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Elevated glycohemoglobin is linked to critical illness in CoVID-19: a retrospective analysis

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Abstract

Background: Several studies have explored hospitalization risk factors with the novel coronavirus disease 2019 (COVID-19) infection. Our goal was to identify clinical characteristics outside of laboratory or radiologic data associated with intubation or death within 7 days of admission.

Methods: The first 436 patients admitted to the University of Colorado Hospital (Denver metropolitan area) with confirmed COVID-19 were included. Demographics, comorbidities, and select medications were collected by chart abstraction. Missing height for calculating body mass index (BMI) was imputed using the median height for patients' sex and race/ethnicity. Adjusted odds ratios (aOR) were estimated using multivariable logistic regression and a minimax concave penalty (MCP) regularized logistic regression explored prediction.

Results: Participants had a mean [standard deviation (SD)] age 55 (17), BMI 30.9 (8.2), 55% were male and 80% were ethnic/racial minorities. Increasing age [aOR: 1.24 (1.07, 1.45) per 10 years], higher BMI (aOR 1.03 (1.00, 1.06), and poorly controlled diabetes [hemoglobin A1C (HbA1c) ≥ 8] (aOR 2.26 (1.24, 4.12) were significantly ($p < 0.05$) associated with greater odds of intubation or death. Female sex [aOR: 0.63, 95% CI (0.40, 0.98); p value = 0.043] was associated with lesser odds of intubation or death. The odds of death and/or intubation increased 19% for every 1 unit increase in HbA1c value [OR: 1.19 (1.01, 1.43); $p = 0.04$]. Our final MCP model included indicators of A1C ≥ 8, age > 65, sex, and minority status, but predicted intubation/death only slightly better than random chance [area under the receiver operating characteristic curve (AUC) = 0.61 (0.56, 0.67)].

Conclusion: In a hospitalized patient cohort with COVID-19, worsening control of diabetes as evidenced by higher HbA1c was associated with increased risk of intubation or death within 7 days of admission. These results complement and help clarify previous associations found between diabetes and acute disease in COVID-19. Importantly, our analysis is missing some known predictors of severity in COVID-19. Our predictive model had limited success, suggesting unmeasured factors contribute to disease severity differences.

Keywords: diabetes, COVID-19, intensive care unit, mechanical ventilation, hemoglobin A1c

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Introduction

Coronavirus disease 2019 (COVID-19) was first declared a global pandemic by the World Health Organization (WHO) in March of 2020. Populations initially identified to be at risk for infection and subsequent poor outcomes include institutionalized individuals such as inmates, long-term care residents, and people residing in nursing homes, perhaps reflective of underlying comorbidity burden.[1–3]

Other cohorts have described clinical characteristics specifically associated with COVID-19-related hospitalization and severe disease, including older age, hypertension, diabetes, morbid obesity, and chronic kidney disease[4–8]; however, these studies have variable definitions of "severe" disease, ranging from minimal oxygen requirements to intensive care unit (ICU) admission or death.[4,9] Furthermore, much of the literature regarding prediction of severe COVID-19 relies on data that may not be readily available in the outpatient setting, such as radiologic exams and inflammatory markers.[6,10] In populations where chronic medical conditions are prevalent, a risk score of easily identifiable clinical factors associated with intubation and death could inform public health and infection control strategies to identify and potentially isolate the highest risk individuals within institutions.

In this manuscript, we hypothesized that easily available clinical variables including demographics, comorbidities, and medications would be associated with COVID-19 severity, and that a model utilizing these variables would reasonably predict COVID-19 severity.

Methods

A COVID-19 database was developed beginning in March 2020, including the first 436 consecutive initial admissions to the University of Colorado Hospital. Data from the electronic medical record (EMR) were entered manually by a group of eight clinicians into a REDCap database.[11] All included patients were hospitalized, had a positive COVID-19 PCR between 18 March 2020 and 24 April 2020 at the University of Colorado, and were aged 18 years or older. The idea of this specific analysis was conceived after data collection was complete. The initial observational study was reviewed and approved by the Colorado Multiple Institutional Review Board. The STROBE checklist is included in the supplemental material.

The EMR was reviewed for demographics (age, sex, ethnicity, employment status, current housing situation), substance use (current or former tobacco use, alcohol use, marijuana use, other substance abuse), body mass index (BMI), comorbidities (hypertension, respiratory disease, cardiovascular disease, chronic infectious disease, cancer, chronic kidney disease, autoimmune disease, arthritis, chronic pain syndrome, immunosuppression, type II diabetes mellitus [DMII], and most recent hemoglobin A1c [HbA1c]). For the purpose of this study, morbid obesity was defined as a BMI $\geq 40\,kg/m^2$. Comorbidities were considered present if listed in the past medical history or problem lists in the EMR. Respiratory disease was defined as the presence of chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease, cystic fibrosis, pulmonary fibrosis, pulmonary hypertensions, pulmonary sarcoidosis, previous lung cancer, or pulmonary embolism. Arthritis was defined as the presence of osteoarthritis or rheumatoid arthritis in the patients past medical history section of the EMR. Cardiovascular disease was defined as the presence of heart failure, coronary artery disease, previous myocardial infarction, congenital heart disease, stroke, arrythmia, or peripheral artery disease. Hypertension was considered separately. Infectious disease was defined as the presence of chronic infectious diseases including tuberculosis, non-tuberculous mycobacterium, HIV, hepatitis B, or hepatitis C. Chronic kidney disease (CKD) was defined as ≥CKD stage II or end-stage renal disease. Medications included current use of insulin, angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), chronic steroid, hormone therapy, and statin.

The primary outcome was defined as intubation or death within 7 days of admission. This time period was chosen to reflect initial disease severity and minimize secondary complications of prolonged admission, such as secondary bacterial or fungal infections, thromboembolic disease, volume overload, and other iatrogenic harms.

Categorical and continuous variables were compared using *t* tests or chi-square tests (or non-parametric/exact equivalents), as appropriate. Missing BMI values were calculated for those patients with an available weight using the median observed height value for their sex/gender and reported race/ethnicity. A multivariable logistic regression model was created with the predictors chosen *a priori* based on previous literature,[4–8] with known predictors presence of CKD, autoimmune disease, cancer diagnosis, or immunosuppression left out due to minimal relationship in our univariate analysis. These variables included

age (continuous), BMI, gender/sex, patient identity as a racial or ethnic minority, DM (categorized: no DMII, DMII with HbA1c $<8\%$, DMII with HbA1c $\geq 8\%$), cardiovascular disease, current/former smoker based on the EMR, and presence of hypertension in the past medical history, problem list, or progress note sections of the EMR. The HbA1c of 8% was chosen to represent uncontrolled diabetes. This same model was run for a HbA1c cutoff of $\geq 7\%$ to further characterize moderate diabetic control, as American Diabetes Association guidelines list $<7\%$ as an A1c goal. We then used the model with HbA1c as a continuous variable in all patients with DMII with a HbA1c value to examine the effect of HbA1c control in diabetics. A minimax concave penalty (MCP) regularized logistic regression was used to build a predictive model using the ncvreg R package.[12,13] Ethnic/racial minority, sex, and age ≥ 65 years were forced into the model. Ten-fold cross validation was used to optimize the penalty parameter, and a bootstrap of 1000 samples was used to estimate average area under the receiver operating characteristic curve (AUC).

Results

Baseline characteristics

Among 436 participants, the mean age was 55.4 [standard deviation (SD) 17.3] years, 238 (55%) were male, 339 (78%) self-reported as non-White race or Hispanic ethnicity, and 364 (83.5%) lived in a non-institutional home (Table 1). The average BMI was 31.1 (SD 8.4) kg/m^2, 142 (32.6%) had DMII, the median most recent HbA1c was 7.6 [interquartile range (IQR) 6.7–10.0], and 40 (28%) were on insulin. Participants were hospitalized for a median of 6 (IQR 3–12) days, 126 (29%) were intubated, for a median of 10 (IQR of 6–18.5) days, and 47 (11%) died.

As shown in Table 1, 29% ($n=128$) either died or were intubated within 1 week of hospitalization. The most recent HbA1c was significantly higher among those who required intubation or died. Current employment was less frequent in those who required intubation or died but was limited by unknown data (46.3%). Other differences between those with intubation or death are shown in Table 1.

In the univariable analysis (Table 2), higher HbA1c was shown to have an increased odds of intubation and/or death within 1 week of hospitalization [odds ratio (OR): 1.164 (95% confidence interval (CI) 1.01, 1.35] per 1% increase in HbA1c value; $p=0.042$.

In a multivariable model including variables chosen *a priori* (as shown in Table 3), the odds of intubation and/or death within 1 week were greater with increasing age [OR: 1.24 (1.07, 1.45) per 1 decade; $p=0.006$], increasing BMI [OR: 1.03 (1.00, 1.06) per 1 kg/m^2; $p=0.022$], and DMII with a HbA1c ≥ 8 [OR: 2.26 (1.24, 4.12) ref: no DMII; $p=0.007$]. Female sex [OR: 0.63 (0.4, 0.98); $p=0.043$] was associated with a lower odds of intubation and/or death. A similar but attenuated effect was seen with an HbA1c $\geq 7\%$ [OR: 1.77 (1.03, 3.01); $p=0.036$]. Using this same model restricted to patients with DMII with an available HbA1c ($N=123$), we found that the odds of death and/or intubation within 7 days of admission increased 19% for every 1 unit increase in HbA1c value [OR: 1.19 (1.01, 1.43); $p=0.04$].

Lastly, we created an optimized predictive model using variables chosen *a priori*. The final model included DMII with HbA1c of ≥ 8, with the forced variables age, race/ethnicity, and sex; all other variables were excluded. The estimated AUC over the bootstrap samples was 0.61 (0.56, 0.67), indicating minimal predictive ability for this outcome.

Discussion

In a retrospective cohort, we identified an association between poorly controlled DMII and an increased risk of intubation or death within 7 days of admission for COVID-19 infection. We also identified a significant relationship between increasing HbA1c and increasing risk of intubation or death within 7 days of admission for COVID-19. Taken together, this study shows that there is a link between poor chronic blood glucose control and initial severity of outcomes in admitted CoVID-19 patients. The poor performance of our combined predictive model may suggest that other factors not represented here contribute to critical illness in COVID-19, or that factors differ considerably across populations.

Table 1. Baseline characteristics of admitted COVID-19 patients.

	Total (*N* = 436)	Missing (%)	Not intubated/alive (*N* = 308)	Intubated/dead (*N* = 128)	*p* value
Demographics					
Age, mean (SD)	55.4 (17)	0 (0)	54.5 (18)	57.7 (17)	0.083
Female (%)	198 (45)	0 (0)	146 (47)	52 (41)	0.24
Racial/ethnic minority (%)	339 (78)	16 (4)	234 (76)	105 (82)	0.21
Employed (%)	122 (28)	202 (46)	99 (32)	23 (18)	0.004*
Lives at home (%)	364 (84)	21 (5)	263 (85)	101 (80)	0.23
Current/former smoker (%)	110 (25)	13 (3)	82 (27)	28 (22)	0.36
Alcohol use (%)	103 (24)	47 (11)	75 (24)	28 (22)	0.67
Marijuana use (%)	21 (5)	64 (15)	16 (5)	5 (4)	0.74
Substance abuse (%)	16 (4)	0 (0)	12 (4)	4 (3)	0.79[a]
BMI, mean (SD)	31.1 (8.4)	44 ((10)	30.8 (8)	32 (9.2)	0.18
Imputed BMI, mean (SD)	30.9 (8.2)	2 (1)	30.5 (7.8)	31.8 (9.2)	0.13
Comorbidities					
Number of comorbidities, median (IQR)	2.00 (1.00, 3.00)	0 (0)	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)	0.35[b]
⩾3 Comorbidities (%)	187 (43)	0 (0)	130 (42)	57 (45)	0.73
Hypertension (%)	208 (48)	0 (0)	147 (48)	61 (48)	1.000
Morbid obesity (%)	98 (23)	0 (0)	64 (21)	34 (27)	0.23
Respiratory disease (%)	97 (22)	0 (0)	70 (23)	27 (21)	0.81
Hyperlipidemia (%)	88 (20)	0 (0)	62 (20)	26 (20)	1.000
Cardiovascular disease (%)	65 (15)	0 (0)	41 (13)	24 (19)	0.19
Infectious disease (%)	21 (4.8)	0 (0)	16 (5)	5 (4)	0.74
Auto-immune disease, cancer, or other immunosuppression (%)	50 (12)	0 (0)	33 (11)	17 (13)	0.55
CKD (%)	25 (6)	0 (0)	16 (5)	9 (7)	0.60
Arthritis (%)	28 (6)	0 (0)	18 (6)	10 (8)	0.58
Chronic pain syndrome (%)	24 (6)	0 (0)	20 (7)	4 (3)	0.24
DMII, (%)	142 (33)	0 (0)	93 (30)	49 (38)	0.13
Most recent hemoglobin A1c among those with DMII, median (IQR)	7.6 (6.7, 10.0)	18 (13)	7.5 (6.5, 9.5)	8.5 (7.3, 10.5)	0.034*[b]
Medications					
Insulin use,(%)	40 (28)	0 (0)	23 (25)	17 (33)	0.36
ARB/ACE-I use (%)	111 (26)	0 (0)	73 (24)	38 (30)	0.24
Chronic steroid use (%)	17 (4)	0 (0)	10 (3)	7 (6)	0.40
Statin use (%)	116 (27)	0 (0)	75 (24)	41 (33)	0.11

[a]Exact test.
[b]Non-parametric test.
*$p < 0.05$.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DMII, type 2 diabetes Mellitus; IQR, interquartile range; SD, standard deviation.

Table 2. Univariable analysis of intubation and/or death within 1 week of admission in COVID-19 patients.

	OR	95% CI	*p* value
Demographics			
Age	1.01	(1.00, 1.02)	0.084
Female	0.76	(0.50, 1.15)	0.196
Racial/ethnic minority	1.44	(0.87, 2.47)	0.168
Employee	0.46	(0.27, 0.76)	0.003
Lives at home	0.69	(0.41, 1.20)	0.180
Current/former smoker	0.70	(0.47, 1.25)	0.299
Alcohol use	0.87	(0.53, 1.41)	0.580
Marijuana use	0.74	(0.24, 1.94)	0.568
Substance abuse	0.80	(0.22, 2.33)	0.697
BMI	1.02	(0.99, 1.04)	0.183
Imputed BMI	1.02	(0.99, 1.04)	0.135
Comorbidities			
Number of comorbidities	1.05	(0.93, 1.17)	0.431
⩾3 Comorbidities	1.10	(0.72, 1.66)	0.655
Hypertension	1.00	(0.66, 1.51)	0.989
Morbid obesity	1.38	(0.85, 2.22)	0.189
Respiratory disease	0.91	(0.54, 1.49)	0.709
Hyperlipidemia	1.01	(0.6, 1.67)	0.965
Cardiovascular disease	1.50	(0.86, 2.59)	0.148
Infectious disease	0.74	(0.24, 1.94)	0.568
Auto-immune disease, cancer, or other immunosuppression	1.28	(0.67, 2.36)	0.444
CKD	1.38	(0.57, 3.15)	0.454
Arthritis	1.37	(0.59, 2.99)	0.447
Chronic pain syndrome	0.47	(0.13, 1.26)	0.170
DMII	1.43	(0.93, 2.20)	0.102
Most recent hemoglobin A1c	1.16	(1.01, 1.35)	0.042
Medications			
Insulin use	1.52	(0.71, 3.22)	0.272
ARB/ACE-I use	1.36	(0.85, 2.15)	0.192
Chronic steroid use	1.74	(0.62, 4.63)	0.273
Statin use	1.49	(0.94, 2.35)	0.084

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DMII, type 2 diabetes mellitus; IQR, interquartile range; SD, standard deviation.

Table 3. Multivariable analysis for intubation and/or death within 1 week of admission.

	Adjusted OR	95% CI	*p* value
Age, per decade	1.24	(1.07, 1.45)	0.006*
Female	0.63	(0.40, 0.98)	0.043*
Racial/ethnic minority	1.41	(0.82, 2.49)	0.230
Imputed BMI, per 1 kg/m^2	1.03	(1.00, 1.06)	0.022*
DMII with a hemoglobin A1c $\geqslant$ 8	2.26	(1.24, 4.12)	0.007*
Cardiovascular disease	1.33	(0.70, 2.49)	0.379
Hypertension	0.81	(0.49, 1.31)	0.389
Current or former smoking history	0.71	(0.42, 1.20)	0.210

*$p < 0.05$.
BMI, body mass index; CI, confidence interval; DMII, type 2 diabetes mellitus; OR, odds ratio.

The relationship between diabetes and severity of other viral illnesses has previously been established: influenza patients with diabetes have been shown to be four times more likely to be admitted to the ICU than non-diabetics and two times more likely to die.[14,15] A higher mortality rate in severe acute respiratory syndrome (SARS) was seen in diabetics and non-diabetics with above average increased fasting plasma glucose levels on admission,[16] although HbA1c itself was not examined. A meta-analysis that examined the severity of COVID-19 and glucose levels found higher blood glucose levels in patients with severe disease,[17] while a retrospective study of COVID-19 patients admitted to the ICU found an increased mortality rate amongst those with mean serum glucose levels >140 mg/dl *versus* those <140 mg/dl.[18] It is possible that the presence of diabetes is, in part, representative of poor overall health and that our findings of HbA1c and intubation or death may be a marker for patients who do not receive regular, preventive care. It is more likely that the link between hyperglycemia and diabetes is multifaceted, not only that HbA1c is a marker of overall health, but that acute and chronic hyperglycemia also actively effects the immunologic response to viral infection.

The underlying mechanisms between diabetes and severity of illness in COVID-19 is likely multifactorial and complex, and acutely elevated blood glucose may have different underlying mechanisms than chronically elevated blood glucose. It is likely that patients with elevated HbA1c would have changes associated with both acute and chronically elevated blood glucose. Acute blood glucose changes could be induced by cytokines and endogenous steroid release seen in many stress states. Beta-cells in the pancreas have been shown to have ACE-2 receptors integral to viral entry, and these may become upregulated with COVID-19 infection,[19] with subsequent infection and damage exacerbating hyperglycemia. Acute hyperglycemia can affect the innate immune system through neutrophil dysfunction, inhibition of circulating complement and immunoglobulin function, and stimulation of cytokine release.[20] In COVID-19, neutrophils are thought to react infection in a multitude of ways, with the production of neutrophil extracellular traps as an important mechanism for viral clearance.[21] Previous studies have shown that high levels of glucose impede and delay the formation of neutrophil extracellular traps both *in vitro* and through stimulation of diabetic patients serum.[22] Complement has been implicated in binding to severe acute respiratory syndrome coronavirus (SARS-CoV) to help prevent viral infection of cells and increase clearance of viral particles.[23] An *in vitro* study showed decreased opsonization and binding to pathogens of crucial complement C3 in hyperglycemia conditions.[24] TypeI interferon response induces an antiviral state in cells infected with viruses, as well as surrounding cells, and likely plays a role in the response to CoVID-19 infections.[25,26] An *in vitro* study of peripheral blood mononuclear cells incubated in various glucose concentrations showed decreasing typeI interferon production with higher levels of glucose.[27]

Similarly, chronic hyperglycemia has been linked with immune system dysregulation, as well as endothelial dysfunction resulting in coagulation and loss of the barrier between tissue and blood. Impaired cytokine production, as well as neutrophil, macrophage, and complement function, are all seen in chronic hyperglycemia. Monocytes from insulin dependent diabetic patients were show to have lower interleukin (IL)-1 and IL-6 levels when stimulated as compared with healthy controls.[28] Diabetic mouse models have implicated chronic hyperglycemia in reduced recruitment of neutrophils from the vascular compartment in to infected tissue.[28,29] Glycated macrophages have been shown to have reduced phagocytic capacity in the setting of chronically elevated blood glucose levels,[30] likely contributing to decreased clearance of viral infections.[31]

Glycation of complement decreases fixation to IgG needed for antibody-mediated virus neutralization,[32] and presumably would be worse in patients with higher baseline HbA1c. The predilection for coagulopathy in chronic hyperglycemia could exacerbate the coagulopathy and thrombosis seen in COVID-19.[33] Dysfunction of lung endothelial barrier could lead to increased edema and respiratory failure seen in COVID-19 imaging and autopsies.[33,34] Both acute and chronic changes induced by elevated blood glucose levels likely lead to decreased pathogen clearance and an increased or deranged inflammatory milieu contributing to severe lung injury seen in COVID-19 pneumonia in diabetic patients with high HbA1c levels.

Previously, diabetes has been linked to intubation due to COVID-19,[35] and elevated HbA1c has been linked with risk for hospitalization,[36] as well as hypercoagulability and worse oxygen saturation in hospitalized patients with COVID-19.[37] A large-scale retrospective study found an association between risk for intubation and death with poorer blood glucose control during hospitalization amongst patients with DMII and COVID-19.[38] In addition to DMII, many studies have found greater risk of severe COVID-19 with increasing age, male sex, and greater BMI, consistent with our findings.[4] Not all DMII patients are equal in their risk for poor outcomes in CoVID-19 despite being grouped together in previous analyses. As such, our study is the first to thoroughly analyze the relationship between chronically elevated blood glucose, as represented by HbA1c, and severity of outcomes in COVID-19 pneumonia.

Our finding of worsening HbA1c and worsening initial outcomes in hospitalized COVID patients is clinically relevant in multiple ways. Although the predictive model we showed was not able to accurately predict severity, it is important for clinicians triaging patients to be aware of associations with decompensation upon admission, especially in a disease like DMII that affects a large population and has a very heterogenous disease state. Identifying associations like this could be used in a public health role to help determine quarantining policies and risk stratification in institutionalized patients as HbA1C should be regularly obtained and available in patients who are diagnosed with diabetes. Finally, this data can be used to help clinicians emphasize the need for better control of diabetes to patients by providing an association between a clinically relevant and actionable measure with an easily understandable outcome.

A surprising finding of our study was the association between self-identified Hispanic ethnicity and decreased risk of death or intubation within 7 days of admission, which has not been reported previously. Although age was included in our multivariate model, it is possible that differences in age were not fully accounted for: the age of our Hispanic/Latino patients was considerably younger than the non-Hispanic/Latino patients (data not shown). It is possible that this protective effect may be seen due to this overall younger age in this subgroup.

This study has several limitations that should be noted. The retrospective nature was restricted to the initial period of COVID-19. Our population included one academic center in Colorado servicing urban and suburban areas. Our study population was smaller than other epidemiologic studies. We purposefully limited our primary outcome to look at initial severity, but further studies should be done with long-term outcomes such as 28 day mortality or 3 month mortality. Although interesting associations were seen in our analysis, there was substantial missing elements to our data set regarding place of housing, employment, substance use, and tobacco use due to the inherent nature of retrospective chart review. The variables for our multivariate model were chosen using previous literature. Limitations to our predictive model specifically included a lack of variables known to be associated with COVID-19 severity such as laboratory and radiologic findings. All patients were drawn from one academic center that services urban and suburban Colorado, as well as rural parts of neighboring states. It is possible that some of these findings may differ based on geography or more rural areas. Ethnic or racial minorities made up a large section of our population, and therefore may not be generalizable to more heterogenous areas with dissimilar ethnic or racial make up.

Conclusion

In summary, an elevated HbA1c may be a factor for severe COVID-19, and may identify those who would benefit from reverse quarantining or minimizing exposures, especially in institutionalized settings. Our findings should be should be viewed cautiously due to a lack of some known predictors of severity in our analysis that may be confounders for HbA1c and severity. Our findings may provide

further evidence that improving diabetes care may have tangible impact upon patients, and ensuring appropriate care of existing comorbidities may be important in decreasing the severity of disease during the COVID-19 pandemic.

Author Contributions

All authors helped with data collection, data analysis, as well as writing and editing of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical approval

The study was reviewed and approved by the Colorado Multiple Institutional Review Board under COMIRB Protocol Number 20-0690. Due to the retrospective nature of this study, individual consent from patients was not required.

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