Original Article



# Procalcitonin levels and antibiotic use associations with COVID-19 disease severity in hospitalized adults and the potential for an increase in antibiotic resistance: a cross-sectional clinical and public health analysis

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**Background:** Elevated procalcitonin (PCT) levels guide clinicians in antibiotic use for suspected bacterial infections and subsequent need for antimicrobial therapy. Our aim was to ascertain the usefulness of this laboratory marker in patients hospitalized with COVID-19, its effect on patterns of antibiotic use in this subset of patients and the public health implications of these use patterns.

**Methods:** Electronic medical records (EMRs) were interrogated in a cohort of hospitalized adults with COVID-19 (n=78) who experienced moderate and severe disease as defined by the Yale Impact Score. Patients were recruited from the Northern Colorado region from July 2020 to March 2021 and multiple data metrics were gathered on 55 patients, including demographics, PCT level on admission, disease severity, bacterial co-infections (BcI), and antibiotic usage. *T*-tests, ANCOVA, and ANOVA were used for continuous data while Fisher's exact or chi square were used to analyze categorical data.

**Results:** Antibiotics were administered to 37 (47.4%) of all patients enrolled in the biorepository, while the rate of BcI in this patient population was 8 (18.7%). Of the 55 hospitalized patients with PCT levels, those with severe COVID-19 had significantly higher LnPCT levels 0.18 (0.12–0.26) ng/mL than those with moderate disease 0.12 (0.09–0.15) ng/mL, P=0.048. Thirty (54.5%) of the 55 were given antibiotics while 25 (45.5%) were not, and only 7 patients had BcI, confirmed by blood, respiratory, or urine culture positivity.

**Conclusions:** In the setting of COVID-19 infection, PCT is more closely linked to viral disease severity and less associated with BcI. This association is driving an increase in antibiotic use in patients with COVID-19 regardless of a confirmed co-infection leading to antibiotic overuse, potential for resistance and associated increase in multidrug resistant organisms (MDROs). Currently available lower respiratory tract infection (LRTI) guidelines for the use of PCT to initiate and de-escalate antibiotics can safely be followed in the setting of COVID-19 infection, although modification of blood-level cutoffs require further study. Such an approach would minimize the public health impact of antibiotic overuse.

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## Introduction

### *Background*

Since the initial identification in December 2019, SARS-CoV-2, the virus responsible for COVID-19, has spread around the globe, infecting over 219 million people, and claiming 6.4 million lives (1,2). The disease course observed in COVID-19 patients is highly variable, with some patients experiencing mild respiratory symptoms, while others develop acute respiratory distress and require hospitalization (3). Understanding the factors that drive disease severity is important to maximize early treatment regimens and efficiently use healthcare resources. Demographic characteristics, such as male sex, advanced age, smoking history, hypertension, diabetes, and cardiac/respiratory disease, have been identified as risk factors for a severe disease course (4). Several clinical laboratory parameters may predict disease severity thereby promoting earlier use of treatment modalities to improve COVID-19 disease outcomes (5). Bacterial co-infection (BcI) in COVID-19 was a major concern and led to increased antibiotic use during the first pandemic wave (6). Procalcitonin (PCT) is frequently used to identify bacterial infections in hospitalized patients and has been shown to reduce antibiotic exposure (7-11). PCT levels are higher in those with bacteria co-infections (BcI) than in those without, suggesting that PCT could be a helpful tool in distinguishing BcI from exuberant inflammatory responses to SARS-CoV-2 and inform decisions regarding antibiotic use in COVID-19 patients (12-15).

**Highlight box**

**Key findings**
- Procalcitonin (PCT) is associated more closely with COVID-19 disease severity and less with bacterial coinfections (BcI).

**What is known and what is new?**
- Bacterial co-infection with COVID-19 is rare.
- Currently available lower respiratory tract infection (LRTI) guidelines for the use of PCT to initiate and de-escalate antibiotics may also be useful in COVID-19, however, some alterations in cutoffs for blood levels may be indicated.
- With an ongoing worldwide increase in MDROs, analysis of antibiotic usage trends in COVID-19 is important in identifying means to increase antibiotics stewardship

**What is the implication, and what should change now?**
- Our data show that PCT has a role in public and global health as a guide to increase appropriate antibiotics usage and decrease the development of multi-drug resistant organisms (MDROs).
- PCT can be used by providers to carefully select patients who will benefit from antibiotic therapy and should play a role in antibiotic stewardship.

### *Rationale and knowledge gap*

PCT elevation is highly specific for detecting bacterial infection and elevation typically resolves with antibiotic treatment (16,17). Evidence suggests that PCT levels may also rise in viral infections even in the absence of BcI (18). Many patients hospitalized for SARS-CoV-2 are put on empiric antibiotics, without documentation of a bacterial infection (19). A recent study found that of 1,705 patients hospitalized with COVID-19 in 38 Michigan hospitals, 56.6% of patients were prescribed early empiric antibacterial therapy while only 3.5% had a confirmed community-onset bacterial infection (20). The role of an elevated versus normal PCT level in this cohort was not examined. Historical use of PCT elevation, when detected in patients with COVID-19, has prompted the initiation of antibiotic use for suspected BcI. A survey of 82 hospitals operating in 23 different countries revealed that antibiotic use in COVID-19 patients is widespread, with some hospitals reporting a prescription rate of over 70% (21). This same study revealed that PCT elevation was the primary diagnostic tool used to justify antibiotic therapy (21). Despite the widespread use of antibiotics in COVID-19 patients, the rate of BcI has been shown to be quite low, with some studies indicating less than 5% of patients present with a concurrent bacterial infection (20,22). Consequently, the COVID-19 pandemic has increased use of antimicrobial therapy in patients both with and without documented co-infections (15).

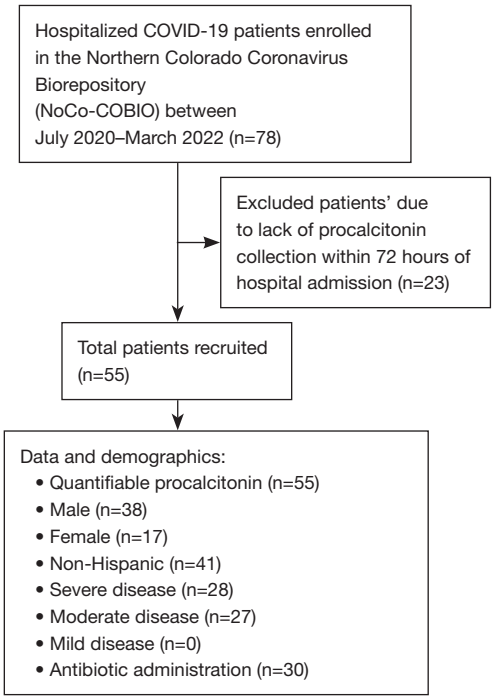


**Figure 1** Study recruitment design and collected data parameters.

Increased antibiotic use is a risk factor for development of multidrug resistant organisms (MDROs) and future MDROs outbreaks associated with seasonal influenza and antimicrobial resistance to gram-negative pathogens (23). Although development of resistance is multifactorial, this association has been hypothesized to be driven by increased rates of antimicrobial use during influenza season (23). There is potential that additional antimicrobial therapy use in patients with COVID-19 will likewise result in increase of antimicrobial resistance. This has public health ramifications. Recent literature is mixed regarding the prevalence of MDROs outbreaks, but there is evidence for an increase in antibiotic resistance during the COVID-19 pandemic (24). One study suggested an increase in MDROs outbreaks due to increased stress on healthcare systems and personal protective equipment (PPE) shortages (24). A more recent epidemiological study in Northeast Iran, which was heavily impacted by COVID-19 pandemic, found an increase in gram-negative anti-microbial resistance rates between January 2020 and January 2022 in the setting of the COVID-19 pandemic (25).

### *Objective*

The objective of this study was to evaluate the relationship between PCT levels, antibiotic use, and the incidence of BcI in hospitalized patients in our COVID-19 cohort. We present this article in accordance with the STROBE reporting checklist (available at https://jphe.amegroups.com/article/view/10.21037/jphe-22-77/rc).

## Methods

### *Data acquisition of clinical parameters*

Data for this study were obtained from hospitalized participants who were admitted during the acute stage of COVID-19 infection [as diagnosed by positive SARS-CoV-2 polymerase chain reaction (PCR) test]. The patients included in this study were enrolled in the Northern Colorado Coronavirus Biorepository (NoCo-COBIO), with data collection dates ranging between July 2020 and March 2021. All patients were admitted to one of three tertiary care hospitals, Medical Center of the Rockies in Loveland, Colorado, Greeley Hospital in Greeley, Colorado, and Poudre Valley Hospital in Fort Collins, Colorado. Prior to the collection of patient information, the NoCo COBIO project was approved under Colorado State University's (CSU) Research Integrity and Compliance Institutional Review Board [IRB; protocol ID 2105 (and 20-10063H)] and University of Colorado Health (UCHealth) IRB (Colorado Multiple IRB 21-3507). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from patients for their anonymized information to be published in this article.

The complete description of all procedures and clinical parameters obtained as part of the NoCo COBIO study was previously described (26). Data used for the purposes of this study were obtained from the UCHealth electronic medical record (EMR), Epic, and stored in a secure database (REDCap) with password protection. Only research personnel who had undergone privacy and patient confidentiality training accessed the REDCap database. Exclusion criteria included those who were not capable of making their own decisions due to mental capacity concerns and individuals who were under the age of 18. Additionally, patients who were diagnosed with COVID-19 via home test kits or rapid antigen tests were not included in this analysis. Our study recruitment and exclusion criteria are detailed in *Figure 1*.

Data collected from EMR included PCT level (hospital generated), demographic data, oxygen requirements, and in-hospital complications, including co-infections. PCT was

**Table 1** Hospitalized patient demographics (N=55). Includes only participants with PCT levels in EMR upon 72 hours of admission

| Variables | Mean ± SD or frequency (%) | Minimum–maximum (range) |
|---|---|---|
| Age (years) | 60.7±13.3 | 30–85 |
| BMI (kg/m$^2$) | 34.8±9.0 | 23.0–64.5 |
| Sex | | |
| Male | 38 (69.1) | |
| Female | 17 (30.9) | |
| Race | | |
| Hispanic | 14 (25.5) | |
| Non-Hispanic | 41 (74.5) | |
| COVID-19 disease severity | | |
| Moderate disease | 27 (49.1) | |
| Severe/fatal | 28 (50.9) | |
| PCT (ng/mL) | 0.23±0.30 | 0.059–1.49 |
| LnPCT (ng/mL) | 0.15 (0.12–0.18) | |
| Coinfection (N=55) | 7 (12.7) | |
| PCT >0.15 (ng/mL) | 21 (38.2) | |
| On antibiotic | 30 (54.5) | |
| Complications | 10 (18.2) | |
| Moderate to severe CKD | 0 (0.0) | |

PCT, procalcitonin; EMR, electronic medical record; BMI, body max index; CKD, chronic kidney disease.

drawn within 72 hours of admission. Disease severity was defined using the Yale COVID-19 severity index as follows: moderate (1–5 L/min of supplemental oxygen required) and severe/fatal (>5 L/min of supplemental oxygen required) (27). Severity was adjudicated at the highest level of supplemental oxygen for the whole hospitalization.

Patients defined as mild on the Yale index were not admitted to the hospital or available for blood draws. In-hospital complications included thrombotic events, acute-kidney injury (AKI), gastrointestinal (GI) bleed, or any acute conditions diagnosed during the hospitalization. Laboratory values, including complete blood counts (CBC), white blood cell (WBC) differential percentages, and culture reports for respiratory, blood, and urine samples, were obtained from the EMR. Antibiotic use and duration were also recorded. Other medications or treatments received (e.g., systemic steroids, convalescent plasma, remdesivir, monoclonal antibodies) were not included in the analysis.

### *Statistical analysis*

PCT was checked for the distributional assumption of normality using the Shapiro-Wilk's test. A natural log transformation was applied which created a normal distribution. The resulting variable is referred to as LnPCT. If PCT was < than 0.06, then a value of 0.059 was used so that a natural log transformation could be performed. The primary goal of the study was to determine if there was a difference between moderate and severe disease in PCT using an independent samples *t*-test. The second goal was to determine if there was a difference in LnPCT among body max index (BMI) groups: underweight/normal, overweight, and obese (28) as answered by performing ANOVA with a Tukey-Kramer P value adjustment to determine which groups differed. As a categorical variable, PCT elevation was defined as any value >0.15 ng/mL (per UCHealth lab reference range). ANCOVA was then used to determine if covariates such as age and gender affected the results.

The next study endpoint was to determine the incidence of BcI in the setting of primary SARS-CoV-2 infection and to see if LnPCT differed between those with co-infection and those without co-infection. Diagnosis of BcI was determined by any indication of bacterial growth in blood, respiratory or urine cultures or stool culture for Clostridium difficile (C. diff) colitis as well as clinical documentation of symptoms consistent with an infection.

It was determined that a sample size N=66 would provide 93% power to detect a medium effect size of 0.5 with a two-sided alpha =0.05. However, all samples available at the time of abstraction were used. Data were presented as mean ± SD for normally distributed data. The geometric mean and 95% CI was presented for transformed data and frequency and percent were presented for categorical variables. P<0.05 was considered significant. All analyses were performed using SAS 9.4 (Cary, NC, USA).

## Results

Seventy-eight patients admitted to the hospital were enrolled into the NoCo-COBIO database. Of those, 55 (71%) had values for PCT within 72 hours of admission to the hospital for COVID-19 while 23 (29%) did not. Of the 55 hospitalized COVID-19 patients included, the majority were male (N=38, 69.1%) and 41 (74.5%) were non-Hispanic (*Table 1*). Those with severe disease had significantly higher

**Table 2** Level of PCT in patients categorized by COVID-19 disease severity

| Variables | Moderate (N=27) | 95% CI | Severe/fatal (N=28) | 95% CI | P value |
|---|---|---|---|---|---|
| PCT (ng/mL) | 0.14±0.11 | 0.10–0.18 | 0.31±0.40 | 0.15–0.46 | 0.0380 |
| LnPCT (ng/mL) | 0.12 | 0.09–0.15 | 0.18 | 0.12–0.26 | 0.048 |

Data were presented as mean ± standard deviation. Geometric means and 95% CIs were reported for the natural log of procalcitonin. PCT, procalcitonin; CI, confidence interval.

**Table 3** Procalcitonin levels in the presence and absence of BcI

| Variables | No BcI (N=48) | 95% CI | BcI (N=7) | 95% CI | P value |
|---|---|---|---|---|---|
| PCT (ng/mL) | 0.22±0.31 | 0.13–0.31 | 0.28±0.23 | 0.07–0.50 | 0.60 |
| LnPCT (ng/mL) | 0.14 | 0.11–0.18 | 0.20 | 0.08–0.47 | 0.27 |

Data were presented as mean ± standard deviation. BcI, bacterial co-infection; PCT, procalcitonin; CI, confidence interval.

**Table 4** Association of co-infection, elevated procalcitonin, complications, and the use of antibiotics (N=55)

| Variables | No antibiotics (N=25), n (%) | Antibiotics (N=30), n (%) | Chi square or Fisher's exact P value |
|---|---|---|---|
| Co-infection | | | 0.1117 |
| No (N=48) | 24 (50.0) | 24 (50.0) | |
| Yes (N=7) | 1 (14.3) | 6 (85.7) | |
| Procalcitonin | | | 0.1559 |
| Not elevated (N=34) | 18 (52.9) | 16 (47.1) | |
| Elevated (N=21) | 7 (33.3) | 14 (66.7) | |
| Complication | | | 0.3095 |
| No (N=45) | 22 (48.9) | 23 (51.1) | |
| Yes (N=10) | 3 (30.0) | 7 (70.0) | |

Complication refers to any additional acute diagnoses received during hospital admission.

LnPCT 0.18 (0.12–0.26) ng/mL than those with moderate disease 0.12 (0.09–0.15) ng/mL, P=0.048 (*Table 2*).

Of the 55 patients for which PCT levels were available, 30 (54.5%) were administered an antibiotic despite the highest PCT level being 1.49 (ng/mL). Only 7 (12.7%) had a documented BcI based on culture positivity as well as symptoms consistent with an infection. There was no difference in LnPCT levels in those with co-infections 0.20 (0.08–0.47) versus those without co-infections 0.14 (0.11–0.18), P=0.27 (*Table 3*). In those with moderate disease, only 1 (3.7%) had a co-infection while 6 (21.4%) of those with severe disease had a co-infection (P=0.10).

Of the N=30 given antibiotics, 13 (43.3%) were classified as having moderate disease and 17 (56.7%) were classified as severe disease (P=0.35). There was no association between receiving an antibiotic and the presence of a co-infection, as 6 out of 7 (85.7%) with a co-infection did receive antibiotics (*Table 4*) (P=0.1117). The 7 co-infections were as follows: 3 (5.5%) had blood borne infections, 2 (3.6%) had pneumonia and 2 (3.6%) had urinary tract infections.

Next, we looked at the relationship between elevated PCT, defined >0.15 ng/mL in our health system. Of the 55, N=21 (38.2%) had elevated PCT. Fourteen (66.7%) of the 21, with elevated PCT, were given an antibiotic. There was no association between antibiotic use and elevated PCT (P=0.1559) (*Table 4*).

## Discussion

### *Key findings*

There were significant differences in LnPCT levels between

patients with moderate versus severe disease. Yet, the rate of confirmed co-infections was low and in this cohort and there was no association between elevated PCT and co-infection. Patients were grouped based on disease severity and the presence of any co-infection including bacterial pneumonia, positive blood cultures, *C. diff* colitis, and urinary tract infection. Our data show that in the setting of COVID-19 infection, PCT may be linked to viral disease severity rather than bacterial infection. Given the low BcI in our study and others, use of clinical indicators alongside use of existing PCT guidelines for the treatment and de-escalation of antibiotics for lower respiratory tract infections (LRTI), could reduce antibiotic overuse in this population (9,17). For those patients with higher PCT values, serial testing may be indicated.

### *Strengths and limitations*

These findings have important global and environmental health implications related to antimicrobial resistant bacterial infections and unnecessary costly resource utilization. These findings signal an important evolving public health risk and confirm that existing guidelines for diagnosing bacterial infection or co-infection in patients with COVID-19 remain useful. An elevated PCT should be interpreted using other indicators of clinical infection and demonstrates support for robust evidence-supported guidelines to guide antibiotic use in patients hospitalized with COVID-19. Expanded awareness of the low probability for BcI in patients presenting with COVID-19 could also decrease the use of empiric antibiotics in this patient population and the associated risks of MDROs outbreaks. Study limitations for this cross-sectional investigation include inability to control which labs were ordered by the overseeing physician and the lack of a hospitalized cohort without COVID-19 infection that were administered antibiotics for different procedures/conditions. We were also limited by a specific enrolment period from July 2020 and March 2021 which has the potential to miss some seasonal bacterial infections. Additionally, patients with "documentation" or microbiological diagnostic criteria of BcI may underrepresent the number of patients who had BcI. There is potential for inadequate or poor samples and cultures may not have been obtained due to attempt to diminish health care worker exposure. The relationships identified between LnPCT levels and disease severity, rate of co-infection, and rate of antibiotic use merit attention in a larger cohort across the nation. Finally, PCT levels used were those obtained within 72 hours of admission, with 49% (27 patients) having a PCT drawn at admission. PCT levels have a half-life of 24 hours We could not control time of initial lab draw at admission, nor for the time of disease onset to time of admission. Antibiotics also alter PCT level but again, 49% of patients had the PCT upon admission, and thus levels would be concurrent with antibiotic administration.

### *Comparison with similar research*

The low rate of BcI with COVID-19 has been widely observed in other studies and should be taken into consideration when making the decision for antibiotic use (20,22). Despite the low BcI rate in this group 7 (12.7%), 55% participants received antibiotics. Our findings are consistent with the previously observed overuse of antibiotics in hospitalized COVID-19 patients that contributes to an ongoing public health concern for diligent antibiotic stewardship. Antibiotics are life-saving therapy in cases of bacterial infection; however, unnecessary use is costly and places patients at risk for opportunistic infections, which may further complicate the disease course (29). Additionally, overuse of antibiotics increases bacterial resistance and adverse reactions with other medications (29,30). Currently, there are no clinical guidelines for antibiotic use in patients with COVID-19 and suspected co-infections. PCT is typically a helpful diagnostic measure in predicting bacterial infection, though the findings described herein demonstrate that this may not be the case for COVID-19 patients. The PCT levels that address the inflammatory insult due to COVID-19 needs to be carefully examined. Thus, the prescription of antibiotics in this patient population should consider PCT levels within a broader clinical picture that includes temperature curve, WBC count, blood cultures, patient history, and physical exam. A better use of PCT in this group may be to observe trends in PCT levels as a guide for de-escalation of antibiotics in patients admitted to the ICU (31). Additionally, other biomarkers, including C-reactive protein, interleukin-6, stress-response hormones, and certain cell markers may provide better sensitivity in diagnosing bacterial infection (29,32-34). Neutrophil assays and -omic (genomic/transcriptomic/metabolomic) approaches have also been identified as emerging methods for rapid, specific detection of bacterial infection (35). Thus, the diagnostic criteria of bacterial infection in the future may include a suite of biomarker and -omic tests to ensure

antibiotic treatment is not overused.

### *Explanation of findings*

Our data suggest that PCT may have prognostic value in determining disease severity and subsequent oxygen requirements and/or need for intubation. It can also be used to limit antibiotic usage and prevent over prescription of antibiotics. Elevation of PCT in patients with COVID-19 should be nuanced and used in conjunction with a broad range of clinical information before the decision is made to start antibiotics.

### *Implications and actions needed*

Recent literature demonstrates an increase in MDROs outbreaks and antimicrobial resistance in the setting of the COVID-19 pandemic (35), and we set out to analyze PCT and antibiotic usage trends for its role in global and public health. Reframing the interpretation of PCT in COVID-19 patients as an indicator of viral disease severity is warranted without associated concomitant BcI. We have also re-demonstrated a unique opportunity to incorporate PCT in adoption of a public health-based protocol within hospitals to decrease antibiotic overuse in COVID-19 patients. This approach was pioneered by Chow *et al.* prior to the COVID-19 pandemic and showed the use of a PCT-based protocol for evaluation and treatment of sepsis may be associated with decreased antibiotic use and significant cost savings, with no change in mortality (36).

Current guidelines used to distinguish LRTI from bacterial versus viral etiology can be safely used to start and de-escalate antibiotics if used in conjunction with other clinical parameters described above. The utility of PCT as a biomarker for bacterial infection and COVID-19 disease severity is an area of inquiry that warrants further investigation and may assist with reducing antibiotic overuse that promotes spread of MDROs.

## Conclusions

PCT has important implications for public health and global antibiotic usage. In the setting of COVID-19 infection, PCT is more closely linked to viral disease severity and less associated with BcI. This association is driving an increase in antibiotic use in patients with COVID-19 regardless of a confirmed co-infection leading to antibiotic overuse, potential for resistance and associated increase in MDROs. Our data show that findings of an elevated PCT in a patient with COVID-19 should be interpreted cautiously when deciding whether to initiate anti-microbial therapy. Using an elevated PCT as justification for starting antibiotics leads to overuse and will further contribute to the spread of antibiotic resistance, jeopardizing global public health. Our findings also show the potential benefits of using PCT in a public health-based protocol within hospitals that will decrease resource over-utilization and development of antimicrobial resistance. In both cases, providers can use PCT to help limit over-use of antibiotics and decrease the development of MDROs. Currently available guidelines for the use of PCT to initiate and de-escalation can safely be followed in the setting of COVID-19 infection, although blood level cut-offs require further study.

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## Footnote

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*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jphe.amegroups.com/article/view/10.21037/jphe-22-77/rc

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jphe.amegroups.com/article/view/10.21037/jphe-22-77/coif).

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was jointly approved by Colorado State University Research Integrity and Compliance Review Office Institutional Review Board [IRB; protocol ID 2105 (20-10063H)] and Colorado Multiple IRB (COMIRB 21-3507). Written informed consent was obtained from patients for their anonymized information to be published in this article.



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