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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Clinical Infectious Diseases* (*WJCID*, *World J Clin Infect Dis*) is to provide scholars and readers from various fields of infectious diseases with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical significance of anti-nucleocapsid-IgG sero-positivity in SARS-CoV-2 infection in hospitalized patients in North Dakota

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Abstract

BACKGROUND
During the peak of the coronavirus diseases 2019 (COVID-19) pandemic, clinicians actively studied the utility of various epidemiologic-clinical parameters to determine the prognosis for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Serum IgG antibody level, D-Dimer, C-reactive protein and neutrophil to lymphocyte ratio, *etc.* were studied to assess their association with the clinical course in hospitalized patients and predict who may be at increased risk for poor clinical outcome. However, the influence of SARS-CoV-2-anti-nucleocapsid-IgG antibody (IgG-N) sero-positivity on the clinical outcome of patients with COVID-19 is largely unknown.

AIM
To study the influence of SARS-CoV-2 anti-nucleocapsid-IgG seropositivity on clinical course and diseases severity in hospitalized COVID-19 patients.

METHODS
We conducted a retrospective study of adults admitted to a tertiary care community hospital in North Dakota with COVID-19. Included patients had severe

COVID-19 disease or worse and so required supplemental oxygen on admission. They were serologically tested for SARS-CoV-2-anti-nuceocapsid-IgG (IgG-N). The IgG-N positive group were 26 patients and the IgG-N negative group had 33 patients. The groups received similar treatment for COVID-19 as approved by our healthcare system from Day 1 of admission until discharge or death. Measurable parameters for monitoring the patients' clinical course included the following: Length of hospitalization (LOS), use of high flow nasal canula (HFNC), use of noninvasive bilevel positive pressure ventilation (BiPAP), admission into the intensive care unit, need for mechanical ventilation (VENT); and the patient outcome/discharge or death. Other variables included were age, gender and body-mass-index, and duration of symptoms before presentation. For each variable, the outcome was modeled as a function of SARS-CoV-2-IgG-N status (positive or negative) using a generalized linear model. For LOS-days, a negative binomial distribution was used as it had a better fit than a Poisson or Gaussian distribution as evidenced by a Pearson chi-square/df value closer to 1.0. All other outcomes utilized a binary logistic regression model.

RESULTS
After a thorough examination of patient data, it was found that admission rates to the Intensive Care Unit, as well as the usage of BiPAP, HFNC and VENT support, in conjunction with patient outcomes, were not significantly different across IgG-N status. However, the LOS variable when assessed by IgG-N status was found to be significant (t value = 2.16, P value = 0.0349). IgG-N negative patients had higher than average LOS in comparison to IgG-N positive patients (15.12 *vs* 9.35 d). Even when removing the extreme value (an LOS of 158 d), IgG-N negative patients still had slightly higher than average stays (10.66 *vs* 9.35 d) but the relationship was no longer significant. For patient outcome/death, only age (numerical) was a significant predictor (F value = 4.66, P value = 0.0352). No other variables for any of the outcomes were significant predictors of clinical course or disease severity.

CONCLUSION
Our study demonstrated that IgG-N seroconversion had no significant association with clinical outcomes in hospitalized COVID-19 patients.

Core Tip: We intended to study an immunologic marker to predict the need for advanced oxygen supplement system and clinical outcome in order to support our hospital crisis management system during the peak of the pandemic. Our study demonstrated that presence of anti-nucleocapsid-IgG (IgG-N) against severe acute respiratory syndrome coronavirus 2 infection had no impact on the clinical outcome or disease severity in hospitalized coronavirus disease 2019 (COVID-19) patients. We did not find a correlation of statistical significance to use IgG-N as a biomarker to predict clinical outcome in COVID-19 patients admitted to a community hospital in North Dakota.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus which belongs to the family of *Coronaviridae*, the causative agent for coronavirus diseases 2019 (COVID-19)[1]. SARS-CoV-2 emerged out of Wuhan in China and soon after, it spread to the entire world and thereby becoming a "Pandemic"[2-4]. After two years of rapid spread and the virus claiming over five million lives, healthcare system continues to scramble to protect patients from the atypical pneumonia-like illness caused by COVID-19. Diagnosis of SARS-CoV-2 infection is primarily dependent on reverse-transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab samples with more recent progress into rapid antigen testing[5,6]. Rapid community spread of the infection and dev-

elopment of herd immunity by community exposure has been a favorite topic of discussion by epidemiologists while the scientific community have successfully raced to design several effective vaccines for COVID-19.

Taking a dive into the pathophysiology of COVID-19, a strong comprehension of the role of the humoral immunity becomes very pertinent. It is known that infection with SARS-CoV-2, elicits an adaptive immune response by producing target specific antibodies which includes IgM, IgG and IgA[7-9]. Among these antibodies, IgG has been of tremendous interest to the scientific community due to its role in long-term protection against the virus[10]. After an infection with SARS-CoV-2, it takes about 10-14 d to produce IgG antibodies which peak around the third week and continues to remain detectable for about 8-12 mo[11,12]. SARS-CoV-2 is a positive sense single stranded RNA virus comprised of four different structural proteins. Those are the nucleocapsid protein (N protein), spike protein (S-protein), matrix protein (M-protein) and the envelope protein (E-protein)[13]. Antibody against the S-protein (IgG-S) is believed to be the neutralizing antibody that is the primary target of the vaccine trials. There have been reports showing a positive correlation between higher IgG-S levels and diseases severity[14, 15]. On the contrary, another study cited no association of IgG-S with patient outcomes such as need for maximal oxygen support, intensive care unit (ICU) admission, duration of hospitalization and death [16]. Alternatively, it could be argued that the non-neutralizing antibodies against the nucleocapsid protein (IgG-N) leads to robust inflammation cascade and release of cytokines thus contributing to debilitating pulmonary injury. It is believed that the cytokine storm plays a key role in the pathogenesis and COVID-19 prognosis[17,18]. A report by Batra *et al*[19] studied the role of IgG-N in COVID-19 and based on the findings the authors recommended using IgG-N titers as a prognostic factor for the clinical course in patients. In this study, a higher IgG-N titer was associated with extended duration of stay in the hospital and increased rate of admission into the ICU. Another study demonstrated that the stronger IgG-N seroconversion response is associated with more diseases severity compared to the weak responders[20]. There is still a paucity of data about the functionality of IgG-N in the pathophysiology of COVID-19. Given this concept of targeting various structural components of this prolific virus, study of the seroconversion and IgG-kinetics has gained a lot of importance to the researchers. Literature on the long-term kinetics of IgG antibody levels and their corresponding neutralizing effectiveness is sparse.

Practicing in a tertiary care community-based teaching hospital in North Dakota, United States, we have had experience with the pre-vaccine phase of COVID-19 pandemic. Noncompliance with public mask usage and rapid community transmission led to a sharp rise in COVID-19 illness and hospitalizations in North Dakota. In the midst of a healthcare crisis, we decided to investigate whether a qualitative IgG-N could be used as a molecular marker to determine the prognosis in the hospitalized patients. Basing our hypothesis on a theory that a rampaging community spread of SARS-CoV-2 infection led to a measurable IgG-N seroconversion of our population, thus impacting outcomes from hospitalization due to COVID-19, we retrospectively analyzed the data provided by the single-center community hospital from which we practiced.

MATERIALS AND METHODS

Study population and data collection

All patients were admitted to the community hospital between December 1, 2020 and August 30, 2021. Fifty-nine patients were included in the study who were screened for IgG-N within 48 h of admission. We excluded all patients that had been admitted to the hospital with a non-COVID-19 diagnosis who incidentally tested positive for SARS-CoV-2 during screening. Patients with severe or critical COVID-19 illness as per the definition of National Institute of Health were included in the study. Those with mild and moderate illness were excluded from the study as most of them did not meet criteria for hospitalization. None of the included patients had been vaccinated against COVID-19. All the patients were confirmed positive for SARS-CoV-2 infection using RT-PCR from nasopharyngeal swab samples at admission. Both male and female patients aged 28 to96 were included in the study. All patients were checked for the presence of SARS-CoV-2-IgG-N within 48 h of admission by using Abbott SARS-CoV-2-IgG assay, that uses a two-step chemiluminescent microparticle immunoassay method with acridinium-labeled anti-human IgG, performed at North Dakota state laboratory. Admission blood samples identified 26 patients positive for IgG-N against SARS-CoV-2 and 33 negatives. In October 2021, we started data acquisition, reviewing the electronic medical record of included patients.

Study design

As this retrospective cohort study investigated the study population from patient admission to outcome, a thorough review of the electronic medical record was performed to capture data. This data was inclusive of the following: age, gender, body mass index (BMI), duration of symptoms prior to hospitalizations (DOS), length of hospital stay measured in days (LOS), admission to ICU, need for high flow nasal cannula (HFNC), bilevel positive airway pressure ventilation (BiPAP) or mechanical ventilation (VENT) for supplemental oxygen/support, as well as the final patient outcome - discharge or death.

(Table 1)

Statistical analysis

Formatting: Age, BMI and DOS were numerical variables. However, additional constructs split Age and BMI into two and three-group categories for some analyses. For example, BMI_2, patients with a BMI of < 29.9 were put in one group, and those > 30 in a second group. For BMI_3, patients with a BMI of < 25 were put into one group, those between BMI of 25-29.9 in a second group, and those with BMI > 30 in a third. For the variable labelled Age_2, patients < 75 were put in one group, and those 75+ in a second group. For Age_3, patients with an age of < 40 were put into the first group, those between 40-75 in a second, and those 75+ in a third group. It should be noted here that one patient had an extreme value for their LOS at-158 d. Models were run with both the patient included and excluded to determine the sensitivity of the models to this extreme value.

Correlation of outcomes: For each pair of outcomes (Death, ICU, BiPAP, VENT and HFNC), the phi coefficient (measure of association between binary variable, comparable to the Pearson coefficient for continuous normal variables) was calculated (Table 2).

Outcomes by IgG status alone: For each variable, the outcome was modeled as a function of IgG-N status (positive or negative) using a generalized linear distribution. For LOS, it was determined that a negative binomial distribution had a better fit than a Poisson or Gaussian distribution, as evidence by a Pearson chi-square/df value closer to 1.0. The negative binomial distribution is also less sensitive to outliers. All other outcomes utilized a binary logistic regression model.

Outcomes by IgG-N status full model: For any single models that were significant, a multiple regression model was utilized, accounting for the consequential effect (if any) of the defined confounding variables of age, sex, BMI, and duration of symptoms.

Outcomes by other factors

LOS was modeled as a function of age using a negative binomial model. From there, age (categorical), BMI (numerical), and the interaction of BMI and age were each run with and without the extreme patient LOS-value noted in the previous section. The patient outcome/death was modeled as a function of LOS using a logistic model. Then, death was modeled as a function of age (numerical), and then age (categorical). The same was done for BMI. Finally, death was modeled as a function of sex. ICU, BiPAP, VENT, and HFNC were each modeled as a function of age (numerical), BMI (numerical), and sex separately.

Statistical analysis used SAS Studio V.3.8 (Cary, North Carolina, United States). The statistical review of the study was performed by a biomedical statistician.

RESULTS

We conducted a retrospective cohort study among fifty-nine adults aged between 28-96, admitted to the hospital with severe or critical COVID-19 illness between December 2020 and August 2021.

Correlation of outcomes

Unsurprisingly, most outcomes were strongly correlated. VENT and ICU rates were very strongly correlated (Phi Coeff = 0.94). All but one patient who went on mechanical ventilation was also admitted to the ICU. In contrast, VENT and HFNC rates were only moderately correlated (Phi Coeff = 0.43).

Outcomes by IgG status alone

Patient outcome, ICU admissions, HFNC, BiPAP and VENT rates were not significantly different across IgG-N status (Figure 1A-E). However, LOS by IgG-N status was found to be significant (*t* value = 2.16, *P* value = 0.0349) when including the extreme value (LOS > 150 d). IgG-N negative patients had higher average LOS than IgG-N positive patients (15.12 *vs* 9.35 d). However, when removing the extreme value (LOS of 150 d), IgG-N negative patients still had slightly higher average LOS (10.66 *vs* 9.35 d), but the relationship was no longer significant (Figure 1F). Furthermore, median LOS was lower in IgG-N negative patients (6.5 *vs* 7.5 d).

Outcomes by IgG-N status full model

Because LOS-days and IgG-N status was significant, at least when not removing the extreme value, the full model was considered which included age, BMI, and sex, and duration of symptoms. However, in the full model, IgG-N was not significant when controlling for the other variables. This remained true when using a model without the extreme value.

Table 1 Summary statistics by IgG-N status

	IgG-N positive	IgG-N negative
Demographic information		
Number	26 (19 male, 7 female)	32 (20 male, 12 female)
Mean age	61.1 (17.6)	60.0 (16.1)
Median age	63.5 (25)	63.5 (21)
Mean BMI	33.7 (7.4)	33.9 (7.7)
Median BMI	32.8 (12)	33.9 (10.1)
Mean DOS-d	7.5 (5.6)	6.5 (4.1)
Median DOS-d	5.5 (6.0)	7.0 (7.0)
Outcome		
Mean LOS-d	9.3 (5.6)	10.7 (10.4)
Median LOS-d	7.5 (7)	6.5 (7)
Proportion of death	0.23	0.19
Proportion of ICU	0.19	0.16
Proportion of BiPAP	0.27	0.22
Proportion of VENT	0.15	0.16
Proportion of HFNC	0.38	0.25

Standard deviation and Interquartile Range are found in parentheses for mean and medians respectively. DOS: Duration of symptoms (days); LOS: length of stay (days); ICU: Intensive care unit; BiPAP: Bilevel positive airway pressure ventilation; VENT: Mechanical ventilation; HFNC: High flow nasal cannula.

Table 2 Matrix of Phi coefficient for binary outcomes

|	Death	ICU	BiPAP	VENT	HFNC
Death	1	-	-	-	-
ICU	0.67	1	-	-	-
BiPAP	0.71	0.70	1	-	-
VENT	0.60	0.94	0.65	1	-
HFNC	0.58	0.48	0.67	0.43	1

ICU: Intensive care unit; BiPAP: Bilevel positive airway pressure ventilation; VENT: Mechanical ventilation; HFNC: High flow nasal cannula.

Outcomes by other factors

For death, only age (numerical) was a significant predictor (*F* value = 5.07, *P* value = 0.0283). As age increased, the probability of having an endpoint of one (Death) increased (Figure 2). No other variables for any of the outcomes were significant.

DISCUSSION

SARS-CoV-2 infection causes an atypical pneumonia like respiratory illness known as COVID-19 characterized by fever, dyspnea, anosmia and a worsening hypoxia[21,22]. Among those hospitalized with COVID-19, patients often required supplemental oxygen using HFNC, BiPAP and an increased admission into the ICU requiring mechanical ventilation depending on the severity of the respiratory failure and lung parenchymal involvement. The pathophysiology of COVID-19 is primarily an immune-mediated process with a variety of antibody signatures among which the IgG signatures were of interest to our study. A robust immune-mediated inflammatory cascade guides the pathophysiology of the COVID-19 illness[22-24]. Different proinflammatory cytokines such as IL-6 and TNF-α have been
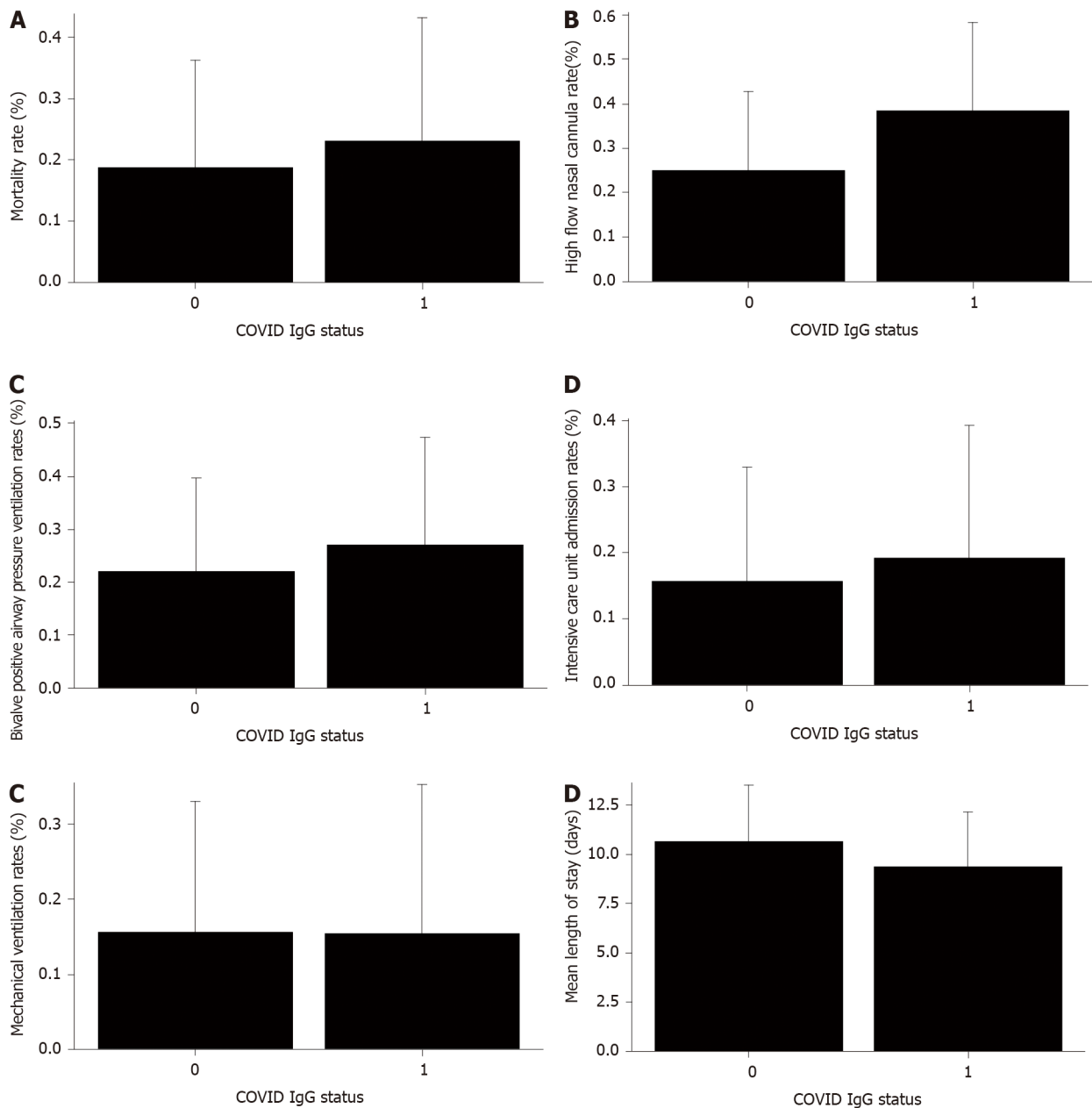
Figure 1 Clinical outcomes across Covid IgG status (0 = negative, 1 = positive). A: Mortality rates; B: High flow nasal cannula rates; C: Bilevel positive airway pressure ventilation rates; D: Intensive care unit admission rates; E: Mechanical ventilation rates; F: Mean length of stay. COVID: Coronavirus disease.

correlated with diseases severity[25].

There is some data available to understand the humoral response to SARS-CoV-2 infection and role of various IgG subtypes in the body's line of defense. Much of it was inherited from the studies of SARS-CoV-1[26]. IgG antibodies directed towards the spike protein (IgG-S) and that of the nucleocapsid protein (IgG-N) are the two important components of humoral immunity against SARS-CoV-2 infection. SARS-CoV-2 uses the spike protein to bind to the target cell through its receptor-binding domain and therefore is the target site for neutralizing antibody, IgG-S[27]. The role of IgG-S in early viral clearance is crucial for favorable clinical course and survival[28-30]. IgG-S is considered the neutralizing antibody which may elicit a protection against SARS-CoV-2 by interfering with virion binding to host cell receptors, blocking cellular uptake and preventing endosomal processing of viral genome[13,27]. However, the kinetics of the antibody response becomes more complex to understand with current available literature, which is conflicting. In one interesting study, there is a link between the IgG-S response and COVID-19 severity, but the antibody response has to develop in a specific time window to improve viral clearance and disease outcomes. A faster antibody response was associated with better survival (within the first 14 d of infection) and deceased patients showed a slower antibody response although they reached higher IgG titers later in the disease trajectory[31]. Other studies have shown that, severely ill patients exhibit higher peak, faster and stronger antibody response compared to mildly
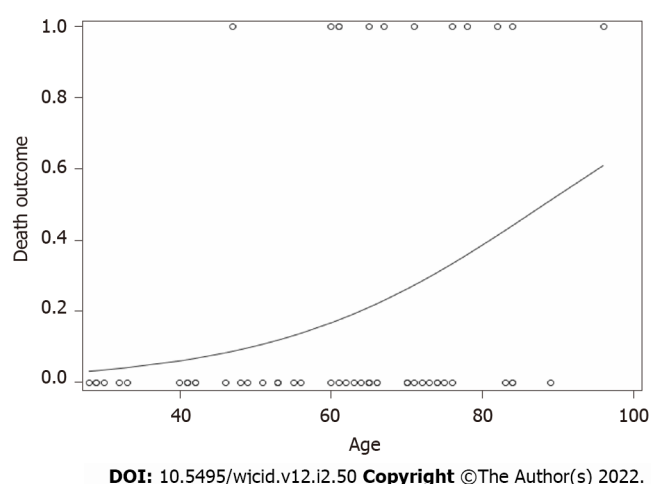
Figure 2 Logistic regression results of death outcome by age (Death = 1, Recovery = 0) by age (numerical). As age increased, the probability of mortality increased (F value = 5.07, P value = 0.0283).

symptomatic patients[13,32]. Severely ill COVID-19 patients have been found to produce a unique serologic signature with increased IgG-S with afucosylated Fc glycans. The Fc modification of IgG-S triggers activation of natural killers cells and enhances production of IL-6 and TNF-α by primary monocytes that results in more severe disease[33].

The role of IgG-N in the pathogenesis and clinical course of COVID-19 remains largely unknown. As to our current knowledge, severe COVID-19 is characterized by a series of inflammatory signatures including a cytokine storm, inflammatory alveolar infiltrates and formation of vascular microthrombi [33]. During the peak of the pandemic, clinicians took their chance to use different inflammatory markers such as C-reactive protein, platelet count, D-dimer and Ferritin, to name a few to monitor diseases progression and crisis planning. However, data to support the specificity of these inflammatory signatures as reliable prognostic markers for COVID-19 is limited[34,35]. As per one report by Batra *et al* [19], showed that titers of IgG-N at the time of admission can be a prognostic factor in the clinical course of the diseases and was associated with increased incidence of hypoxemia, admission into the ICU and extended length of stay in the hospital. In our study, we hypothesized that the presence of IgG-N at the time of admission into the hospital could be used as a marker of impending diseases severity and determine hospital course. We pursued a qualitative measurement of IgG-N on all our patients. Some key parameters such as the degree of hypoxemia, mean length of hospitalization, ICU admission, need for mechanical ventilation and patient outcome as in-hospital datasets were examined in our study group. We enrolled a total of 59 patients who were admitted with hypoxia secondary to COVID-19, out of which 26 (44%) patients had IgG-N antibody at the time of admission into the hospital. Our goal was to investigate the role of IgG-N as a marker to anticipate the clinical course in hospitalized patients. Based on our results, we concluded that IgG-N might not be a reliable predictor of COVID-19 diseases severity.

Our data indicate that age was a single independent predictor of death following hospitalization, which is in support of reports published earlier[36,37]. As age increased, the probability of death increased (Figure 2). Mortality rate was not significantly different in IgG-N positive group *vs* negative (Figure 1A). We did not find any statistical difference with the need to use HFNC between the two groups (Figure 1B). Many of our patient population had clinically progressive diseases with worsening respiratory failure requiring BiPAP or transfer to ICU to be intubated and placed on mechanical ventilation. After following the patient pool until discharge, we did not find any significant difference with the need to use BiPAP between the two groups with and without IgG-N at the time of admission (Figure 1C). The admission rate into the ICU and need for mechanical ventilation was not statistically significant either (Figures 1D and E). Although we saw an extended LOS among the IgG-N negative group, but after adjusting for the extreme outlier, the findings were no longer significant (Figure 1F). Furthermore, median LOS was actually lower in the IgG-N negative group, showing that the extreme value was skewing the LOS average.

Our study had several limitations. We did not measure the IgG-N antibody titers in our study and so we cannot imply if high *vs* low antibody titers have any direct impact on the disease severity and mortality in COVID-19. Since every individual patient was enrolled into the study only when they were symptomatic enough to meet criteria for hospitalization, especially hypoxic with oxygen saturation < 90%, it could be argued that they may be at different stage of the diseases course and different phase of the seroconversion. This could have confounded our findings since seroconversion and viral kinetics are time dependent phenomena. We did not standardize our patients based on their underlying comorbidities, which further could have influenced our results. More investigation using a larger

sample size and different IgM/IgG subtypes is warranted to put more light in this area.

CONCLUSION

We have analyzed the presence or absence of IgG-N in patients admitted to the hospital with severe or critical COVID-19 illness and evaluated the effects of presence of IgG-N on clinical severity and outcome. Age happens to be the single independent risk factor for a worse outcome. Our analysis revealed no significant correlation between IgG-N status and degree of respiratory failure or mortality. The degree of respiratory failure was characterized by the utilization of high flow nasal canula, bilevel positive pressure ventilation and intubation with mechanical ventilation. IgG-N seroconversion had no significant effect on mean length of stay in the hospital. Further studies with large cohorts and risk-adjusted comorbidities are needed to demonstrate the more accurate role of IgG-N seroconversion on clinical outcome.

ARTICLE HIGHLIGHTS

Research background
During the peak of the coronavirus disease 2019 (COVID-19) pandemic, hospitals and clinicians had to adapt quickly to the rapid spread of the infection in the community. In the absence of adequate literature, clinicians hypothesized and studied the utility of various protein markers to prognosticate their patients. We intended to study the correlation of anti-nucleocapsid-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody (IgG-N) presence with the clinical outcome in severely ill hospitalized COVID-19 patients.

Research motivation
We were interested in characterizing a correlation between presence or absence of IgG-N and clinical outcome in hospitalized COVID-19 patients. We wanted to test the ability of IgG-N in predicting the severity of illness, maximal oxygen support needed and final outcome in order to mobilize staff, manage intensive care unit (ICU) beds and ventilators as a part of the crisis management planning.

Research objectives
To study the effect of SARS-CoV-2 anti-nucleocapsid-IgG on COVID-19 diseases severity and outcome. We studied the effect of presence or absence of IgG-N on mean length of stay in the hospital, maximal oxygen support needed and mortality.

Research methods
We conducted a retrospective cohort study on adults aged between 28-96, being admitted to the hospital with severe or critical COVID-19 illness. Blood sample was collected either at or within 48 h of admission to the hospital to check for SARS-CoV-2-IgG-N. A total of fifty nine patients were enrolled into the study. We utilized a binary logistic regression model to analyze the outcome data.

Research results
Our data demonstrated that the need for maximal oxygen support, mean length of stay in the hospital and mortality were not significantly different between the groups with or without IgG-N at the time of admission.

Research conclusions
We concluded that IgG-N seroconversion had no significant correlation with the need for maximal oxygen support as well as mortality during the course of hospitalization. Length of stay in the hospital was not significantly different across the IgG-N status.

Research perspectives
Our study demonstrated that presence of anti-nucleocapsid-IgG against SARS-CoV-2 infection had no impact on the clinical outcome or diseases severity in hospitalized COVID-19 patients. We did not find a correlation of statistical significance to use IgG-N as a biomarker to predict clinical outcome in COVID-19 patients admitted to a community hospital in North Dakota. Acknowledging the limitation of our study, we look forward to a future study with larger sample size and risk-adjusted comorbidities to investigate the association with better clarity.

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Retrospective Study

Five-year retrospective hospital-based study on epidemiological data regarding human leishmaniasis in West Kordofan state, Sudan

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Abstract

BACKGROUND

Leishmaniasis is a neglected zoonotic disease, endemic in Sudan. Estimating this disease is very important to inform the health care policymakers and the governments to apply proper health and economic policies.

AIM

To find out the frequency and distribution of human leishmaniasis based on sex and age for 5 years in the West Kordofan state, Sudan.

METHODS

A 5-year retrospective study from 2016 through 2020 was carried out using local hospital records of leishmaniasis patients. The positive results were recorded after

performing at least one of the following leishmaniasis standard tests: direct agglutination test, enzyme-linked immunosorbent assay and leishmania skin test. The sex and age of each patient were recorded. The collected data were analyzed using STATA package version 16.

RESULTS
A total of 162443 patient records from 2016 to 2020 were retrieved. Of these, 4.39% were found to be positive for leishmaniasis. The disease has been more common in males (65.3%) than in females (34.7%). The highest reported prevalence (6.58%) was in patients 15-44 years, and the lowest prevalence (1.95%) was among patients ≥ 65 years.

CONCLUSION
The results of the current study indicate that leishmaniasis is endemic in the study area even though the numbers of patients in the 5 consecutive years were varying. In addition, the disease was common in males and adults. The interpretation of these findings should take into consideration the absence of information about some important confounding factors.

Key Words: Epidemiology; Human Leishmaniasis; West Kordofan; Sudan; Endemicity

Core Tip: A 5-year retrospective study was conducted to find the frequency and distribution of human leishmaniasis in the West Kordofan state and was based on sex and age. A total of 162443 patient records were retrieved. Of these, 4.39% were found to be positive for leishmaniasis. The disease has been more common in males than in females. The highest reported prevalence was in patients 15-44 years, and the lowest prevalence was among patients ≥ 65 years. The current study indicates that leishmaniasis is endemic in the study area even though the numbers of patients in the 5 consecutive years were varying.

INTRODUCTION

Leishmaniasis is a parasitic zoonotic disease caused by the *Leishmania* parasite[1]. The disease is mainly transmitted by the bite of infected female phlebotomine sandflies[2]. The World Health Organization classified the disease as a neglected tropical disease[2,3]. There are several forms of human leishmaniasis, and the most common forms are cutaneous leishmaniasis (CL), which causes skin sores, and visceral leishmaniasis (VL), which affects several internal organs (usually the spleen, liver and bone marrow)[4]. All forms of the disease have been strongly associated with poor socioeconomic status, population displacement, a weak immune system and climate change[5-8]. Leishmaniasis cases have been reported in almost all continents in about 89 countries, with an estimated 700000 to 1 million new cases occurring annually. Most cases occur in East Africa, Southeast Asia and South America[4,9]. Outbreaks of human leishmaniasis worldwide were reported from East African countries namely Sudan, South Sudan and Ethiopia[10-15].

Sudan is a highly endemic country for leishmaniasis (both CL and VL). The disease represents a serious health problem that may affect the whole healthcare system[16]. The geographical distribution of the disease in Sudan have a high relation to the distribution of the vectors. Studies revealed that VL is endemic in the savannah area, which starts from the Gadarif state in the east to the White Nile State in the west and from the Kassala state in the northeast to the Blue Nile State in the south. Also, VL was reported in some scattered foci in the Kordofan state and Darfur state. Moreover, CL is found in a fluctuating pattern mainly in the northern, central and western parts of the country[17-26].

West Kordofan is the 18th state of Sudan. It was established in July 2013 on the border with the Republic of South Sudan in the east, North Kordofan state in the North and South Darfur state in the west. People of West Kordofan, especially the Mesairya tribe, continuously move to and from South Sudan where leishmaniasis disease is endemic[7]. The state also contains many south Sudanese refugee camps spread almost all over the state. The geographical location together with the high presence of the suspected infected refugees makes the people of the West Kordofan state very vulnerable to leishmaniasis (for both CL and VL). A community-based study in two West Kordofan cities, namely

Muglad and Babnousa, reported that out of 1781 randomly selected volunteers, 238 persons (13%) tested positive for leishmaniasis[27]. Based on that, there is still a need for a deeper look at the epidemiology of the disease in the whole state, in both males and females and in all age groups, to design and implement suitable prevention and eradication programs for the disease at the state level. Thus, this study aimed to find out the frequency and distribution of human leishmaniasis based on sex and age in the West Kordofan state for 5 years.

MATERIALS AND METHODS

The present retrospective study was conducted among patients who were admitted to any hospital in the West Kordofan state, Sudan from January 1, 2016 to December 31, 2020 to test the presence of human leishmaniasis of any type in the population of West Kordofan. In addition to the clinical symptom and signs, the positive results were recorded after performing at least one of the following leishmaniasis standard tests: direct agglutination test, enzyme-linked immunosorbent assay and leishmania skin test. Data of age, sex and presence of any type of leishmaniasis were retrieved from the medical records department in the Ministry of Health West Kordofan, with the approval of the ministry ethical committee. The medical record department follows the guidelines of the International Classification of Diseases 10 coding.

Statistical analysis

Descriptive statistics and data analysis were done using STATA package version 16 (Stata Corp LLC, College Station, TX). Z test was applied to compare the proportions between the study groups. If the *P* value was less than or equal to 0.05, it indicated that there was a significant difference between the proportions of the two groups.

RESULTS

A total of 162443 patient records (87847 female and 74596 male patients) from 2016 to 2020 were retrieved. Of these, 4.39% were found to be positive for leishmaniasis. Among them, 34.7% were females and 65.3% were males. The diagnostic prevalence of the infection was first found to be very low in 2016 (2.57%). After 1 year in 2017, the highest reported prevalence of 5.83% was observed and then started to decrease (with some fluctuation) to 3.67% in 2020 (Figure 1).

Sex-related differences in leishmaniasis prevalence are presented in Table 1. The prevalence was significantly higher ($P \leq 0.05$) in males compared to females in the period from 2017 to 2020, while in 2016 there was no significant variation between the sexes ($P > 0.05$). The prevalence of leishmaniasis was relatively increased with participant age in both females and males. The prevalence reached its peak in patients 15-44 years, which was 6.58%, then decreased to be the lowest of 1.95% among patients ≥ 65 years (Tables 2 and 3). In addition to that in all age groups, males had a higher prevalence of leishmaniasis than females.

DISCUSSION

Leishmaniasis is an endemic neglected zoonotic disease in Sudan, widespread all over the country from the eastern states to the western states and from southern states to northern states[16]. However, few data about the epidemiological and demographical distribution of the disease in western states is available, especially in West Kordofan, and it seems to be overlooked[20,24,25,27]. Thus the current study is the first comprehensive attempt to describe the epidemiological and demographical distribution of the disease in the state.

In this study, the data on human leishmaniasis was collected from the annual health statistical reports for 5 years (2016–2020) and was analyzed to show the burden of the disease in the West Kordofan state, Sudan. The results highlight that a total of 162443 people were admitted to the hospitals and health care centers in the state. Of these, 7128 people were infected during this period. In 2016 the prevalence of leishmaniasis was found to be very low at 2.57%. Surprisingly, it was raised to 5.83% in 2017, and from then it seemed to decrease. The reason could be that the government of Sudan in collaboration with the World Health Organization and other related international organizations developed diagnostic and control strategies to limit the spread of the disease in October 2014[28,29]. The first 2 years (2015 and 2016) were for training the health care professionals in the state on the new diagnostic and prevention methods. That may explain the low prevalence in the 1st study year because of the use of the low sensitivity diagnostic test. Then after implementing the new diagnostic method in 2017 the rate was raised. In line with that, after 2017 the prevalence of leishmaniasis was decreasing because of implementing the new control strategies.

Table 1 Sex distribution of different patients infected with leishmaniasis classified by year

Year	Female, *n* (%)	Male, *n* (%)	Total, *n* (%)	*P* value
2016	244 (1.85)	405 (3.37)	649 (2.57)	0.2277
2017	780 (3.99)	1322 (7.99)	2102 (5.83)	0.0002
2018	621 (3.45)	1142 (7.49)	1763 (5.30)	0.0002
2019	409 (2.36)	941 (5.83)	1350 (4.03)	0.0015
2020	420 (2.12)	844 (5.77)	1264 (3.67)	0.0008
Total	2474 (2.82)	4654 (6.24)	7128 (4.39)	0.0001

Table 2 Age and sex distribution of patients infected with leishmaniasis

Age group	Female, %	Male, %	Total, %	*P* value
< 1 yr	2.22	5.05	3.52	0.0001
1-4 yr	3.93	4.5	4.19	0.2523
5-14 yr	5.47	7.89	6.57	0.0001
15-44 yr	5.63	7.68	6.58	0.0001
45-64 yr	2.81	4.42	3.55	0.0012
≥ 65 yr	1.73	2.2	1.95	0.3452

Table 3 Comparing the sex-wise proportion of human leishmaniosis reported in each age group

Year	Sex	Age group					
	Females	< 1%	1%-4%	5%-14%	15%-44%	45%-64%	≥ 65%
2016		1.19	2.66	4.52	3.51	1.85	1.06
2017		2.16	1.80	6.00	4.97	2.47	2.01
2018		1.44	3.35	4.97	5.55	2.39	1.55
2019		3.54	3.90	5.54	6.81	2.98	1.77
2020		2.51	4.83	5.98	6.73	4.04	2.03
Total		2.22	3.93	5.47	5.63	2.81	1.73
2016	Males	0.92	3.81	6.59	5.20	2.30	1.19
2017		2.06	5.26	8.30	6.90	3.70	2.35
2018		3.26	3.69	7.64	8.50	3.81	2.08
2019		4.64	3.75	6.90	7.20	5.08	2.12
2020		14.11	5.90	9.84	10.23	6.84	3.14
Total		5.05	4.50	7.89	7.68	4.42	2.20

The current study found that the overall prevalence of leishmaniasis in West Kordofan was lower than that reported by Sharief *et al*[27] in 2019. This may be due to the difference in sample size and study period, which were bigger and longer, respectively, in the current study compared with the other study. Nevertheless, the study area could have a great impact on the result. In their study, Sharief *et al* [27] collected data in two districts in the state, but the current study collected data from all 14 districts.

Sex-related distribution of human leishmaniasis in the study revealed that males were highly affected compared to females with an overall percentage of 65.3% and 34.7%, respectively. This is in line with Awadalla *et al*[30], Ebrahim *et al*[25] and Collis *et al*[31] and disagrees with Mohammed *et al*[20]. This result might be justified because the majority of males are nomads. They are moving seasonally to the tropic and subtropic areas in South Sudan whereby the exposure to the risk of sandflies bites is high. The same exposure of males in different agricultural areas may be a contributing factor to the infections. Consequently, males are more vulnerable than females.
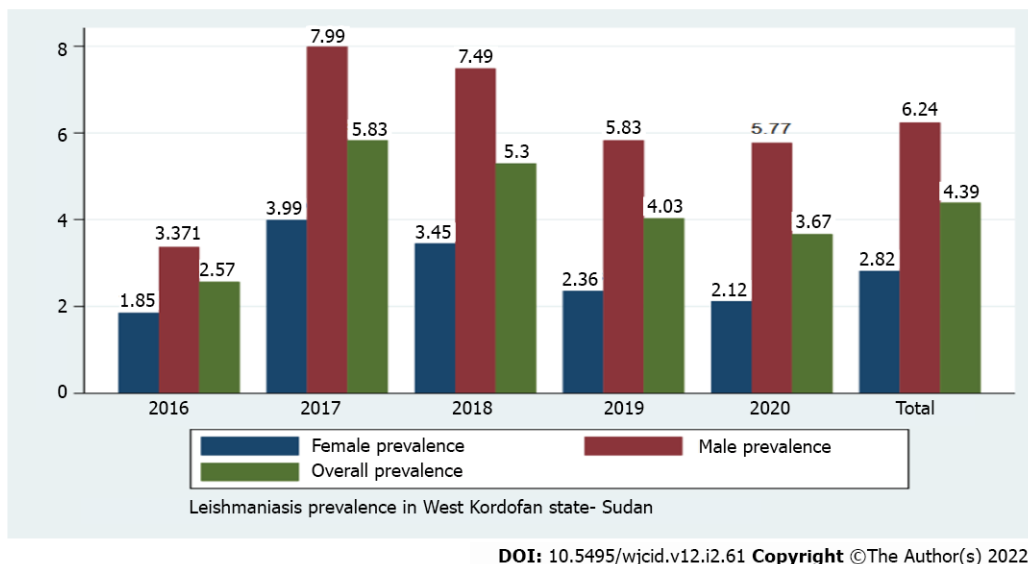
Figure 1 Prevalence of leishmaniasis during 2016-2020 according to sex.

Age-wise distribution found that people in the age group 15-44 had the highest prevalence among all populations. Similar results were reported by Awadalla *et al*[30], Osman *et al*[24], Ebrahim *et al*[25] and Collis *et al*[31]. These studies indicated that the adult men and women aged between 15-44 years were more affected by the disease compared to the lower and higher age groups. This can be put in the context that this age group is the working-age group in all fields, especially the agricultural field. In contrast, a study conducted by Mohammed *et al*[20] indicated that the most affected age groups were children between 1-year-old and 5-years-old.

In addition, the lowest reported prevalence in this study was found in the age group > 65 years. Although this group of people is more vulnerable to infections because the immune system weakens, they have a relevant low prevalence of the disease. The possible reason that these patients might have less exposure to the infection is due to their lifestyle, which keeps them away from the areas where the carrier host exists, especially in the agricultural areas.

This study provided important epidemiological information about human leishmaniasis in West Kordofan, which is missing from the scientific literature despite its urgent need to design a collaborative effort and immediate action by policymakers and governments (federal and state government) for prevention and eradication programs in light of the one health concept. However, the absence of data about the infection (type, site and status), *Leishmania* parasite and other potential risk factors in some included studies are considered as limitations of the current study.

CONCLUSION

The results of the current study indicate that leishmaniasis is endemic in the study area even though the numbers of patients in the 5 consecutive years were varying. In addition, the disease was common in males and adults. The interpretation of these findings should take into consideration the absence of information about some important confounding factors. Further studies need to be carried out to clarify the economic impact of the disease on the public health sector in the state and the role of domestic animals in the epidemiology of the disease in Sudan.

ARTICLE HIGHLIGHTS

Research background

In Sudan, human leishmaniasis is endemic, and the prevalence of the disease varies throughout the country. Although the disease in Sudan is serious, there is no overall estimation of the prevalence of human leishmaniasis in the western parts of the country, especially in the West Kordofan state.

Research motivation

The lack of published studies about human leishmaniasis in the western parts of Sudan especially in the West Kordofan state may cause a problem for the policymakers and local governments to develop and

adopt a suitable prevention program to deal with the disease at the state level and the country level.

Research objectives

The objective of this study was to find the frequency and distribution of human leishmaniasis based on sex and age in West Kordofan, Sudan for 5 years.

Research methods

A 5-year retrospective study from 2016 through 2020 was carried out using local hospital records of leishmaniasis patients. The positive results were recorded after performing at least one of the following leishmaniasis standard tests: direct agglutination test, enzyme-linked immunosorbent assay and leishmania skin test.

Research results

A total of 162443 patient records from 2016 to 2020 were retrieved. Of these, 4.39% were found to be positive for leishmaniasis. The disease has been more common in males (65.3%) than in females (34.7%). The highest reported prevalence (6.58%) was in patients 15-44 years, and the lowest prevalence (1.95%) was among patients ≥ 65 years.

Research conclusions

The results of the current study indicate that leishmaniasis is endemic in the study area even though the numbers of patients in the 5 consecutive years were varying. In addition, the disease was common in males and adults.

Research perspectives

Further studies need to be carried out to clarify the economic impact of the disease on the public health sector in the state and the role of domestic animals in the epidemiology of the disease in Sudan.

FOOTNOTES

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CASE REPORT

Incidental diagnosis of intestinal spirochetosis in a patient with chronic hepatitis B: A case report

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Abstract

BACKGROUND

Intestinal spirochetosis (IS) is caused by *Brachyspira* colonization of the gastrointestinal tract. Some patients are asymptomatic, while others present with gastrointestinal complaints such as abdominal pain, diarrhea, or gastrointestinal bleeding. However, the clinical significance of asymptomatic IS is unclear, and guidelines are lacking regarding decision to treat.

CASE SUMMARY

A 73-year-old male with peptic ulcer disease and gastroesophageal reflux was evaluated for elevated liver enzymes. He was diagnosed with chronic hepatitis B virus and prescribed entecavir. Additionally, he was leukopenic and had stage 4 liver fibrosis on transient elastography. After 5 mo, the patient returned for esophagogastroduodenoscopy and screening colonoscopy. He denied any gastrointestinal symptoms at that time. Findings included grade I distal esophageal varices, mild portal hypertensive gastropathy, and patchy nodular gastric antral mucosa. On colonoscopy, several polyps were removed. Hematoxylin and eosin stain of mucosa adjacent to the polyps revealed a "false brush border," and Steiner stain identified spirochetes adherent to the mucosa. These pathology findings confirmed the diagnosis of IS. He was managed conservatively with careful observation and without antibiotic therapy *via* a multidisciplinary approach between gastroenterology and infectious disease. He remained asymptomatic at the 7-wk follow-up.

CONCLUSION

This case reports the finding of incidental, asymptomatic IS in a leukopenic

patient with hepatitis B virus. Conservative management was appropriate.

Key Words: Intestinal spirochetosis; Hepatitis B; Colonoscopy; Histology; Leukopenia; Case report

Core Tip: Intestinal spirochetosis is caused by *Brachyspira* colonization of the gastrointestinal tract. Some patients are asymptomatic, while others present with gastrointestinal complaints such as abdominal pain, diarrhea, or gastrointestinal bleeding. However, the clinical significance of asymptomatic intestinal spirochetosis is unclear, and guidelines are lacking regarding decision to treat. We report the case of an asymptomatic 73-year-old male with chronic hepatitis B and leukopenia who was incidentally diagnosed with intestinal spirochetosis on pathology of polyps resected during routine screening colonoscopy. He was managed conservatively with careful observation and without antibiotic therapy *via* a multidisciplinary approach between gastroenterology and infectious disease.

INTRODUCTION

Intestinal spirochetosis (IS) is a condition of intestinal colonization with *Brachyspira* species, typically *Brachyspira aalborgi* or *Brachyspira pilosicoli*[1]. The prevalence of IS varies with geographic location. Estimates suggest a prevalence of 11%-64% in developing countries and 1%-5% in North America and Europe[2]. Colonization is more common in people with HIV and men who have sex with men[1]. Patients with IS are more often male, and the mean age at diagnosis is 51[3]. The mode of transmission is not clear; however colonization may result from exposure to infected water, animals, birds, or feces [4]. A literature review was performed focusing on asymptomatic or incidental IS with the following search terms: Intestinal spirochetosis, intestinal spirochaetosis, colonic spirochetosis, colonic spirochaetosis, asymptomatic, and incidental. Only reports describing adults without gastrointestinal symptoms and including decision to treat were considered. This search revealed a paucity of literature describing the clinical implications of infection or evidence-based treatment recommendations in asymptomatic patients with IS. We present the case of an asymptomatic patient with an incidental finding of IS during colonoscopy and discuss the management strategy.

CASE PRESENTATION

Chief complaints

A 73-year-old male presented to our gastroenterology practice for follow-up esophagogastroduodenoscopy (EGD) 5 mo after an initial EGD. He simultaneously underwent screening colonoscopy as his last colonoscopy was more than 10 years prior. He was feeling well and reported no gastrointestinal symptoms.

History of present illness

This patient initially underwent EGD 5 mo prior to this visit due to melena and symptomatic anemia. EGD findings were notable for Los Angeles Grade A esophagitis and a large, cratered gastric antral ulcer with pigmented spots. He was diagnosed with peptic ulcer disease and gastroesophageal reflux and was discharged on pantoprazole 40 mg twice daily. At that time, a workup for abnormal liver enzymes revealed a new diagnosis of chronic hepatitis B virus (HBV). He tested negative for HIV, and entecavir was eventually initiated. Transient elastography showed stage 4 liver fibrosis. He was also leukopenic with a white blood cell count ranging from 2700 to 3900.

History of past illness

Additional medical history was notable for hypertension. He denied previously undergoing diagnostic workup for congenital immunodeficiencies. Medications included vitamin D_3 50000 units oral daily and folic acid 1 mg oral daily.

Personal and family history
Pertinent social history included a history of military service with international travel to Guantanamo Bay, Cuba, and Greece, and remote alcohol and tobacco use. He had one tattoo that was obtained 50 years prior. He denied recent or remote history of unprotected sexual intercourse and denied history of sexually transmitted diseases. Family history was non-contributory.

Physical examination
The patient was evaluated 1 wk prior to his EGD and colonoscopy, at which time he was afebrile and mildly hypertensive to 148/80. Body mass index was 28.6. The patient's exam was benign, with a soft, non-tender, and non-distended abdomen. Bowel sounds were present and normal.

Laboratory examinations
Laboratory results are shown in Table 1. Notably, ALT was 72 and AST was 57, recorded 5 mo prior to this visit. Prothrombin time and activated partial thromboplastin time were within normal limits at that time. ALT and AST decreased to 41 and 39, respectively, 1 wk prior to this visit. Alkaline phosphatase, bilirubin, total protein, and albumin levels remained within normal limits. He was leukopenic, thrombocytopenic, and had a normocytic anemia 1 wk prior. Infectious disease workup 5 mo prior revealed a positive HBV DNA, positive HBV surface antigen, and negative HBV E Antigen. The patient was retested 1 wk prior to this visit, revealing positive HBV DNA, positive HBV total core antibody, positive HBV E antibody, and negative HBV core IgM.

Imaging examinations
EGD revealed grade I varices in the distal esophagus, irregular Z-line, mild portal hypertensive gastropathy, and patchy nodular mucosa in the gastric antrum. No ulcers were seen. Colonoscopy revealed multiple small polyps that were resected, diffuse diverticulosis, and non-bleeding hemorrhoids (Figure 1).

MICROBIOLOGICAL IDENTIFICATION
Pathology results of the resected colon polyps showed tubular adenomas, a sessile serrated lesion, and a hyperplastic polyp. Incidentally, a hematoxylin and eosin stain of the colonic mucosa adjacent to the polyps identified intestinal spirochetosis appearing as a "false brush border" (Figure 2A), with a Steiner stain confirming the presence of spirochetes (Figure 2B).

FINAL DIAGNOSIS
The final diagnosis in this case is asymptomatic IS.

TREATMENT
In this case of asymptomatic IS, the patient was managed conservatively without antibiotics.

OUTCOME AND FOLLOW-UP
The patient followed up with both gastroenterology and infectious disease specialists. He remained asymptomatic at the 7-wk follow-up, and a repeat HIV screen at that time was negative. Thus, he was not prescribed antibiotics and was closely followed for development of any gastrointestinal symptoms.

DISCUSSION
We describe an asymptomatic case of IS diagnosed *via* histology of tissue obtained during routine colonoscopy. Histologic findings in IS classically include a "brush-like" appearance of organisms oriented perpendicular to the epithelial surface of the intestine[5]. This is consistent with the findings seen on stains of our patient's colonic tissue. A large study found that 90% of IS biopsies showed no changes on histology other than the presence of spirochetes[6]. However, there have been several reports of histologic changes, notably inflammation with macrophages, neutrophils, eosinophils, and lymphoid follicles on biopsy[6-8]. Our patient represents a case of isolated IS, with identification of

Table 1 Laboratory results at 5 mo and 1 wk prior to colonoscopy

Parameter	5 mo prior	1 wk prior
ALT	72	41
AST	57	39
Alkaline phosphatase	77	88
Total bilirubin	0.9	0.5
Direct bilirubin	Not obtained	0.2
PT/INR	12.9/1.2	Not obtained
aPTT	29.1	Not obtained
Total protein	7.2	7.0
Albumin	3.7	3.8
WBC count	3.9	3.1
Hemoglobin	9.4	10.2
Hematocrit	27.3	30.6
Mean corpuscular volume	96	85
Platelet count	111	104
HBV DNA quantitative viral load	8.22 log IU/mL	8.14 log IU/mL
HBV surface antigen	Positive	Not obtained
HBV core total antibody	Not obtained	Positive
HBV core IgM antibody	Not obtained	Negative
HBV E antigen	Negative	Not obtained
HBV E antibody	Not obtained	Positive

ALT: Alanine transaminase; AST: Aspartate transaminase; PT: Prothrombin time; INR: International normalized ratio; aPTT: Activated partial thromboplastin time; WBC: White blood cell; HBV: Hepatitis B virus.
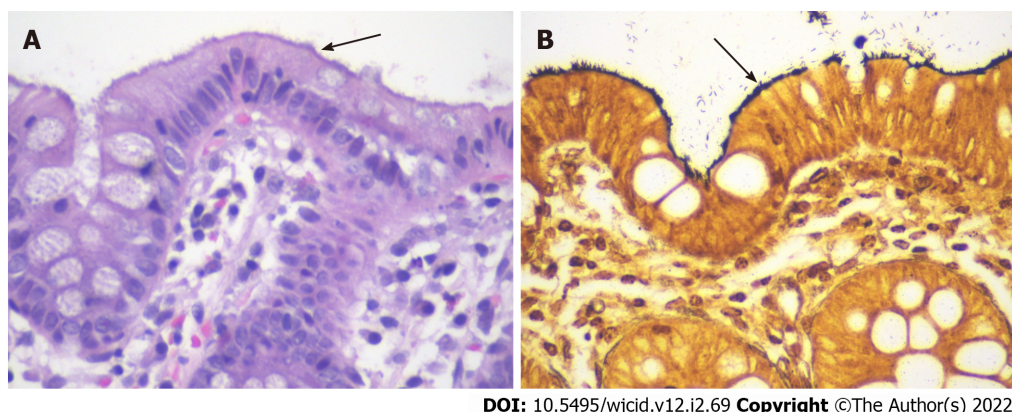

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Figure 1 Colonoscopy image of polyp in the transverse colon.

spirochetes without any changes on the cellular level.

Additionally, this report describes a case of IS associated with a hyperplastic polyp, tubular adenomas, and a sessile serrated lesion. On colonoscopy, some patients with IS have no remarkable findings, while others have had polyps, mucosal erosions, or ulcerations[5,9]. Several case reports describe findings of IS in patients with colon polyps of varying histology (including adenomatous,

Figure 2 Pathology images of samples taken during colonoscopy. A: Hematoxylin and eosin stain (× 600 magnification) showed intestinal spirochetosis appearing as a basophilic, fuzzy lining over the luminal surface of colonocytes ("false brush border"); B: Steiner stain (× 600 magnification) highlighted spirochetes overlying the luminal surface.

hyperplastic, sessile serrated lesions, and other polyps)[10-14].

IS is often an incidental finding, and its clinical implications are unclear. Several reports describe asymptomatic patients found to have spirochete colonization[11,15-18]. However, other reports have described the presence of various gastrointestinal symptoms including diarrhea, changes in bowel habits, abdominal pain, and overt or occult gastrointestinal bleeding[12,17,19-21]. A study of 209 patients with IS found 46% of patients reported abdominal pain, 51% diarrhea, and 13% alternating constipation and diarrhea[3].

Notably, IS has been frequently reported in immunocompromised patients, such as those with HIV or taking immunosuppressive drugs[22-24]. There are additional case reports of IS in patients with chronic HBV[5] and hepatitis C[8,25]. In the present case, leukopenia in the setting of chronic liver disease secondary to HBV may have played a role in the development of spirochete colonization. The origin of this patient's HBV infection is not certain. His history is notable for having one tattoo, but he denied sexual or military exposures that would otherwise suggest a source for his HBV infection.

As the clinical significance of IS is controversial, need for treatment has been debated. Recommendations from the 2021 European Academy of Dermatology and Venereology Guidelines support treatment for IS with metronidazole 500 mg twice daily or 250 mg three times daily for a 14-d course[1]. However, this recommendation does not differentiate between symptomatic and asymptomatic patients. A large study found that 40% of IS patients received treatment, and of these 86% were treated with metronidazole. However, only 52% of treated patients reported improvements in symptoms[3]. In an earlier study, 17 patients were treated with metronidazole 500 mg three times daily for 10 d, and 15 patients had resolution of symptoms[9]. Evidence is lacking for treatment guidelines in the asymptomatic population. A comprehensive literature search identified a limited number of publications reporting decision to treat in 5 cases of asymptomatic adults with IS. Of these cases, 4 patients were not treated[5,11,16,18]. The fifth patient was treated with metronidazole and experienced resolution of the IS infection[15]. Due to our patient's continued lack of symptoms, he was not treated with antibiotics and is being managed with close follow-up.

CONCLUSION

IS is a condition that has not been well-studied. Clinical implications are not clear, and thus treatment guidelines are lacking. Particularly in patients who are asymptomatic, the need for treatment is controversial. This report describes an incidental finding of IS in an asymptomatic patient with a history of HBV and leukopenia. This patient was managed without antibiotics and was followed carefully. He remained asymptomatic 7 wk after diagnosis. When evaluating immunocompromised patients, including those with HIV or viral hepatitis, one should consider the possibility of IS colonization, particularly in patients with gastrointestinal symptoms. This case highlights the feasibility and success of conservative management without use of antibiotic therapy in asymptomatic IS. Additionally, close monitoring with collaboration and shared decision-making between gastroenterologists and infectious disease specialists for asymptomatic IS was beneficial. Future research is needed to evaluate the impact of *Brachyspira* colonization of the gastrointestinal tract and to establish recommendations for treatment and follow-up, specifically in asymptomatic patients.

FOOTNOTES

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