Coronavirus disease 2019 (COVID-19) and its causal pathogen, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), have been classified by the World Health Organization as a pandemic with over 6 000 000 cases confirmed globally [1, 2]. The majority of available United States (US)-published reports present populations with community spread in urban areas [3, 4]. In this letter, we describe the characteristics, pharmacologic treatment and preliminary outcomes of 150 acute care patients with COVID-19 within three hospitals of Sanford Health, an integrated healthcare system in the upper Midwest. North Dakota and South Dakota represent rural areas of the USA. The median incomes of North Dakota and South Dakota in 2018 were $ 63 837 and $ 56 274, respectively. As of April 2020, North Dakota has a civilian labour force of 407 100 people with an unemployment rate of 8.5%, while South Dakota has a civilian labour force of 470 100 people with an unemployment rate of 10.2% [5]. Infectious Diseases Society of America COVID-19 Treatment Guidelines published on 11 April 2020 only recommend treatment of COVID-19 with pharmacological agents in the context of a clinical trial; however, rural health systems may not always have the capabilities and resources necessary to rapidly join open clinical trials and encourage larger comparative studies evaluating treatment efficacy.

In our study, patients with confirmed SARS-CoV-2 infection by positive nasopharyngeal polymerase chain reaction test seen in the emergency department or admitted to one of three Sanford Health hospitals between 21 March 2020 and 30 April 2020 were included. Participants were enrolled in an IRB-approved registry-based cohort with a waiver of informed consent. The data presented were collected through review of secure, confidential electronic health records that were accessed with permission from the IRB, but are not publicly available.

A total of 150 patients were included; 56.7% were male (n = 85), with a median age of 56 years (range: 1 month–95 years), and 95 (63.3%) were Caucasian. Demographic and clinical characteristics are described in Table 1. The most common comorbidities observed were cardiovascular (CV) disease and diabetes mellitus. Fourteen patients were never admitted for inpatient treatment, but rather discharged home after their emergency department encounter. Abnormal chest radiograph findings were observed in 89 patients and common admission sequelae are summarised in Table 1. Patients were selected to receive different pharmacological treatments prescribed for the treatment of COVID-19 and its related outcomes of 150 acute care patients with COVID-19 in a rural health system in the Dakotas

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Abstract
The majority of available US-published reports present populations with community spread in urban areas. The objective of this report is to describe a rural healthcare system’s utilisation of therapeutic options available to treat Coronavirus Disease 2019 (COVID-19) and subsequent patient outcomes. A total of 150 patients were treated for COVID-19 at three hospitals in the Dakotas from 21 March 2020 to 30 April 2020. The most common pharmacological treatment regimens administered were zinc, hydroxychloroquine plus azithromycin and convalescent plasma. Adjunctive treatments included therapeutic anticoagulation, tocilizumab and corticosteroids. As of 1 June 2020, 127 patients have survived to hospital discharge, 12 patients remain hospitalised and 11 patients have expired. The efficacy of hydroxychloroquine and azithromycin use has yet to be determined but was not without risks of corrected QT interval prolongation and arrhythmias in our cohort. We did not appreciate any adverse effects that appeared related to tocilizumab or convalescent plasma administration in those patient subsets. These findings may provide insight into disease severity and treatment options in the rural setting with limited resources to participate in clinical trials and encourage larger comparative studies evaluating treatment efficacy.
Table 1. Baseline characteristics, treatment and preliminary outcomes of 150 hospitalised patients with COVID-19

| Demographics | Value |
|--------------|-------|
| Age (in years), median (range) | 56 (1 month–95 years) |
| Sex, number (%) | |
| Male | 85 (56.7) |
| Female | 65 (43.3) |
| Race, number (%) | |
| Caucasian | 95 (63.3) |
| American Indian | 26 (17.3) |
| African-American | 18 (12.0) |
| Asian | 5 (3.3) |
| Hispanic/Latino | 3 (2.0) |
| Pacific Islander | 2 (1.3) |
| Not documented | 2 (1.3) |

Baseline characteristics |
| Number (%) of patients |
|-------------------------|
| Asthma | 27 (18.0) |
| Chronic obstructive lung disease | 16 (10.7) |
| Sleep apnoea | 22 (14.7) |
| Congestive heart failure | 16 (10.7) |
| Cardiovascular disease | 77 (51.3) |
| Diabetes mellitus | 43 (28.7) |
| Rheumatologic disease | 7 (4.7) |
| Chronic kidney disease | 23 (15.3) |
| End-stage renal disease | 8 (5.3) |
| Liver cirrhosis | 4 (2.7) |
| History of solid organ transplant | 0 |
| Current smoker | 24 (16.0) |
| Immunosuppression | 7 (4.7) |

Admission symptoms |
|------------------|
| Cough | 93 (62.0) |
| Shortness of breath | 95 (63.3) |
| Fever | 92 (61.3) |

Admission chest radiograph findings |
|-----------------------------|
| Airspace opacities | 27 (18.0) |
| Atelectasis | 21 (14.0) |
| Groundglass opacities | 9 (6.0) |
| Focal consolidation | 4 (2.7) |
| Pleural effusion | 28 (18.7) |
| Clear | 24 (16.0) |

Laboratory test |
|----------------|
| Value median (range) | Reference range |
| White blood cell (count/μl) | 2.5 (1.6–20.3) | 4.0–11.0 |
| Absolute lymphocyte count (K/μl) | 1.0 (0.2–4.8) | 0.8–4.1 |
| Haemoglobin (g/dl) | 13.0 (5.8–17.1) | 13.5–17.5 |
| Platelets (× 10^9 μl) | 195 (56–622) | 140–400 |

(Continued)
Table 1. (Continued.)

| Demographics               | Value                  |
|----------------------------|------------------------|
| Ferritin (ng/ml)           | 385 (2–14,801)         |
| Glucose (mg/dl)            | 112 (57–614)           |
| Sodium (mEq/l)             | 137 (120–149)          |
| Creatinine (mg/dl)         | 0.93 (0.47–12.1)       |
| Alkaline phosphatase (U/l) | 78 (22–336)            |
| Aspartate aminotransferase (U/l) | 41 (10–724) |
| Alanine aminotransferase (U/l) | 27 (7–477)            |
| Creatinine kinase (U/l)    | 96 (25–1215)           |
| Venous lactate (mmol/l)    | 1.2 (0.5–5.3)          |
| D-dimer (μg/ml)            | 0.8 (<0.27–8.0)        |
| CRP (mg/l)                 | 57.5 (0.9–299)         |
| Procalcitonin (ng/ml)      | 0.13 (0.02–2.64)       |

| Treatment or outcome       | Number (%) of patients |
|----------------------------|------------------------|
| Pharmacologic agent        |                        |
| Hydroxychloroquine + azithromycin" | 66 (44.0) |
| Hydroxychloroquine monotherapy | 9 (6.0)   |
| Lopinavir/ritonavir        | 3 (2.0)                |
| Convalescent plasma        | 16 (10.7)              |
| Tocilizumab                | 12 (8.0)               |
| IL-6 value, median (range) | 40.1 (1.0 to >400)     |
| Zinc                       | 93 (62.0)              |
| Ascorbic acid              | 13 (8.7)               |
| Angiotensin receptor blocker² | 6 (4.0)   |
| Corticosteroid             | 39 (26.0)              |
| Non-steroidal anti-inflammatory | 12 (8.0)  |
| Therapeutic anticoagulant  | 52 (34.7)              |
| Intravenous immune globulin| 1 (0.7)                |

| Potential adverse effects  |                        |
|----------------------------|                        |
| Retinopathy                | 0                      |
| Arrhythmia confirmed by ECG after H + A initiation\$ | 14 (18.7)\%
| QTc > 500 ms confirmed by ECG after H + A initiation | 15 (20.0)\%

| Outcomes                   |                        |
|----------------------------|                        |
| ICU admission              | 38 (25.3)              |
| O₂ requirement             | 89 (59.3)              |
| Non-invasive positive pressure ventilation | 23 (15.3) |
| Invasive mechanical ventilation | 28 (18.7) |
| Acute respiratory distress syndrome³ |                        |
| None                       | 110 (72.3)             |
| Mild                       | 6 (4.0)                |
| Moderate                   | 21 (14.0)              |
| Severe                     | 13 (8.7)               |
| Vasopressor use            | 28 (18.7)              |
| AKI\$                      | 31 (20.7)              |

(Continued)
treatments based on physician discretion with the support of an internal COVID-19 treatment guidance document that was continuously updated as new peer-reviewed literature became available. Risks and benefits of each treatment were explained within this document as well as guidance on which subsets of patients may benefit from certain treatments over others. The median length of time after admission that patients received pharmacological treatment was less than 1 day. At least a 5-day course of hydroxychloroquine and azithromycin was prescribed to 66 out of 150 COVID-19 patients. Sixteen patients received convalescent plasma. Of note, tocilizumab was administered to 12 patients with critical illness and elevated interleukin-6 (IL-6) levels (>1.8 pg/mL) and/or elevations in other inflammatory markers. Five patients received two doses. Other therapies included zinc, ascorbic acid, lopinavir/ritonavir, non-steroidal anti-inflammatory agents, therapeutic anticoagulation and corticosteroids. When critically ill patients appeared refractory to other therapies or supportive care, convalescent plasma was pursued. No patient in our cohort received remdesivir, as it was not yet available to our hospitals outside of the manufacturer’s compassionate use programme for pregnant or paediatric patients.

Preliminary outcomes are also described in Table 1. As of 1 June 2020, acute respiratory distress syndrome (ARDS) occurred in 40 out of 150 patients, with 28 of 40 ARDS patients requiring mechanical ventilation. Vasopressor support was administered for 28 patients, and acute kidney injury diagnosed in 31 patients. A total of 127 patients have survived to hospital or emergency department discharge to date. All 14 patients who were never admitted for inpatient treatment remain alive as of 1 June 2020. Of those 14 patients, only three received pharmacologic treatment specifically for COVID-19 diagnosis, which was in the form of a 5-day course of azithromycin. Follow-up was completed in the form of appointments with a provider (in-person or via telephone) after emergency department discharge. Four of the 14 patients not admitted for inpatient treatment do not have follow-up appointments scheduled as of 1 June 2020. Of the 10 patients who had follow-up appointments, the mean follow-up period was 14 days after their emergency department visit. As of 1 June 2020, 12 patients remain alive and hospitalised (eight intensive care unit, three general ward) and 11 patients did not survive to discharge. Of the 11 patients who did not survive to discharge, seven received hydroxychloroquine and azithromycin. Of note, one patient was transferred to a higher level of care for extracorporeal membrane oxygenation. The average length of stay (not including patients still hospitalised in a Sanford facility as of 1 June 2020) in our cohort as of 1 June 2020 (the first confirmed COVID-positive patient was admitted to our hospital system on 21 March 2020). All patients but one who received tocilizumab had an IL-6 serum level above the upper limit of normal of 1.8 pg/mL. The patient who received tocilizumab without an elevated IL-6 serum level had elevations in other inflammatory markers (ferritin, C-reactive protein and D-dimer). As with other therapies, the impact of convalescent plasma on survival is not yet clear.

This report potentially signals a lower hospital mortality rate than the current national average. However, it is unknown how the COVID-19 mortality rate in the Dakotas will change as the projected surge in COVID-19 approaches [2]. The efficacy of hydroxychloroquine and azithromycin use, with or without tocilizumab, has yet to be clarified but was not without risks of QT prolongation and arrhythmias in our cohort. Of the 75 patients who received hydroxychloroquine, 14 (18.7%) developed an arrhythmia and 15 (20.0%) developed a QTc > 500 ms after initiation of therapy. Baseline EKGs did not reveal the presence of arrhythmias or prolonged QTc in these patients prior to the initiation of hydroxychloroquine and azithromycin therapy. Additionally, 10 of 14 (71%) patients with arrhythmia development had underlying CV disease, while 10 of 15 (67%) patients with prolonged QTc > 500 ms had underlying CV disease. Of the nine patients that received hydroxychloroquine without azithromycin, none developed an arrhythmia or QTc > 500 ms after therapy initiation. The incidence of arrhythmias after initiation of hydroxychloroquine and azithromycin in our cohort (18.7%) appears to be higher than

### Table 1. (Continued.)

| Demographics          | Value |
|-----------------------|-------|
| Length of stay (days) |       |
| Mean                  | 8.1   |
| Median (range)        | 5 (1–64) |
| In-hospital mortality | 11 (7.3) |

CRP, C-reactive protein; AKI, acute kidney injury; ECG, electrocardiogram; ICU, intensive care unit; IL-6, interleukin-6; O2, oxygen; QTc, corrected QT interval.

1Defined as history of coronary artery disease, myocardial infarction, valvular disease, heart transplant or hypertension.

2Defined as chemotherapy use, outpatient prescription of greater than 10 mg/day of prednisone for ≥3 week duration or use of non-steroidal immunosuppressive agents for transplant or for autoimmune disease.

3Defined as temperature greater than 100.4°F.

4According to radiologist physician interpretation in medical record.

52 out of 66 patients who received H+A received hydroxychloroquine 400 mg twice daily for 2 doses, followed by 200 mg twice daily as well as azithromycin 500 mg on day 1, followed by 250 mg daily thereafter.

6All patients had previously been taking an angiotensin receptor blocker prior to hospital admission and was continued for blood pressure control.

7Hydroxychloroquine and azithromycin.

8Percentage of the 75 patients who received hydroxychloroquine.

9Based on Berlin Criteria.

10Based on criteria defined by Kidney Disease Improving Global Outcomes.

11Not including patients still hospitalised in a Sanford facility as of 1 June 2020.
the incidence of arrhythmias after initiation of hydroxychloroquine and a macrolide antibiotic (8.1%) in the largest multinational registry analysis (over 96,000 patients) of hospitalised COVID-19 patients to date, although caution should be exercised in interpreting this comparison given the small size of our cohort [7]. Diarrhoea occurred in 19 (12.7%) patients, constipation developed in 9 (6.0%) patients and nausea and/or vomiting occurred in 22 (14.7%) patients. Of note, it is possible that these gastrointestinal occurrences could be attributed to the SARS-CoV-2 virus itself rather than side effects of medications. Furthermore, we did not appreciate any adverse effects that appeared related to tocilizumab or convalescent plasma administration in those patient subsets.

Similar to other recent US reports, our data are limited by a small but important sample and the use of preliminary outcomes. However, our findings may provide insight into the severity of the disease across a rural acute care cohort and the agents utilised for treatment when rapid clinical trial access may not be feasible. We recognise that the unavailability of symptom duration prior to inpatient admission is a limitation of our report, which may have helped to better characterise disease progression and duration. Statistical comparisons between treatment groups were also not pursued given the non-randomised patient selection and small sample size. The use of medications in rural hospitals to treat COVID-19 infection has yet to be clarified, but is not without risks, especially with regards to the combination of hydroxychloroquine and azithromycin in patients with CV comorbidities. Larger trials with randomisation methods examining the efficacy and safety of pharmacologic therapies to treat COVID-19 are needed urgently.

Conflict of interest. None.

Data availability statement. The data that support the findings of this study are available from Sanford Research. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Sanford Research and the Sanford Institutional Review Board.

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### Appendix A

See Table A1.

#### Table A1. Baseline characteristics and preliminary outcomes by treatment group

|                  | Hydroxychloroquine + azithromycin cohort (n = 66)\(^b\) | Tocilizumab cohort (n = 12) | Convalescent plasma cohort (n = 16) | All hospitalised patients (n = 136) |
|------------------|----------------------------------------------------------|----------------------------|-----------------------------------|-----------------------------------|
| Asthma           | 13 (19.7)                                                | 3 (25.0)                   | 4 (25)                            | 25 (18.4)                         |
| Chronic obstructive lung disease | 8 (12.1)                                                | 2 (16.7)                   | 3 (18.8)                         | 16 (11.8)                        |
| Sleep apnoea     | 12 (18.1)                                                | 3 (25.0)                   | 3 (18.8)                         | 21 (15.4)                        |
| Congestive heart failure | 7 (10.6)                                                | 1 (8.3)                    | 1 (6.3)                           | 16 (11.8)                         |
| Cardiovascular disease\(^a\) | 40 (60.6)                                               | 9 (75.0)                   | 12 (75)                          | 70 (51.5)                       |
| Diabetes mellitus| 26 (39.4)                                                | 7 (58.3)                   | 7 (43.8)                         | 43 (31.6)                        |
| Rheumatologic disease | 2 (3.0)                                                | 1 (8.3)                    | 0                                | 6 (4.4)                           |
| Chronic kidney disease | 16 (24.2)                                               | 4 (33.3)                   | 3 (18.8)                         | 22 (16.2)                        |
| End-stage renal disease | 6 (9.1)                                                | 2 (16.7)                   | 0                                | 8 (5.9)                           |
| Liver cirrhosis  | 2 (3.0)                                                  | 0                          | 0                                | 4 (2.9)                           |
| History of solid organ transplant | 0                                                | 0                          | 0                                | 0                               |
| Current smoker   | 10 (15.2)                                                | 1 (8.3)                    | 3 (18.8)                         | 21 (15.4)                        |
| Immunosuppression\(^d\) | 4 (6.1)                                                | 0                          | 0                                | 6 (4.4)                           |
| Outcomes         |                                                          |                            |                                   |                                   |
| ICU admission     | 29 (43.9)                                                | 12 (100)                   | 15 (93.8)                        | 38 (27.9)                        |
| O\(_{2}\) requirement | 53 (80.3)                                               | 12 (100)                   | 14 (87.5)                        | 89 (65.4)                        |
| Non-invasive positive pressure ventilation | 16 (24.2)                                               | 9 (75.0)                   | 10 (62.5)                       | 23 (16.9)                       |
| Invasive mechanical ventilation | 25 (37.9)                                              | 10 (83.3)                  | 11 (68.8)                       | 28 (20.6)                       |
| Acute respiratory distress syndrome\(^e\) |                                                          |                            |                                   |                                   |
| None             | 35 (53.0)                                                | 0                          | 0                                | 96 (70.6)                        |
| Mild             | 5 (7.6)                                                  | 1 (8.3)                    | 2 (12.5)                         | 6 (4.4)                           |
| Moderate         | 17 (25.8)                                                | 5 (41.7)                   | 10 (62.5)                       | 21 (15.4)                        |
| Severe           | 9 (13.6)                                                 | 6 (50.0)                   | 4 (25.0)                         | 13 (9.6)                          |
| Vasopressor use  | 24 (36.4)                                                | 12 (100)                   | 13 (81.3)                       | 28 (20.6)                         |
| AKI\(^f\)        | 20 (30.3)                                                | 7 (58.3)                   | 7 (43.8)                         | 31 (22.8)                        |
| Length of stay (days) |                                                          |                            |                                   |                                   |
| Mean             | 8.0                                                      | 26.4                       | 20.6                             | 8.1                               |
| Median (range)   | 5 (1–64)                                                 | 22 (10–64)                 | 19 (8–36)                        | 5 (1–64)                         |
| In-hospital mortality | 7 (10.6)                                                | 3 (25.0)                   | 5 (31.3)                         | 11 (8.1)                          |

AKI, acute kidney injury; ICU, intensive care unit; O\(_{2}\), oxygen.

\(^a\)Treatment cohorts are not mutually exclusive.

\(^b\)52 out of 66 patients received hydroxychloroquine 400 mg twice daily for 2 doses, followed by 200 mg twice daily as well as azithromycin 500 mg on day 1, followed by 250 mg daily thereafter.

\(^c\)Defined as history of coronary artery disease, myocardial infarction, valvular disease, heart transplant or hypertension.

\(^d\)Defined as chemotherapy use, outpatient prescription of greater than 10 mg/day of prednisone for \(\geq3\)-week duration or use of non-steroidal immunosuppressive agents for transplant or for autoimmune disease.

\(^e\)Based on Berlin Criteria.

\(^f\)Based on criteria defined by Kidney Disease Improving Global Outcomes.