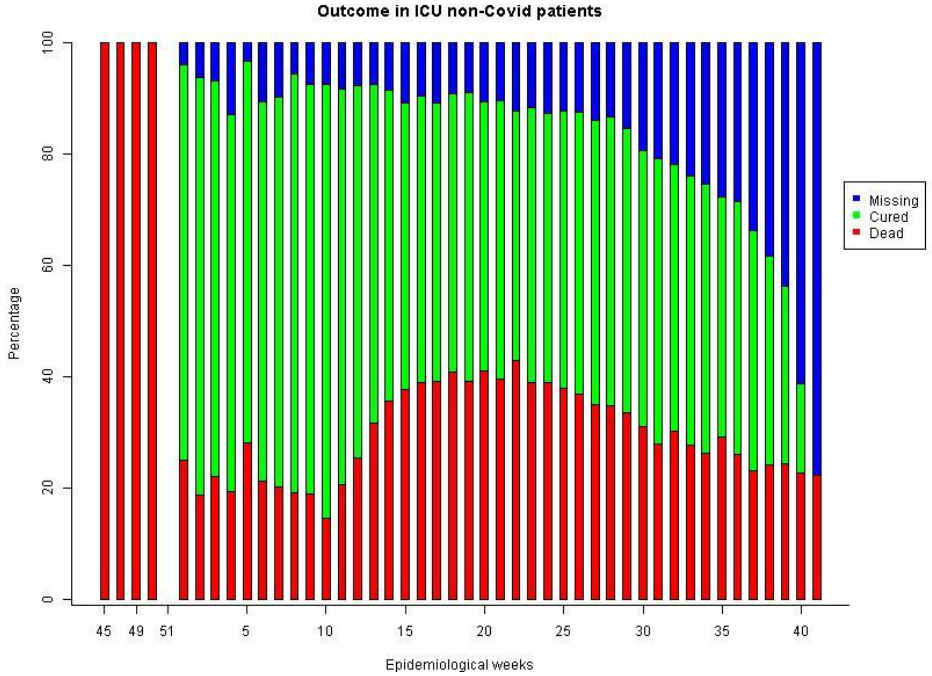


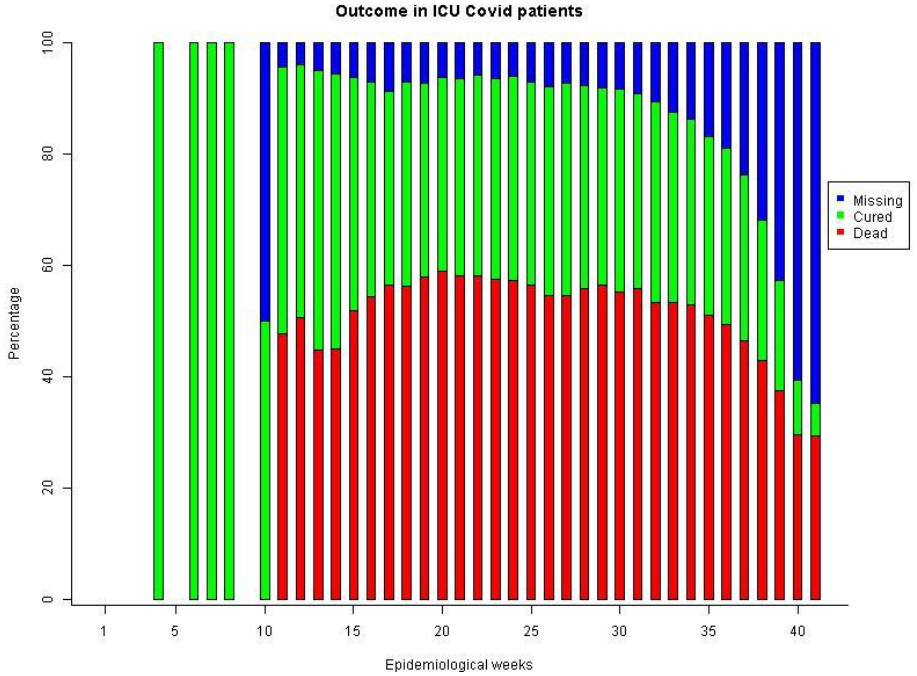
Outcome evolvement over time – non-Invasive Ventilatory Support (non-IVS)



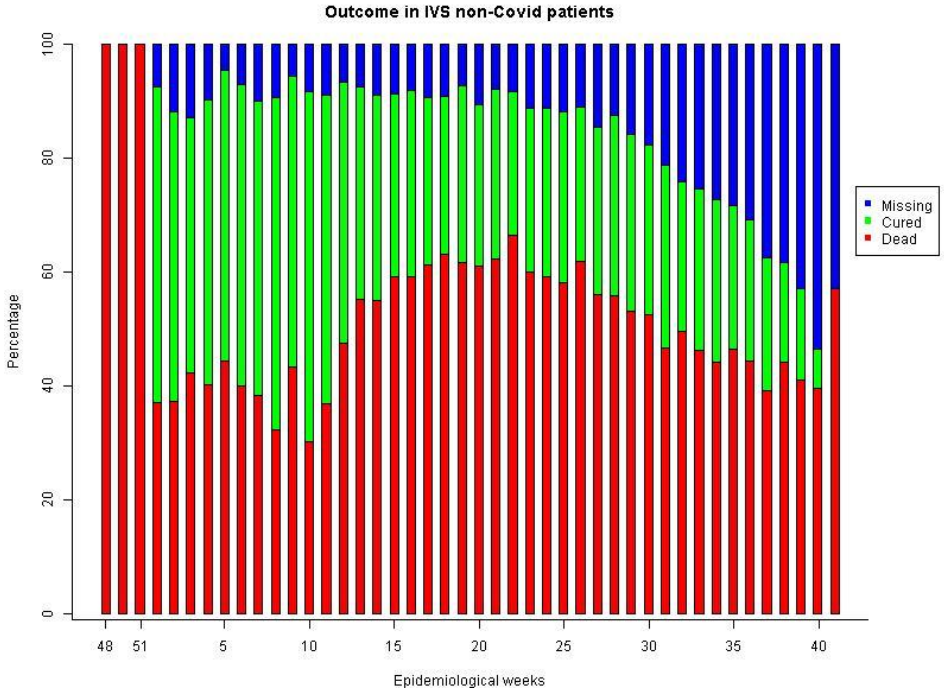


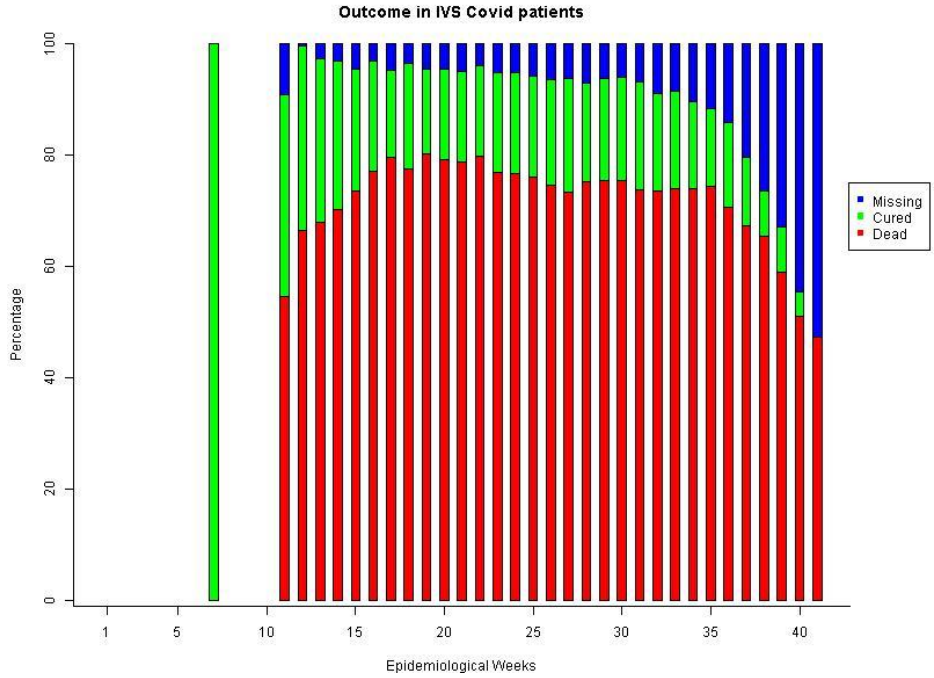
Outcome evolvement over time – ICU admitted patients



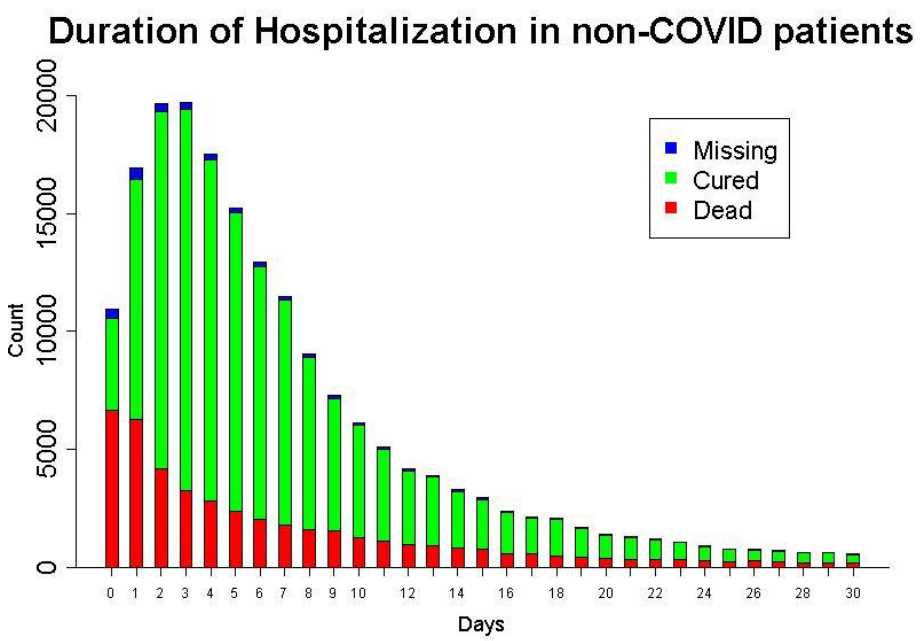


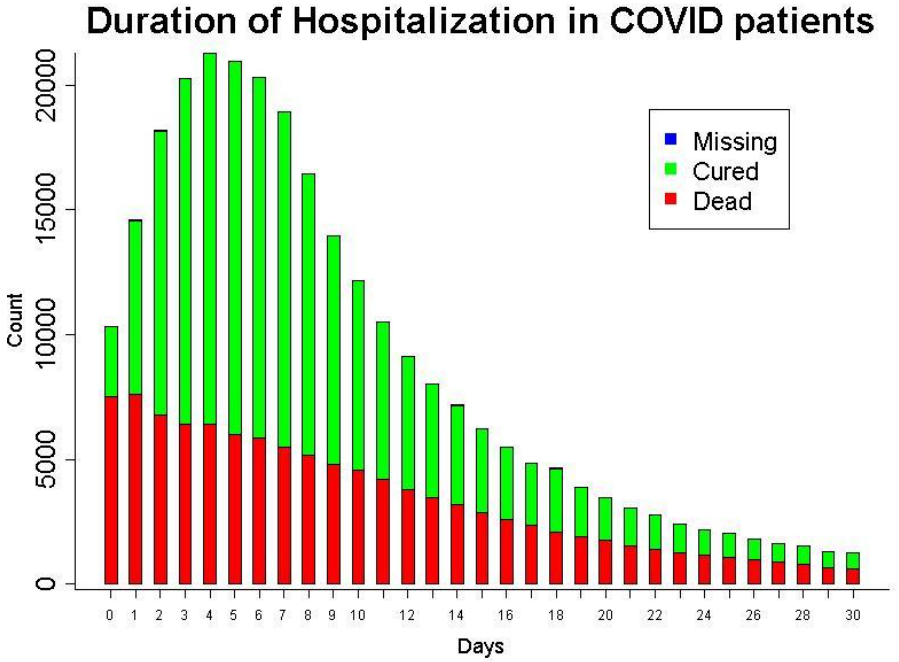
Outcome evolvement over time – Invasive Ventilatory Support (IVS)



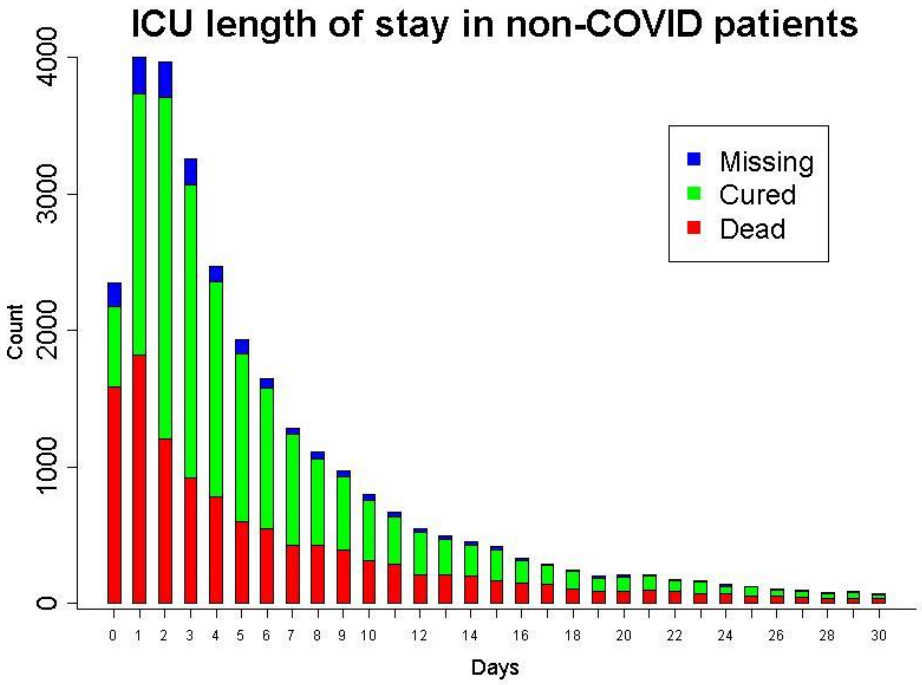


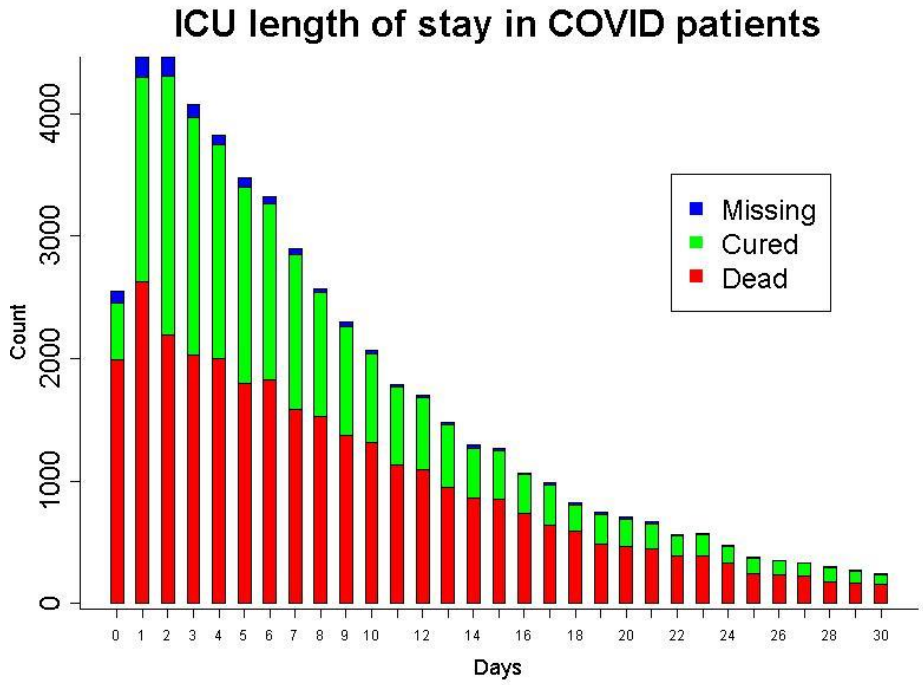
Duration of Hospitalization and outcome (Evolution determination – hospitalization)





ICU length of stay and outcome (Date discharge ICU– date enter ICU)





Effect on ICU Admission

Variable	β	SE	P value	OR
Intercept	-1.98	0.02	<.0001	
Covid*	0.27	0.01	<.0001	1.31 (1.29; 1.33)
Severity ‡				
Asymptomatic	1.06	0.10	<.0001	2.90 (2.37, 3.54)
Severe	0.65	0.02	<.0001	1.91 (1.85; 1.96)
Heart Disease*	0.23	0.01	<.0001	1.26 (1.24; 1.28)
Lung Disease*	0.24	0.01	<.0001	1.27 (1.23; 1.31)
Diabetes*	0.18	0.01	<.0001	1.19 (1.18; 1.21)
Asthma*	-0.16	0.02	<.0001	0.85 (0.82; 0.88)
Immunodepression*	0.27	0.02	<.0001	1.31 (1.26; 1.35)
Renal disease*	0.48	0.02	<.0001	1.62 (1.57; 1.67)
Liver disease*	0.33	0.03	<.0001	1.4 (1.31; 1.48)
Obesity*	0.48	0.02	<.0001	1.62 (1.57; 1.67)
Age	0.01	0	<.0001	1.01 (1.01; 1.01)
Sex†	-0.11	0.01	<.0001	0.89 (0.88; 0.91)
Race¶				
Others	0.001	0.01	0.9934	1.0 (0.97; 1.03)
White	0.08	0.01	<.0001	1.09 (1.06; 1.12)

*Reference category is 'No'
† Reference category is 'Male'
‡ Reference category is 'Mild'
¶ Reference category is Black

The model is contrasting outcome of being addmited to ICU vs reference 'No')

Effect on type of Ventilatory Support (VS)

Variable	Non Invasive VS (vs no VS)				Invasive VS (vs no VS)			
	β	SE	P value	OR	β	SE	P value	OR
Intercept	-1.81	0.02	<.0001		-3.44	0.03	<.0001	
Covid*	0.27	0.01	<.0001	1.31 (1.29; 1.33)	0.39	0.01	<.0001	1.47 (1.44; 1.5)
Severity ‡								
Asymptomatic	-0.06	0.13	0.6220	0.94 (0.73, 1.21)	1.01	0.15	<.0001	2.76 (2.09, 3.63)
Severe	1.58	0.02	<.0001	4.84 (4.70; 4.98)	1.84	0.02	<.0001	6.34 (6.04; 6.66)
Heart Disease*	0.26	0.01	<.0001	1.3 (1.28; 1.32)	0.3	0.01	<.0001	1.35 (1.32; 1.38)
Lung Disease*	0.28	0.02	<.0001	1.32 (1.27; 1.36)	0.47	0.02	<.0001	1.61 (1.54; 1.67)
Diabetes*	0.14	0.01	<.0001	1.15 (1.13; 1.18)	0.3	0.01	<.0001	1.36 (1.32; 1.39)
Asthma*	0.26	0.02	<.0001	1.29 (1.25; 1.34)	-0.04	0.03	0.1039	0.96 (0.91; 1.01)
Immunodepression*	-0.02	0.02	0.3714	0.98 (0.94; 1.02)	0.28	0.02	<.0001	1.32 (1.26; 1.38)
Renal disease*	-0.05	0.02	0.0146	0.95 (0.92; 0.99)	0.32	0.02	<.0001	1.38 (1.33; 1.44)
Liver disease*	-0.06	0.04	0.1054	0.94 (0.87; 1.01)	0.38	0.04	<.0001	1.46 (1.35; 1.59)
Obesity*	0.33	0.02	<.0001	1.38 (1.33; 1.44)	0.68	0.02	<.0001	1.98 (1.89; 2.07)
Age	0.01	0	<.0001	1.01 (1.01; 1.01)	0.02	0	<.0001	1.02 (1.02; 1.02)
Sex†	-0.06	0.01	<.0001	0.94 (0.92; 0.95)	-0.18	0.01	<.0001	0.83 (0.82; 0.85)
Race¶								
Others	0	0.02	0.8252	1 (0.97; 1.04)	0.05	0.02	0.0073	1.06 (1.02; 1.1)
White	0.01	0.02	0.6576	1.01 (0.98; 1.04)	-0.11	0.02	<.0001	0.9 (0.86; 0.93)

*Reference category is 'No'
† Reference category is 'Male'
‡ Reference category is 'Mild'
¶ Reference category is Black

Effect on Length of hospitalization and ICU stay

Variable	Length of hospitalization			Length of ICU stay		
	β	SE	P value	β	SE	P value
Intercept	1.98	0.003	<.0001	1.95	0.01	<.0001
Covid*	0.23	0.001	<.0001	0.35	0.001	<.0001
Severity (Severe)‡						
Asymptomatic	0.27	0.02	<.0001	0.33	0.04	<.0001
Severe	0.05	0.002	<.0001	0.11	0.01	<.0001
Heart Disease*	0.07	0.001	<.0001	0.05	0.001	<.0001
Lung Disease*	0.1	0.002	<.0001	0.05	0.001	<.0001
Diabetes*	0.04	0.001	<.0001	0.03	0.001	<.0001
Asthma*	-0.11	0.003	<.0001	-0.07	0.01	<.0001
Immunodepression*	0.23	0.003	<.0001	0.08	0.01	<.0001
Renal disease*	0.15	0.002	<.0001	0.05	0.001	<.0001
Liver disease*	0.08	0.005	<.0001	-0.04	0.01	<.0001
Obesity*	0.08	0.003	<.0001	0.12	0.001	<.0001
Age	0	0.001	<.0001	0	0.001	<.0001
Sex†	-0.04	0.001	<.0001	-0.03	0.001	<.0001
Race						
Others¶	0.03	0.002	<.0001	-0.01	0.01	0.1128
White¶	0	0.002	0.4361	0.06	0.01	<.0001

*Reference category is 'No' ‡ Reference category is 'Mild'
† Reference category is 'Male' ¶ Reference category is Black

Effect on Survival

Variable	β	SE	P value	OR
Intercept	-4.9	0.03	<.0001	
Covid*	0.62	0.01	<.0001	1.85 (1.82; 1.89)
Ventilatory Support*				
Non-Invasive	0.37	0.01	<.0001	1.45 (1.42; 1.48)
Invasive	2.70	0.01	<.0001	14.9 (14.5; 15.31)
Severity (Severe) §				
Asymptomatic	-0.32	0.18	0.07	0.74 (0.51; 1.03)
Severe	0.45	0.02	<.0001	1.56 (1.5; 1.63)
Heart Disease*	-0.03	0.01	0.0012	0.97 (0.95; 0.99)
Lung Disease*	0.08	0.02	<.0001	1.08 (1.05; 1.12)
Diabetes*	0.15	0.01	<.0001	1.16 (1.13; 1.18)
Asthma*	-0.33	0.03	<.0001	0.72 (0.69; 0.76)
Immunodepression*	0.77	0.02	<.0001	2.17 (2.08; 2.26)
Renal disease*	0.47	0.02	<.0001	1.6 (1.54; 1.66)
Liver disease*	0.68	0.04	<.0001	1.97 (1.83; 2.13)
Obesity*	0.13	0.02	<.0001	1.14 (1.09; 1.19)
Age	0.04	0	<.0001	1.05 (1.05; 1.05)
Sex†	-0.16	0.01	<.0001	0.85 (0.83; 0.86)
Race¶				
Others	0.06	0.02	0.0012	1.06 (1.02; 1.1)
White	-0.36	0.02	<.0001	0.7 (0.67; 0.72)

*Reference category is 'No'
† Reference category is 'Male'
‡ Reference category is 'Mild'
¶ Reference category is Black

The model is contrasting outcome of death vs reference 'Cured')

Conclusions

- Increased reporting of non-Covid cases compared to last year. PCR test has been inconclusive/non-detectable for a great proportion of them.

- Low education is associated with lower odds of PCR being detectable.
- Having a PCR test result different from detectable is associated with higher odds of dying in non-Covid patients.

- While going from all reported, to non-Invasive VS, ICU admitted, and Invasive VS death proportion goes from as low as 20% to as high as 80%.
- Proportion of death in general is higher in Covid patients during the entire considered period.

- Length of Hospitalization and ICU stay is higher in Covid patients

Conclusions

- Compared to non-Covid cases, Covid cases have higher odds of worse outcomes.
- Among comorbidities, heart disease, lung disease, obesity, immunosuppression, and diabetes are associated with worse outcomes in both groups.
- Analysis shows Asthma to play a protective role against bad outcomes. This is supported from research [9].
- Females have better outcomes compared to Males. Age also is associated with higher odds of death.
- Whites have 30% lower odds of dying compared to blacks.

Discussion & Limitations

- Clinical manifestations, presence of comorbidities and their effect is consistent with other studies.

- Detectability rates of PCR are lower in Non-Covid cases (misdiagnosis?).

- Observational data coming from surveillance – inconsistencies in data reporting.
- (E.g. Some cases with congenital heart disease are reported as having chronic heart disease, even though the form requires reporting of comorbidities of chronic nature).

- Missing data generated from observational study.

References

1. Gorbalenya, A.E., et al., *The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.* Nature Microbiology, 2020. **5**(4): p. 536-544.
2. Weekly epidemiological update - 24 November 2020. (n.d.). Retrieved October 24, 2020, from https://www.who.int/publications/m/item/weekly-epidemiological-update---24-november-2020
2. Dhama, K., et al., *Coronavirus Disease 2019-Covid-19.* Clin Microbiol Rev, 2020. **33**(4).
3. Plataforma IVIS. Available from: http://plataforma.saude.gov.br/coronavirus/dados-abertos/ (accessed on 12 November 2020).
4. FICHA DE REGISTRO INDIVIDUAL - CASOS DE SÍNDROME RESPIRATÓRIA AGUDA GRAVE HOSPITALIZADO. Available from: http://plataforma.saude.gov.br/coronavirus/dados-abertos/sivep-gripe/ficha-SIVEP-GRIPE-SRAG-hospital-Sivepgripe.pdf (accessed on 12 November 2020).
5. Clinical Spectrum of SARS-CoV-2 Infection. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed on 14 November 2020).
6. Agresti, A., *Logistic Regression*, in *An Introduction to Categorical Data Analysis*. 2007, Wiley. p. 106-109.
7. Agresti, A., *Generalized Linear Models for Count Data*, in *An introduction to categorical data analysis*. 2007, Wiley. p. 74-83.
8. Li, N., et al., *Molecular diagnosis of Covid-19: Current situation and trend in China (Review).* Exp Ther Med, 2020. **20**(5): p. 13.
9. Carli, G., et al., *Is asthma protective against Covid-19?* Allergy, 2020: p. 10.1111/all.14426.

Thank you!

Q&A