COVID-19

Predictors of survival in older adults hospitalized with COVID-19

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Abstract

Objective This study was designed to investigate clinical characteristics associated with mortality and predictors of survival in older adults hospitalized with COVID-19 with a focus on neurological comorbidities and presenting neurological manifestations.

Methods We compared clinical characteristics in an age- and gender-matched sample of 75 deceased and 75 recovered patients ($M_{Age} = 78$) hospitalized with COVID-19 and developed a logistic regression to predict likelihood of survival.

Results Deceased patients were more like to have dementia, altered mental status (AMS), acute respiratory distress syndrome (ARDS), sepsis, mechanical ventilation, and balance difficulties; higher heart rate, respiratory rate, blood urea nitrogen, creatinine, and absolute neutrophils; lower oxygen saturation and absolute lymphocytes; and shorter length of hospitalization. Logistic regression based on three mortality predictors (ARDS, AMS, and length of hospitalization) correctly predicted 87% of the outcome (89% sensitivity at 85% specificity).

Conclusions Dementia and AMS were strong predictors of death in older adults hospitalized with COVID-19. Our findings add to the rapidly growing neurology of COVID-19 literature and underscore the importance of early recognition and the incorporation of a mental status examination into the medical assessment of COVID-19.

Keywords COVID-19 · Neurology · Psychiatry · Neuropsychology · Dementia · Delirium

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19) presents with a range of manifestations such as fever, cough, shortness of breath/difficulty breathing, fatigue, nausea/vomiting, and diarrhea. Multiple medical comorbidities have been linked to severe disease and mortality including cardiovascular diseases, cancer, chronic kidney disease, chronic lung diseases, diabetes mellitus, and obesity. Additional mortality-related factors have included older age and male gender with the overall COVID-19 case-fatality ratio approximately 2.4 times higher among men [1, 2].

Neurological manifestations are also common in COVID-19, particularly altered mental status (AMS), headache, dizziness, myalgia, hyposmia, hypogeusia, balance difficulties, seizure, and stroke [3–9]. Approximately 35–58% of hospitalized COVID-19 patients experience neurological manifestations with much higher rates reported in older, more vulnerable samples [8–12]. Neurological manifestations in general, and AMS in particular, are associated with severe disease and death due to COVID-19 [4, 5, 9–11]. Neurological comorbidities have also been associated with severe disease and mortality in COVID-19, particularly dementia and stroke [1, 9, 13–15].

The current study seeks to contribute to this rapidly accumulating neurology of COVID-19 literature by comparing neurological comorbidities and presenting neurological manifestations in an age- and gender-matched sample of deceased and recovered patients hospitalized with COVID-19. We expected baseline dementia and AMS to be significantly related to death due to COVID-19, regardless of the age or gender of our sample. In addition, we aimed to

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identify and develop a simple and user-friendly model of mortality predictors.

Method

Participants

Data were collected through a clinical chart review of 512 consecutive patients with SARS-CoV-2 infection seen between February 20, 2020, and July 6, 2020, at EvergreenHealth Medical Center in Washington State, the first hospital with reported cases in the USA. All patients had SARS-CoV-2 infection confirmed by polymerase chain reaction testing of a nasopharyngeal sample. The study was approved by an institutional review board and ethical standards committee. A total of 75 deaths due to COVID-19 were identified. The comparison group consisted of the first 75 survivors who matched the age and gender of the deceased sample and were still alive at the time of data analysis. The sample was predominately Caucasian (85%), evenly male and female, with an average age of 78. The majority of patients came from assisted living facilities and nursing homes (58%), the initial epicenter of COVID-19 in our region.

Materials

Data included demographic characteristics, medical history, presenting symptoms, vital signs and laboratory measures at hospital admission, hospitalization characteristics, and patient outcomes. Chart notes were independently reviewed by a neurologist and neuropsychologist, and data were cross-referenced for accuracy. Core COVID-19 symptoms included fever, shortness of breath, cough, weakness/fatigue, anorexia, diarrhea, and nausea/vomiting. Presenting neurological manifestations included AMS, myalgia, headache, dizziness, balance difficulties, hyposmia, hypogeusia, seizure, and stroke. AMS was defined as acute alterations in mental status, representing a change from baseline, with keywords in chart review including confusion, decreased level of consciousness, impaired consciousness, delirium, encephalopathy, somnolent, obtunded, unresponsive, and/or coma.

Statistical analysis

Descriptive statistics [M, SD, percentage, likelihood ratios (LR)] were computed where relevant. The statistical significance of between-group differences was determined using independent t-tests (two-tailed) and Chi-square. Effect size estimates were expressed in Cohen's d and point-biserial correlation coefficients (r_{pb}).

A logistic regression classifier with lasso regularization was used to predict the final clinical outcome of patient recovery versus death. This method was chosen due to the large number of clinical metrics surveyed in our study, given that it offers an objective and systematic framework for modeling a high-dimensional set of predictors without succumbing to overfitting or selection bias. The mathematical details of lasso regularization in logistic regression are discussed in detail elsewhere, but in short, lasso regularization only differs from traditional logistic regression in that the cost function contains an additional term beyond the traditional logistic loss function: a regularization term scaled by a constant lambda which penalizes the addition of new predictors to the model. For predictors that offer no consistent predictive value, lasso regularization aims to set the logistic coefficients of these terms to zero, effectively removing them from the final model. Our implementation used MATLAB's statistics and Machine Learning Toolbox function "lassoglm." We partitioned our data per convention into 80:20 training: test sets. We fit our regression on the training set using tenfold cross-validation with gradient descent over one hundred values of lambda and repeated this process one thousand times to explore which clinical characteristics routinely survived regularization (differing each iteration due to the random initialization of gradient descent and tenfold cross-validation) suggesting they offer high predictive value. This repetition also allowed the generation of confidence intervals for model performance on the randomly partitioned testing sets. We then created a compact logistic regression classifier from our set of high-yield clinical predictors and evaluated its performance on our testing set. Our results were robust to changes in our classifier's hyperparameters, which were chosen by applying an identical methodology to a synthetic data set mirroring the dimensionality and baseline characteristics of our own.

Results

Univariate analyses

Medical comorbidities were nearly universal (94% of total sample) with no significant differences between deceased and recovered patients (Table 1). Cardiovascular diseases were the most common comorbidity (81% of total sample). Neurological comorbidities were present in 56% of the sample with dementia being most frequent (42%). The only comorbidity significantly more common in deceased patients was dementia. Patients with dementia were significantly older ($M = 84.4$) than those without dementia ($M = 74.1$): $t(148) = 6.48$, $p < 0.001$, $d = 1.09$ (large effect), $r_{pb} = 0.47$. In addition, dementia was more common in female patients (48.8%) than male patients (34.3%): [LR = 1.42; $\chi^2(1) = 3.21$,

Table 1 Demographic information and medical history

Demographic/clinical characteristics	Discharged	Deceased	p-value
Age	M = 77.6	M = 79.3	0.335
	SD = 10.5	SD = 11.2	
Ethnicity			
Caucasian	67 (89%)	60 (80%)	0.113
Asian/Pacific Islander	5 (7%)	10 (13%)	0.174
Hispanic	0 (0%)	4 (5%)	0.043
African American	2 (1%)	0 (0%)	0.155
Unknown/unavailable	1 (1%)	1 (1%)	1.00
Medical comorbidities	72 (96%)	69 (92%)	0.302
Cardiovascular disease	63 (84%)	58 (77%)	0.301
Diabetes	25 (33%)	26 (35%)	0.863
Chronic kidney disease	20 (27%)	18 (24%)	0.707
Obesity	18 (24%)	13 (18%)	0.333
Chronic lung disease	14 (19%)	16 (21%)	0.683
Cancer	15 (84%)	15 (84%)	0.301
Obstructive sleep apnea	12 (16%)	15 (20%)	0.524
Asthma	5 (7%)	8 (11%)	0.384
Neurologic comorbidities	37 (49%)	47 (63%)	0.119
Dementia	25 (33%)	38 (50%)	0.032
Stroke	11 (15%)	15 (20%)	0.388
Brain tumor	2 (3%)	5 (7%)	0.246
Seizure disorder	3 (4%)	5 (7%)	0.467
Parkinson's disease	2 (3%)	2 (3%)	1.00
Multiple sclerosis	0 (0%)	2 (3%)	0.155
Psychiatric comorbidities	41 (55%)	37 (49%)	0.513
Depression	30 (40%)	24 (32%)	0.307
Anxiety	14 (19%)	17 (23%)	0.545
Insomnia	9 (12%)	7 (9%)	0.597
Bipolar disorder	3 (4%)	5 (7%)	0.467
Schizophrenia	1 (1%)	5 (7%)	0.096

Table 2 Presenting symptoms

Core symptoms	Discharged	Deceased	p-value
Fever	47 (63%)	54 (72%)	0.223
Shortness of breath	41 (55%)	53 (71%)	0.058
Cough	55 (73%)	44 (59%)	0.058
Weakness/fatigue	37 (49%)	38 (51%)	0.870
Anorexia	23 (31%)	24 (32%)	0.860
Diarrhea	24 (32%)	13 (17%)	0.037
Nausea/vomiting	7 (9%)	5 (7%)	0.547
Neurologic symptoms	53 (71%)	62 (81%)	0.082
Altered mental status	34 (45%)	50 (67%)	0.008
Coma at admission	0 (0%)	8 (11%)	0.004
Dizziness	11 (15%)	9 (12%)	0.631
Balance difficulties	5 (7%)	14 (19%)	0.027
Myalgia	7 (9%)	12 (16%)	0.220
Headache	10 (13%)	5 (7%)	0.174
Hyposmia	2 (3%)	0 (0%)	0.155
Hypogeusia	5 (7%)	0 (0%)	0.023
Stroke	1 (1%)	3 (4%)	0.311
Seizure	0 (0%)	3 (4%)	0.080

laboratory serology, deceased patients showed lower absolute lymphocytes and higher blood urea nitrogen, creatinine, and absolute neutrophils (medium effects; Table 3).

Complications and hospitalization characteristics observed more frequently in deceased patients included acute respiratory distress syndrome (ARDS), sepsis, mechanical ventilation, and admission to critical care. Higher survival rate was observed in patients treated with hydroxychloroquine [LR = 1.73; $\chi^2(1) = 11.0$, $p = 0.001$] or remdesivir [LR = 1.67; $\chi^2(1) = 3.86$, $p = 0.050$]. Recovered patients had a significantly longer length of hospitalization ($p < 0.001$) with deceased patients averaging just over a week in the hospital ($M = 7.6$ days, $SD = 6.3$) and recovered patients averaging more than 3 weeks inpatient ($M = 23.4$ days, $SD = 18.9$).

Multivariate analyses

Patient outcomes of death versus recovery were classified using logistic regression with lasso regularization. Of 115 variables available in the analysis, our regularized models favored the inclusion of three clinical characteristics: ARDS, AMS, and length of hospitalization. ARDS and AMS were binary predictors (set to 0 if absent, 1 if present), whereas the length of hospitalization took integer values for duration in days. Building a logistic regression with these three clinical predictors improved on the performance of a naive logistic regression (using all 115 predictors) when applied to our testing set by avoiding overfitting, with the added benefit of improving model simplicity. Our final classifier

$p = 0.073$]. Psychiatric conditions were present in half the sample (52%) with depression being most frequent (36%). There was no difference in psychiatric comorbidity between deceased and recovered patients.

Fever, cough, and shortness of breath were the most common symptoms reported in both groups (Table 2). AMS and balance difficulties were the only symptoms significantly more frequent in deceased patients. All eight patients with coma at admission died. Further, all three patients with seizures died, including one patient who presented with non-convulsive status epilepticus at admission. Of the four patients with ischemic strokes, three died. Recovered patients were more likely to have diarrhea and hyposmia or hypogeusia.

On admission vital signs, deceased patients had higher heart rate (large effect), higher respiratory rate (medium effect), and lower oxygen saturation (medium effect). On

Table 3 Admission vital signs and laboratory measures

| | Clinical outcome | | | | | | | |
| | Survived | | Deceased | | | | | |
Vital signs	M	*SD*	M	*SD*	*t*	*p*	*d*	σ_1 vs σ_2
Temperature (°C)	37.3	*0.92*	37.4	*0.83*	0.59	0.558	-	0.426
Respiratory rate	21.3	5.8	25.0	11.2	2.48	0.015	0.41	0.013
Oxygen saturation	94.5	4.84	91.2	7.29	3.26	0.001	0.53	0.003
Heart rate	82.1	16.9	96.0	23.5	4.14	<0.001	0.68	0.016
BP, systolic	134.5	*22.8*	127.0	*23.9*	1.95	0.053	0.32	0.488
BP, diastolic	71.8	*12.5*	73.8	*17.0*	0.79	0.429	-	0.151
Laboratory measures	M	SD	M	SD	*t*	*p*	*d*	σ_1 vs σ_2
White blood cell, /mL	7.9	5.1	8.9	4.8	1.14	0.255	-	0.328
Hemoglobin, g/DL	12.5	2.2	11.9	2.2	1.60	0.111	-	0.930
Hematocrit, %	38.6	6.2	37.1	6.1	1.39	0.167	-	0.873
Absolute platelet,103/ mL	224.7	112.3	207.5	91.2	1.01	0.316	-	0.247
Sodium, mmol/L	137	5.9	137.6	7.4	0.50	0.617	-	0.085
Potassium, mmol/L	4.1	0.6	4.0	0.6	0.28	0.783	-	0.603
Chloride, mEq/L	98.3	6.1	98.6	6.9	0.23	0.821	-	0.386
Carbon dioxide, mEq/L	24.3	3.3	24.1	4.7	0.28	0.780	-	0.185
Blood urea nitrogen, mmol/L	22.7	12.5	32.0	19.1	3.41	0.001	0.58	0.003
Creatinine, mg/dL	1.1	0.6	1.6	1.7	2.24	0.027	0.39	0.008
Glucose, mmol/L	134	54.0	144.2	53.6	1.10	0.275	-	0.851
Alanine aminotransferase, U/L	35.1	38.7	31.5	33.1	0.58	0.565	-	0.362
Aspartate aminotransferase, U/L	46.1	51.1	53.7	54.1	0.82	0.412	-	0.465
Lactic acid, mmol/L	1.7	0.8	2.1	1.5	1.49	0.140	-	0.026
C-reactive protein, mg/DL	9.4	10.0	10.8	6.8	0.62	0.537	-	0.133
Creatine kinase, U/L	210.4	445.2	496.5	1221.6	1.36	0.179	-	0.057
Lymphocyte number, 10E3/uL	1.2	0.8	0.9	0.7	2.22	0.029	0.40	0.190
Neutrophil number, 10E3/uL	5.6	3.7	7.3	4.4	2.28	0.024	0.42	0.088

Note: *BP*, blood pressure; σ_1 *vs* σ_2, *p*-value associated with Levene's test of homogeneity of variance

assigned logistic coefficients of 3.70 to ARDS, 1.97 to AMS, and –0.17 to length of hospitalization, with the logistic constant set to –0.86. This suggests that ARDS, AMS, and short length of hospitalization were associated with poor outcomes. This model performed on our testing sets with a sensitivity of 89% (SE = 6%), a specificity of 85% (SE = 8%), and a total classification accuracy of 87% (SE = 6%).

Discussion

Consistent with an increasing body of literature, dementia and AMS were significant predictors of mortality in older adults hospitalized with COVID-19 [1, 4, 5, 9–15]. Dementia was the only comorbidity associated with death in our sample. Contrary to other studies [16], psychiatric comorbidities were not associated with death in our sample, suggesting this variable is prone to sample-specific fluctuations. Age and gender were unrelated to outcome in our study, contradicting previous reports [1, 2]. However, these demographic variables were correlated with dementia, suggesting

the predictive power of age and gender in previous studies was confounded by another variable, such as dementia.

AMS and balance difficulties were the only presenting symptoms more common in deceased patients. Survivors were significantly more likely to have diarrhea, a finding consistent with research linking digestive symptoms, specifically diarrhea, with milder disease and longer delays before viral clearance [17]. No deceased patients presented with hypogeusia or hyposmia, which is also consistent with these symptoms being more common in large-scale studies comprised of younger patients with milder disease [8, 15, 16, 18]. Further, AMS and dementia likely masked the frequency of these symptoms. The use of hydroxychloroquine and/or remdesivir extended the length of hospitalization for survivors, but we think this was less likely related to the effectiveness of these drugs and more likely because they were used on healthier patients with higher chances of recovery.

Our analysis culminated in a compact and efficient logistic regression based on three parameters readily available to medical professionals: ARDS, AMS, and length of

hospitalization. The model accurately predicted outcomes 87% of the time, providing a balance between sensitivity (89%) and specificity (85%). Although ARDS and AMS as predictors of mortality make intuitive sense, one might think that the length of hospitalization would be a negative predictor of survival. In this view, the healthiest patients are discharged quickly, and the sickest patients endure extended hospitalizations ending in death. Contrary to expectation, patients with longer hospitalizations had more favorable outcomes. There are several potential explanations for this. Our data was gathered at the onset of the pandemic in the USA, when nursing homes and assisted living facilities struggled to contain the virus. Only the most severely ill patients were sent to the hospital, many with do not resuscitate orders, with palliative care as the main goal. Combined with a lack of information regarding early recognition of COVID-19 and its diverse manifestations in older adults, this patient stream likely experienced delays from infection to hospitalization and, as a result, shorter hospitalizations due to more severe disease, rapid deterioration, and death. Given these circumstances, if patients received more immediate medical attention and/or could survive the most critical phase of illness leading up to admission, they were more likely to be hospitalized longer but also more likely to recover. Our model is completely linear, meaning that it can't see a single predictor as being good and bad in different contexts: it couldn't discern if a short length of hospitalization in some cases was a positive (early discharge) or negative (rapid deterioration to death) predictor of survival. The model viewed length of hospitalization unilaterally as a marker of positive outcomes. Thus, longer hospitalization was always associated with a more favorable outcome in our sample.

There were several limitations of the current study worth mentioning. Retrospective chart reviews can result in underassessment and underdocumentation of mild or secondary symptoms. The severity of AMS was ostensibly associated with mortality in our study, as evidenced by all eight of our coma patients dying; however, it would be useful to know the mortality rate at lower ends of the AMS spectrum. To that end, future research would benefit from prospective studies using standardized mental status examinations or other brief cognitive screeners to predict short- and long-term outcomes. The sample size was modest and restricted in terms of racial and ethnic diversity compared to other studies in this area. Our sample was older with multiple medical comorbidities including high rates of dementia, many of whom were residing in nursing homes or assisted living facilities and gathered during the onset of the pandemic from a single hospital in the Northwest United States. These factors limit the generalizability of our findings to younger healthier patients, ethnically diverse patients, community-dwelling older adults, other geographic locations, and later stages of the pandemic. As such, our predictive model needs independent cross-validation to determine its clinical utility in different settings. Finally, our study would also benefit from data on additional hospitalization characteristics associated with death and survival, such as changing laboratory markers over the course of disease progression and results of other diagnostic tests.

In sum, our findings add to the rapidly growing neurology of COVID-19 literature and underscore the importance of early identification and the incorporation of a mental status examination in the medical assessment of COVID-19. As we move into the second year of this pandemic, data on long-term neurological outcomes will quickly accumulate. With survivors increasingly seeking healthcare services in the coming years, clinicians need to consider the high potential of neurological and psychiatric complications due to COVID-19. Ongoing research in recovered patients should include follow-up neurological and neuroimaging studies to record potential long-term neurological complications and neuropsychological evaluation to document the extent of any persisting cognitive, emotional, and behavioral sequelae.

Declarations

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