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Testing-Related and Geo-Demographic Indicators Strongly Predict COVID-19 Deaths in the United States During March of 2020

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Running title: Predicting early COVID-19 Deaths in the United States

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The COVID-19 pandemic has wreaked havoc around the globe and caused significant disruptions across multiple domains^[1]. Moreover, different countries have been differentially impacted by COVID-19 – a phenomenon that is due to a multitude of complex and often interacting determinants^[2]. Understanding such complexity and interacting factors requires both compelling theory and appropriate data analytic techniques. Regarding data analysis, one question that arises is how to analyze extremely non-normal data, such as those variables evidencing L-shaped distributions. A second question concerns the appropriate selection of a

predictive modelling technique when the predictors derive from multiple domains (e.g., testing-related variables, population density), and both main effects and interactions are examined.

To address these questions, we propose a novel statistical approach for analyzing and understanding complex data interactions. Using data collected in the USA during the first month in which COVID-19 testing was performed (March of 2020), we examined the following six predictors of COVID-19 related deaths: (i) the proportion of all tests conducted during the first week of testing; (ii) the cumulative number of (test-positive) cases through 3-31-2020, (iii) the number of tests performed/million inhabitants; (iv) the cumulative number of inhabitants tested; (v) the number of cases/million inhabitants (cases/mill inh); and (vi) the number of diagnostic tests performed in week one of testing/million inhabitants/state-specific population density (w1DT/MI/PD), where "population density" is defined as the number of inhabitants per square kilometer.

The purpose of this study was to examine the ability of the six variables to predict COVID-19 related deaths in the United States during March of 2020. We ran the predictive model twice, once for each dependent variable: mortality count (overall number of deaths), and deaths per million inhabitants. Because our model (a) uses predictors that leverage information from multiple domains, (b) captures both nationwide and state-specific dimensions, and (c) examines two different mortality-related outcomes, the results are expected to have relevance for policy-makers.

All data used in this study were obtained from three sources in the public domain: Worldometer (https://www.worldometers.info/coronavirus/), World Population Review (https://worldpopulationreview.com/states), and Covidtracking (https://covidtracking.com/). The data were processed and analyzed using IBM SPSS, Minitab, and R. Univariate skewness and

kurtosis values indicated that all predictors and outcomes were non-normally distributed, with a few variables evidencing L-shaped distributions. The L-shaped variables were normalized using the rank-based inverse normal (RIN) transformation^[3]. For extremely non-normal data, the RIN method is a highly effective normalizing transformation^[3].

The prediction models were first examined using linear multiple regression, with the RIN-transformed versions of all variables used in the regressions. Because the homoscedasticity assumption (i.e., constant variance of the predicted Y-values) was not met, we re-ran the prediction models using a non-parametric approach known as Kernel Regularized Least Squares (KRLS) Regression^[4]. KRLS is an appropriate method to use when the assumptions of linear regression are not met and the precise functional forms between the predictors and outcomes are unknown. All KRLS regressions used the RIN-transformed variables and all analyses were performed using the KRLS package for *R*. The use of non-parametric, machine learning-based methods such as KRLS is consistent with recent calls to place greater reliance on artificial intelligence systems for understanding the causes and consequences of the COVID-19 pandemic^[5].

The KRLS regression results are presented in Table 1. For number of deaths, the six predictors accounted for 98.8% of the variance. Five of the predictors were statistically significant (p-values ≤ 0.002). Two of the significant predictors (i.e., number of test-positive cases, Cohen's d=2.3; and cases per million inhabitants, Cohen's d=1.3) represent different ways of quantifying the illness burden due to SARS-CoV-2 infection. The ratio of the two d values indicated that the predictive strength of number of test-positive cases was 77% greater than was cases per million inhabitants. Regarding the second dependent variable, the six predictors accounted for 92.6% of the variance in deaths per million inhabitants. Five of the

predictors were significant (p-values ≤ 0.03). For this regression analysis, the number of test-positive cases (d = 1.1) and cases per million inhabitants (d = 1.4) were similar in predictive strength.

Table 1. KRLS regression of potential predictors of COVID-19 related mortality

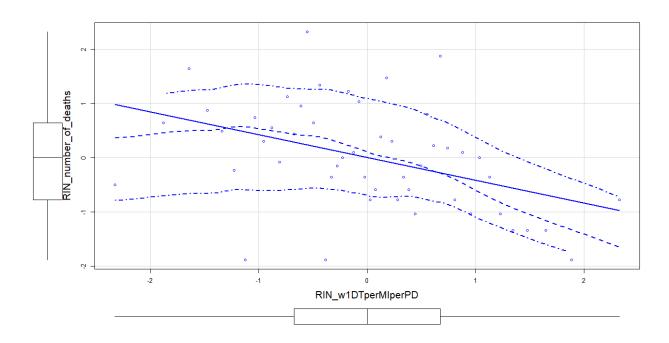
Predictors of number of deaths	1				
		Estimate	Std. Error	t value	p-value
taltestsRIN 0.111		0	.033	3.326	.002
testedpermilRIN	-0.153	0	.026	-5.782	<.0001
wkonepropalltestsRIN		0.044	0.030	1.45	.153
wkonepermilcitperpopdenRIN	0.169	0	.032	5.262	<.0001
confircasesRIN	0.568	0	.035	16.340 < .00	001
casespermilRIN	0.215	0	.023	9.185	<.0001
Predictors of deaths per million	ı inhabita	nts			
		Estimate	Std. Error	t value	p-value
totaltestsRIN		-0.138	0.058	3 -2.3	52 .023
totaticststctrv		0	.048	0.091	.928
	0.004	U	.0-0	0.071	.920
testedpermilRIN	0.004	0.136	0.061		
testedpermilRIN wkonepropalltestsRIN	0.004 0.161	0.136			
testedpermilRIN wkonepropalltestsRIN wkonepermilcitperpopdenRIN confircasesRIN		0.136	0.061	2.23	.031

Note. All predictors were normalized using the rank-based inverse normal (RIN) transformation. Estimates are sample-average partial derivatives. The set of predictors accounted for 98.8% of the variance in number of deaths ($R^2 = 0.9875$). For deaths per million citizens, the predictors accounted for 92.6% of the variance ($R^2 = 0.9264$). Description of predictors: totaltests = number of tests performed in March of 2020; testedpermil = number of all tests conducted per million inhabitants, in March of 2020; wkonepropalltests = all tests conducted during the first week of testing, expressed as the percentage of all tests performed in March 2020; wkonepermilcitperpopden = the number of tests performed during week one per million inhabitants, divided by state-specific population density; confircases = total number of test-positive individuals, in March of 2020; casespermil = number of test-positive individuals per million inhabitants, in March of 2020.

In addition to number of test-positive cases and cases per million inhabitants, another interesting predictor was our geo-demographic variable (i.e., the number of diagnostic tests/million inhabitants/population density performed in week one of testing, or w1DT/MI/PD).

This predictor was significantly associated with both dependent variables. Because w1DT/MI/PD is a complex, ratio-based predictor, discerning the precise nature of its predictive association from a single regression estimate alone is challenging. To further enhance the interpretation of this variable, we created two scatterplots showing the association between w1DT/MI/PD and each dependent variable. Both scatterplots include boxplots for the X and Y variables, a best fitting linear regression line, and a *lowess* line (with accompanying 95% confidence interval). *Lowess* stands for locally weighted scatterplot smoothing. The *lowess* line is the best fitting non-linear curve that tracks the data points in the scatterplot. The *lowess* curves allow us to make inferences about COVID-19 related deaths at low and high levels of w1DT/MI/PD. Such inferences are tantamount to examining COVID-19 related deaths for U.S. states scoring low versus high on the geo-demographic predictor variable. The scatterplots were created using the *car* package for *R*.

As the *lowess* curve in the top panel of Figure 1 indicates, at higher and medium levels of w1DT/MI/PD, the association between the geo-demographic predictor and death count was strongly negative and moderately negative, respectively. In contrast, at lower levels of w1DT/MI/PD, there was little if any association between the geo-demographic variable and number of fatalities. The bottom panel of Figure 1 indicates that at lower levels of w1DT/MI/PD, the association between the geo-demographic variable and deaths per million inhabitants was moderately positive. At medium levels of w1DT/MI/PD, there was little if any association between the two variables. Finally, at higher levels of w1DT/MI/PD, there was a moderately strong negative association between the geo-demographic variable and deaths per million inhabitants.



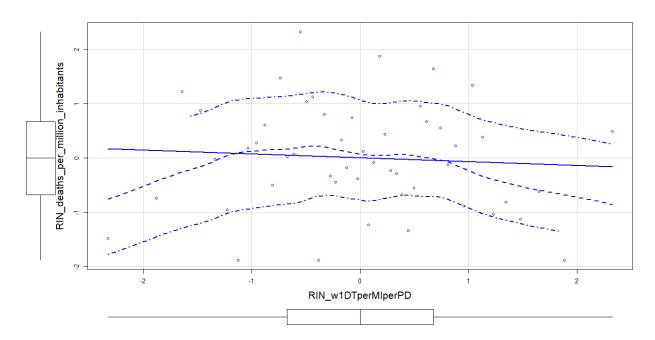
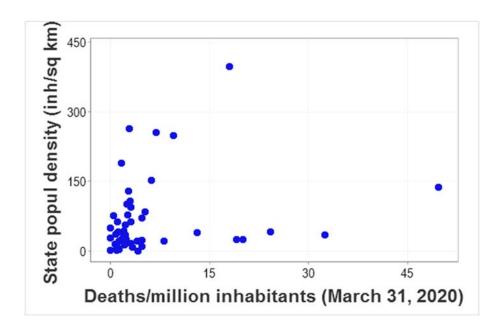


Figure 1. Scatterplots depicting *lowess* curves (the middle dashed lines) and accompanying 95% confidence intervals (top and bottom dashed lines) for the association between number of tests during week 1/million inhabitants/population density and (a) number of COVID-19 related deaths (top panel) and (b) number of COVID-19 related deaths per million inhabitants (bottom panel). All variables were normalized using the rank-based inverse normal (RIN) transformation.



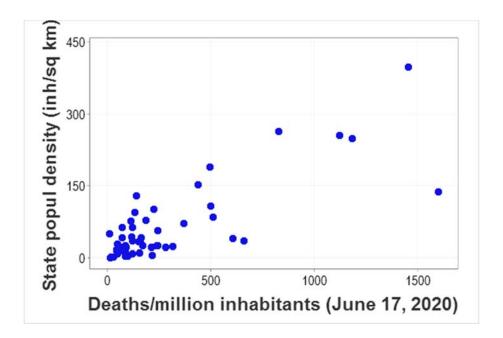


Figure 2. Scatterplots showing the Pearson correlations between population density and cumulative COVID-19 related deaths per million inhabitants through (a) March 31, 2020, top panel (r = 0.228, 95% CI: -0.054, 0.476) and (b) June 17, 2020, bottom panel (r = 0.80, 95% CI: 0.671, 0.882).

In constructing our geo-demographic predictor variable, we controlled for population density because it is an important factor associated with disease transmission^[6]. Moreover, because there typically is a lag time of several weeks or more between being infected with

SARS-CoV-2 and showing disease-related symptoms, the association between population density and disease-related deaths should strengthen over time. To highlight this point, Figure 2 presents scatterplots showing the Pearson correlations between population density and cumulative COVID-19 related deaths per million inhabitants through March $31^{\rm st}$ and June $17^{\rm th}$, 2020, respectively. The correlations were as follow: March $31^{\rm st}$ (r = 0.228, p > 0.05); June $17^{\rm th}$ (r = 0.800, p < 0.01). The difference between the two statistically dependent correlations was evaluated using Hittner, May and Silver's modification of Dunn and Clark's z test^[7]. The two correlations were significantly different (z = 5.85, p < 0.0001), thereby supporting the prediction that the association between population density and COVID-19 related deaths will strengthen over time.

To the best of our knowledge, this is the first study that examines testing-, case countand geo-demographic variables as predictors of COVID-19 related deaths. Using a flexible,
machine learning-based approach (KRLS regression), we found that our predictors accounted for
very high percentages of outcome variance (98.8% and 92.6% for number of deaths and deaths
per million inhabitants, respectively). Furthermore, with very few exceptions, our predictors
were both statistically significant and practically important.

One novel contribution of this study was our examination of a complex, ratio-based geodemographic predictor variable. This variable—the number of diagnostic tests performed in week one of testing/million inhabitants/state-specific population density (w1DT/MI/PD)—significantly predicted COVID-19 related deaths, but did so differently depending on where, along the continuum of geo-demographic values, the predictive association was examined. At the lower end of the geo-demographic predictor, more tests during week one per million inhabitants, normalized by population density, were associated with more deaths per million citizens. In

contrast, at the higher end of the geo-demographic predictor, more tests during week one per million inhabitants, normalized by population density, were associated with fewer deaths per million inhabitants. These different quantitative patterns could reflect different qualitative situations. In the first case (lower values on the geo-demographic variable, where more tests are associated with more deaths), testing seems to pursue a *confirmatory* purpose. In contrast, for the second case (higher values on the geo-demographic variable, where more tests are associated with fewer deaths), *diagnostic* testing appears to be emphasized^[8]. One implication of these findings is that when examining our geo-demographic variable as a predictor of deaths, the inflection points along the *lowess* curves (the positions where the slope rises and falls) can serve as approximate cut-points demarcating three types of testing: confirmatory, diagnostic, and other.

When testing prioritizes symptomatic cases, it is expected that most tested individuals will result in positive results (infection will be confirmed). Because deaths will occur within a subset of infected individuals, when testing is confirmatory (when only symptomatic patients are tested), more tests will be associated with more deaths. In contrast, when asymptomatic individuals are also tested, more tests, conducted earlier, will allow clinicians to detect, treat, and isolate infections earlier and prevent further viral dissemination which, in turn, will result in fewer deaths/million inhabitants. Our findings thus support an important recommendation from the World Health Organization, which is that early and frequent testing helps to prevent deaths^[9].

In addition to the contributions described above, we performed supplemental analyses examining the association between population density and COVID-19 related deaths. The role of population density in predicting epidemic dispersal and epidemic-related deaths is receiving increased research attention^[10]. To the best of our knowledge, the present study is the first to demonstrate that the magnitude of association between population density and COVID-19

related deaths *strengthens* as the time since first infection increases. Understanding how factors such as testing frequency, the relative proportion of confirmatory versus diagnostic testing, and sociodemographic composition influence the temporal association between population density and COVID-19 related deaths is an important priority for future research.

Overall, our findings highlight the importance of considering predictor variables from multiple domains. When ratio-based predictors such as our geo-demographic variable are analyzed, we recommend examining *lowess* curves as a visual interpretational aid for explicating the (often) complex non-linear associations between such ratio-based predictors and various outcomes of interest. An important direction for future research on epidemic dissemination and potential control is to examine both ratio-based composite variables—such as our geo-demographic measure—and traditional multiplicative interaction terms (created as linear products of two or more variables). The joint examination of both types of complex variables might result in greater predictive power and/or might foster additional insights into the dynamics of infectious diseases, such as COVID-19.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author contributions

JBH and ALR designed the study. DM curated the original data. ALH, RP, PK, SDS, JBH and FOF reviewed the literature and extracted and filtered the available data from online repositories. JBH conducted the statistical analyses. All authors contributed to writing of the report.

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Supplementary Table S1. Epidemic data collected in all states of the USA in March, 2020

State	Tests	Total	Wk I/	State	Total	Total	Cases/	State	Wk I	Total	Deaths
	wk I	tests	all	pop/	tests/	cases	mill inh	pop	tests/	deaths	/ mill
			tests	mill	mill inh			dens	mill inh/	(count)	inh
			(%)						state		
									pop		
									dens		
AK	227	3654	6.21	0.734	4978.20	114	155.31	0.425	726.115	3	4.08
AL	352	5014	7.02	4.908	1021.60	830	169.11	36.149	1.984	4	0.81
AR	115	3453	3.33	3.038	1136.60	426	140.22	22.057	1.716	6	1.97
AZ	373	13872	2.68	7.378	1880.18	919	124.56	24.990	2.023	17	2.30
CA	4260	90657	4.69	39.937	2270.00	5708	142.93	94.198	1.132	123	3.07
CO	938	14470	6.48	5.845	2475.62	2307	394.70	21.680	7.402	47	8.04
CT	551	11900	4.63	3.563	3339.88	1993	559.36	248.188	0.623	34	9.54
DE	129	3701	3.48	0.982	3768.84	236	240.33	152.342	0.862	6	6.11
FL	1380	48998	2.81	21.992	2227.99	4950	225.08	129.126	0.485	59	2.68
GA	48	12596	0.38	3.991	3156.10	2683	672.26	25.930	0.463	80	20.04
HI	12	8013	0.14	1.412	5674.93	175	123.93	49.869	0.170	0	0
ID	427	4706	9.07	1.826	2577.22	310	169.77	8.436	27.718	6	3.28
IL	1622	27762	5.84	12.659	2193.06	4596	363.06	84.395	1.518	66	5.21
IN	149	9830	1.51	6.745	1457.38	1514	224.46	71.505	0.308	32	4.74
IO	330	5349	6.16	3.179	1682.60	336	105.69	21.811	4.759	4	1.25
KS	167	4513	3.70	2.910	1550.86	319	109.62	13.655	4.202	6	2.06
KY	207	6018	3.43	4.499	1337.63	439	97.57	42.988	1.070	9	2.00
LA	368	27871	1.32	4.645	6000.22	3540	762.11	34.240	2.313	151	32.50
MA	171	39066	0.43	6.976	5600.06	4955	710.29	255.203	0.096	48	6.88
MD	447	13593	3.28	6.083	2234.59	1239	203.68	189.312	0.388	10	1.64
ME	272	3647	7.45	1.345	2711.52	253	188.10	14.677	13.777	3	2.23
MI	274	17379	1.57	10.045	1730.11	5486	546.14	40.101	0.680	132	13.14
MN	889	17657	5.03	5.700	3097.72	503	88.24	25.314	6.161	9	1.57
MO	236	14107	1.67	6.169	2286.76	903	146.37	34.169	1.119	12	1.94
MS	969	3318	29.20	2.989	1110.07	758	253.59	23.828	13.605	14	4.68
MT	160	4069	3.93	1.086	3746.78	161	148.25	2.851	51.664	1	0.92
NC	17	19072	0.08	10.611	1797.38	1167	109.98	76.123	0.021	5	0.47
ND	393	3724	10.55	0.761	4893.56	98	128.77	4.156	124.260	1	1.31
NE	272	2345	11.59	1.952	1201.33	120	61.47	8.859	15.728	2	1.02
NH	232	5396	4.29	1.371	3935.81	258	188.18	56.622	2.988	3	2.18
NJ	284	35602	0.79	8.936	3984.11	13386	1497.99	395.555	0.080	161	18.01
NM	488	11179	4.36	2.096	5333.49	237	113.07	5.944	39.168	2	0.95
NY	1661	172360	0.96	19.440	8866.26	59513	3061.37	137.582	0.621	965	49.63
NV	262	10534	2.48	3.139	3355.85	920	293.08	10.960	7.614	15	4.77
ОН	148	20665	0.71	11.747	1759.17	1653	140.72	101.180	0.124	29	2.46

OK	206	1634	12.60	3.954	413.25	429	108.50	21.840	2.385	16	4.04
OR	1023	11426	8.95	4.301	2656.59	548	127.41	16.879	14.090	13	3.02
PA	403	33455	1.20	12.820	2609.59	3394	264.74	107.478	0.292	38	2.96
RI	550	3134	17.54	1.056	2967.80	294	278.40	263.934	1.973	3	2.84
SC	97	3789	2.56	5.210	727.26	774	148.56	62.822	0.296	16	3.07
SD	185	3218	5.74	0.903	3563.68	90	99.66	4.521	45.315	1	1.10
TN	73	20574	0.35	6.897	2983.04	1537	222.85	63.186	0.167	7	1.01
TX	48	25760	0.18	29.472	874.05	2552	86.59	42.365	0.038	34	1.15
UT	279	13993	1.99	3.282	4263.56	719	219.07	14.926	5.695	2	0.60
VA	314	10609	2.95	8.626	1229.89	890	103.17	77.861	0.467	22	2.55
VT	291	3701	7.86	0.628	5893.31	235	374.20	25.215	18.376	12	19.10
WA	4415	59206	7.45	7.797	7593.43	4310	552.78	42.223	13.410	189	24.24
WI	259	17662	1.46	5.851	3018.63	1112	190.05	34.491	1.283	13	2.22
WV	38	3108	1.22	1.778	1748.03	124	69.74	28.331	0.754	0	0
WY	308	1641	18.76	0.567	2894.18	87	153.43	2.238	242.707	0	0

Note. Abbreviations of USA states: AK (Alaska), AL (Alabama), AR (Arkansas), AZ (Arizona), CA (California), CO (Colorado), CT (Connecticut), DE (Delaware), FL (Florida), GA (Georgia), HI (Hawaii), ID (Idaho), IL (Illinois), IN (Indiana), IO (Iowa), KS (Kansas), KY (Kentucky), LA (Louisiana), MA (Massachusetts), MD (Maryland), ME (Maine), MI (Michigan), MN (Minnesota), MO (Missouri), MS (Mississippi), MT (Montana), NC (North Carolina), ND (North Dakota), NE (Nebraska), NH (New Hampshire), NJ (New Jersey), NM (New Mexico), NY (New York), NV (Nevada), OH (Ohio), OK (Oklahoma), OR (Oregon), PA (Pennsylvania), RI (Rhode Island), SC (South Carolina), SD (South Dakota), TN (Tennessee), TX (Texas), UT (Utah), VA (Virginia), VT (Vermont), WA (Washington), WI (Wisconsin), WV (West Virginia), WY (Wyoming). Variables: Tests wk I = number of tests performed in the first 7 days of testing; Total tests = total number of people tested; $Wk\ I/all\ tests$ (%) = tests wk I / total tests (i.e., the proportion of all tests conducted during the first week of testing, expressed as a percentage of all tests performed in March, 2020); State pop / mill = the population of each state, expressed in million inhabitants; *Total tests / mill inh* = number of tests performed per 1 million inhabitants by March 31, 2020; *Total cases* = cumulative number of confirmed (test-positive) infections by March 31, 2020; Cases / mill inh = the number of cases in the population (expressed in million inhabitants); State pop dens = the state-specific number of inhabitants per square kilometer; Wk I tests / mill inh / state pop dens = the number of tests performed during week one / million inhabitants / state population density; *Total deaths (count)* = cumulative number of deaths through March 31, 2020; *Deaths / mill inh* = cumulative number of deaths per 1 million inhabitants through March 31, 2020.