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Acute kidney injury in patients with babesiosis: incidence, risk factors, clinical features, and outcomes

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ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**ACUTE KIDNEY INJURY IN PATIENTS WITH BABESIOSIS: INCIDENCE,
RISK FACTORS, CLINICAL FEATURES, AND OUTCOMES**

by

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B.S., University of North Carolina at Chapel Hill, 2022

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requirements for the degree of

Master of Science

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ABSTRACT

Background: Babesiosis is an emerging tickborne illness caused by the intraerythrocytic parasite, *Babesia microti*, which is endemic in the northeastern U.S. Complications have been observed in >20% of hospitalized patients, though acute kidney injury (AKI) remains poorly described, with most data derived from case reports and small case series.

Objectives: We sought to characterize the incidence, severity, clinical features, risk factors, and outcomes associated with AKI, defined as a $\geq 50\%$ increase in serum creatinine above baseline or receipt of kidney replacement therapy (KRT). We used multivariable logistic regression to identify independent risk factors for AKI.

Methods: We reviewed the records of 1317 patients at Mass General Brigham with an ICD code or positive test result for *Babesia* between 2015-2023, of whom 272 (20.7%) were hospitalized. Among those hospitalized, we collected detailed data by manual chart review on demographics, comorbidities, medications, labs, and outcomes.

Results: A total of 93 patients (34.2%) developed AKI, including 52 (55.9%), 23 (24.7%), and 18 (19.4%) with stages 1, 2, and 3, seven of whom (7.5%) received KRT. The most common etiologies of AKI were acute tubular necrosis (ATN), pre-renal azotemia, and hemolysis. Independent risk factors for AKI included older age, smoking,

higher LDH, higher parasitemia load, and hematuria. Eight of 50 patients (16%) with data available had persistent kidney dysfunction at day 90.

Conclusions: In the largest study of babesiosis-associated AKI to date, we found that more than one third of hospitalized patients with babesiosis developed AKI, nearly half of which was moderate or severe (stage 2 or 3). We identified five independent risk factors for AKI, including markers of hemolysis and severity of parasitemia.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	vii
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION	1
Transmission.....	2
Epidemiology.....	5
Clinical Manifestations	7
Diagnosis & Treatment.....	7
Acute Kidney Injury	11
Acute Tubular Necrosis	12
Pre-Renal Azotemia.....	13
Hemolysis	13
Prior Publications on Babesiosis and AKI.....	14
SPECIFIC AIMS	16
METHODS	17
Study Population and Setting.....	17
Study Outcomes	20
Data Collection	21

Statistical Analysis.....	23
RESULTS	23
Study Population.....	23
Co-morbidities	24
Admission Variables.....	25
Laboratory Values.....	27
Babesia-Induced AKI.....	29
Outcomes of Babesia-induced AKI	32
Extrarenal Outcomes.....	33
DISCUSSION	35
CONCLUSION.....	39
Future Directions	40
BIBLIOGRAPHY.....	43
CURRICULUM VITAE.....	50

LIST OF TABLES

Table 1. Staging of AKI	20
Table 2. Patient Demographics Stratified by AKI	24
Table 3. Patient Comorbidities Stratified by AKI.....	25
Table 4. Admission Variables Stratified by AKI	26
Table 5. Laboratory Values Stratified by AKI.....	28
Table 6. Tranfusion Characteristics Stratified by AKI	34
Table 7. Patient Outcomes Stratified by AKI	34

LIST OF FIGURES

Figure 1. The <i>Babesia microti</i> Life Cycle	4
Figure 2. Number of reported cases of babesiosis, by county of residence	6
Figure 3. Reported cases of babesiosis, by year, 2011-2021.....	9
Figure 4. Ixodes Scapularis reference sizing.....	9
Figure 5. Babesia Blood Smears.....	10
Figure 6. Flow Diagram for Inclusion and Exclusion Criteria.....	19
Figure 7. SOFA Score Calculation Guidelines	22
Figure 8. Maximum AKI Stage.....	31
Figure 9. AKI Etiology	31
Figure 10. Risk Factors for AKI.....	32
Figure 11. STOP-BABESIOSIS Site Progression.....	41

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
ALP	Alanine Phosphatase
ALT	Alanine Transaminase
AMS	Altered Mental Status
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Transaminase
ATN	Acute Tubular Necrosis
CDC	Center for Disease Control
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease of 2019
DAT	Direct Antiglobulin Test
DVT	Deep Venous Thrombosis
ESKD	End-Stage Kidney Disease
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
INR	International Normalized Ratio
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney Replacement Therapy
LDH	Lactate Dehydrogenase
MCV	Mean Corpuscular Volume

MGB	Mass General Brigham
MPV	Mean Platelet Volume
MRN	Medical Record Number
PCR.....	Polymerase Chain Reaction
RDW	Red Cell Distribution Width
REDCap	Research Electronic Data Capture
SCr	Serum Creatinine
SOFA	Sequential Organ Failure Assessment
UA.....	Urinalysis
wAIHA.....	Warm Autoimmune Hemolytic Anemia

INTRODUCTION

Human babesiosis is an emerging tick-borne illness caused primarily by the microscopic parasite, *Babesia microti*, which is endemic to the Northeast and Midwest regions of the United States. While the majority of cases can be attributed to the *Ixodes Scapularis* tick, infection can also take place through blood transfusions, with the FDA reporting *Babesia microti* as the most common transfusion-transmitted pathogen (Vannier, 2012; Dean, 2018). Babesiosis can also occur, though very infrequently in North America, from the *Babesia duncani* and *Babesia divergens* species.

While many believe there to be a mention of babesiosis in Exodus 9:3 alongside the plague against Pharaoh Rameses II's cattle, it is more well-established to have been first noted by a Hungarian pathologist, Viktor Babesh (Vannier, 2008). He was studying febrile hemoglobinuria in cattle and found a microorganism infecting red blood cells, which was later determined to be *Babesia* (Babes, 1888; Boustani, 1996). The first human case of babesiosis dates back to 1957 in Zagreb, Croatia. Here, the story follows a young cattle farmer working in tick-infested pastures. He was bitten and developed a fever, anemia, and hemoglobinuria. Importantly, he was asplenic, and the resulting immunocompromised state caused the Croatian cattle farmer to die of renal insufficiency just 2 weeks following his initial infection with *Babesia* (Skrabalo, 1957; Krause, 2019).

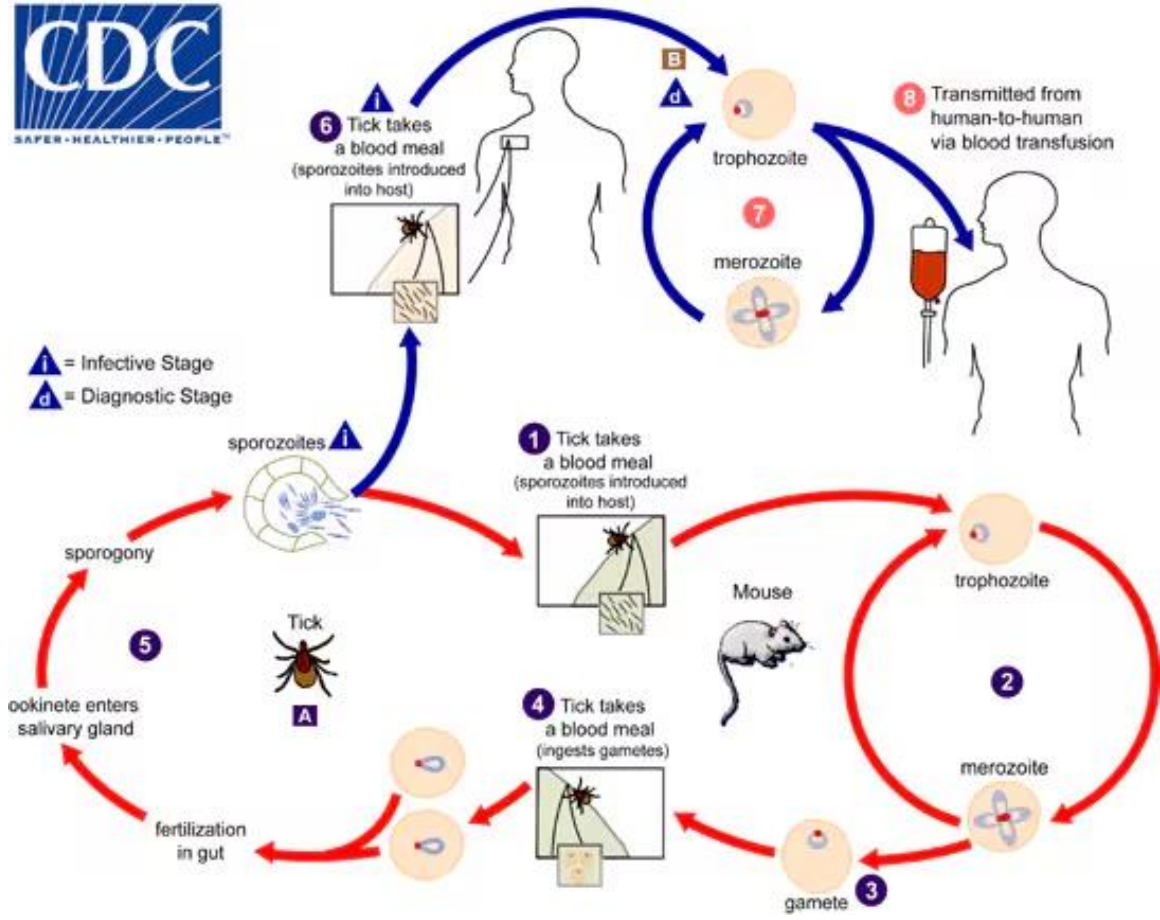
12 years later, the first case of babesiosis in a splenic patient was noted in 1969 on Nantucket Island (Massachusetts, USA). A 59-year-old female presented with persistent fever and headache. She endorsed a cramping abdominal pain, which she reported had been constant for the two weeks prior. She was found to have dry mucous membranes, but no obvious lymphadenopathy or hepatosplenomegaly. Her blood smears revealed a parasitic infection with *Babesia*. This patient's clinical workup and infectious outcome was published in NEJM in 1970 and continues to be cited in publications on the disease, prompting babesiosis to gain the clinical sobriquet of Nantucket Fever (Western, 1970).

Transmission

While human babesiosis remained undiscovered until the 1950s, the parasitic infection was found in canines more than 50 years prior. *Babesia* remains a very common tick-borne illness in canines, but the specific parasite responsible is not the same as that for humans; thus, it cannot be transmitted between the two. Regardless, canine *Babesia* has been studied for many years and animal models of human babesiosis offer insight into the immunological mechanisms that defend against and the pathways that exacerbate *Babesia* infection (Karasová, 2022; Kumar, 2023). Human *Babesia* pathogens infect red blood cells (RBCs) and induce hemolysis. Figure 1 shows the life cycle of a *Babesia*-infected tick and transmission to humans prior to multiplication, at which point clinical manifestations of the disease may occur (Vannier, 2015). The redundancy of the human immune system in the use of both innate and adaptive responses is crucial in eliminating foreign invaders such as *Babesia*. Despite the well-trained biological responses, these

microbes have evolved several mechanisms to evade immune-mediated responses and bypass circulation through the spleen, allowing for completion of their life cycle and persistent infection (Waked, 2022; Reis, 2011; Krause, 1998). For example, once parasitic invasion has taken place, the infected RBCs lack the capability to produce MHC proteins. Normally recognized by CD8⁺ and CD4⁺ T-cells, the dysfunctional cell is no longer identified for destruction. Rather, it traverses throughout the bloodstream until it reaches the spleen, the body's organ for removal of defective RBCs, which is what causes the characteristic splenomegaly in patients with an intact spleen, and the compromised states of asplenic patients (Kumar, 2021).

Figure 1. The *Babesia microti* Life Cycle



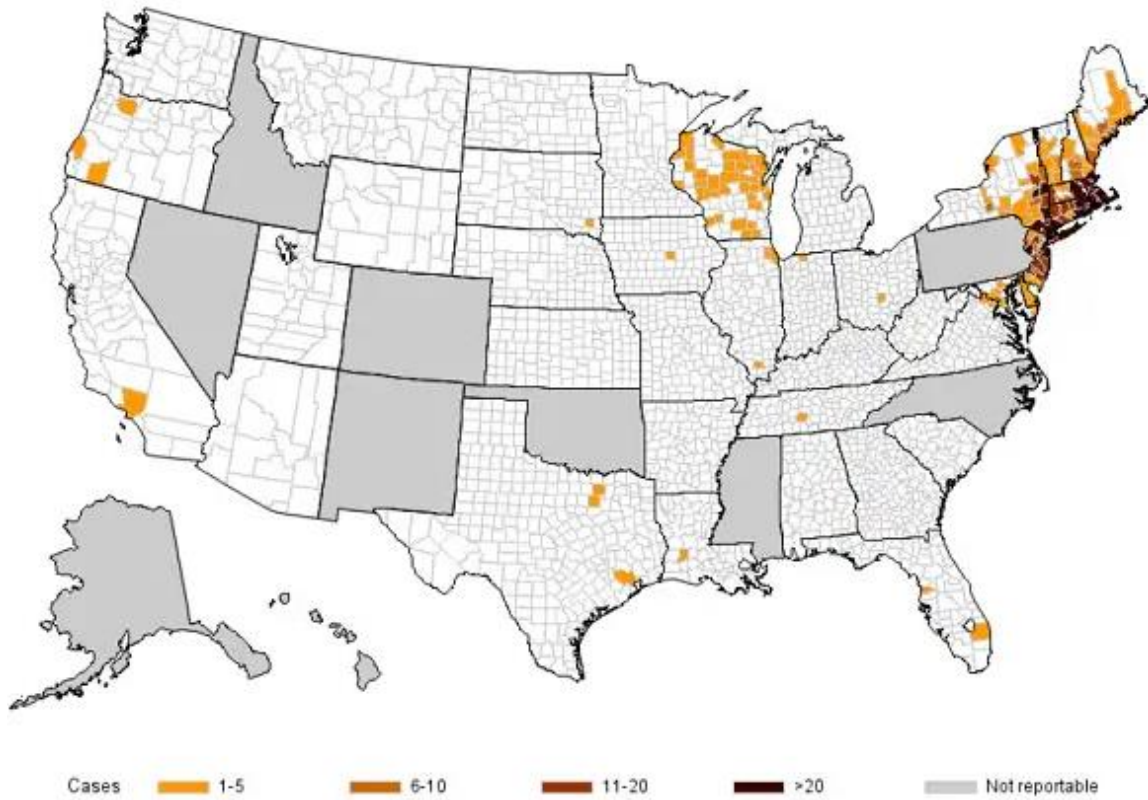
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Epidemiology

In 2011, babesiosis became a nationally notifiable disease, requiring mandatory report to the CDC, with incidence rates across the U.S. increasing each year (Figure 3; Swanson, 2023). The rise in cases of babesiosis during the last decade has been attributed to several factors, including increased recognition by physicians and patients, an increase in the deer population leading to increased transmission of *Babesia microti* by the *Ixodes scapularis* tick, and a rise in housing constructed in heavily wooded areas (Beugnet, 2015; Hahn, 2016; Bloch, 2022). However, researchers also recognize an increase in surveillance efforts, so the precise mechanism causing heightened incidence is difficult to attribute without introducing confounding variables (Eisen, 2023). Nationally, the incidence is around 1 in 100,000 people, whereas on Nantucket the incidence is over 1 in 1,000 (Telford, 2021). Between 2011 and 2019, incidence increased by 25%, totaling over 50,000 cases by 2019. That same year, the FDA required that all blood donations be screened from the 15 states where residents were thought to be at the highest risk of *Babesia* infection (Figure 2; U.S. FDA, 2019).

Babesiosis is frequently compared to Lyme Disease, due to a shared tick vector and similar epidemiological ranges. One study comparing the health burden and hospitalization costs between the two found babesiosis to have increased severity of illness, longer duration of hospitalization, and higher mortality rates when compared to Lyme Disease (Bloch, 2022).

Figure 4. Number of reported cases of babesiosis, by county of residence



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Clinical Manifestations

Higher levels of parasitemia, which measures the proportion of infected RBCs relative to the total, directly correlates to greater severity of infection and has been observed in asplenic and otherwise immunocompromised patients (Kumar, 2021). Complications have been observed in over 20% of hospitalized individuals, though acute organ injury remains poorly described, with most data coming from single-center case series consisting of no more than several dozen patients (Hatcher, 2001). Complications with babesiosis most notably include acute respiratory distress syndrome (ARDS), severe anemia, heart failure, septic shock, splenic rupture, and acute kidney injury (AKI).

Relapse is also very common, with the majority of cases occurring in immunocompromised patients, though there have been case studies published showing recurrence in healthy immunocompetent patients (Selig, 2022; Ho, 2021). In the immunocompromised cohort published by Selig et al., relapse of babesiosis was fatal in about 20% of cases, compared to less than 2% for the population at whole (Smith, 2020). Researchers believe there to be a connection between the use of antimicrobial therapy to treat *Babesia* infection and the incidence of relapsing infection, with genetic mutations in certain *Babesia* strains being responsible for antimicrobial resistance (Marcos, 2023).

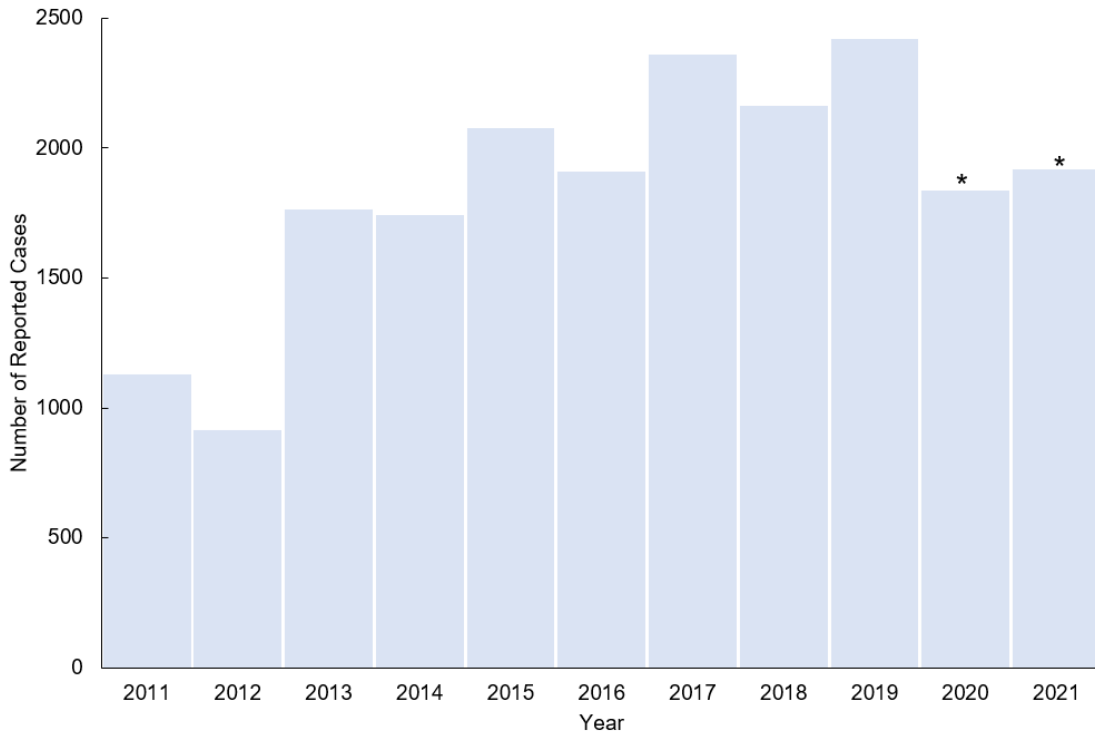
Diagnosis & Treatment

Babesiosis tends to present with nonspecific symptoms, including fever, malaise, and myalgias (Sanchez, 2016). The infecting tick, *Ixodes scapularis*, is only a few

millimeters in length, and many patients have no recollection of the bite occurring (Figure 4). As such, diagnostic confirmation is achieved with blood tests to confirm the presence of intraerythrocytic *Babesia*. A PCR test, or the recently developed reverse transcriptase PCR, which targets the 18S rRNA gene on the parasite, are strong alternatives for diagnosis. IDSA guidelines recommend confirmation with a blood smear or PCR after diagnosis of babesiosis based on epidemiological risk factors and clinical findings (Krause, 2020). Some distinguishing features of a *Babesia*-positive blood smear include tetrads and rings, which form within infected RBCs, as well as variations in cell shape, and the presence of vacuoles within the cells, each of which will flag abnormalities for pathologists reading the smear (Figure 5). A study at Westchester Medical Center found their novel PCR test to be able to detect and quantify parasitic DNA in patients who returned a negative smear test, indicating higher reliability in the latter test (Wang, 2015; Wang, 2015).

Antibody testing is commonly conducted, though it is a less reliable sign of active infection, as seropositivity can remain for over a year following initial infection. However, while less preferred for clinical diagnosis, antibody testing can prove effective for screening blood donations and for epidemiological studies to investigate prevalence and spread of the parasitic disease (Moritz, 2016).

Figure 3. Reported cases of babesiosis, by year, 2011-2021



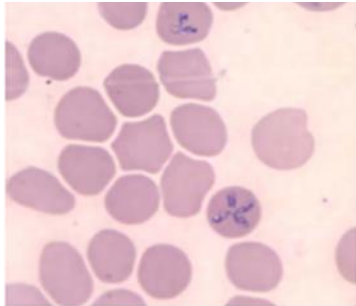
*Per CDC report, 2020 and 2021 data may differ from previous years due to the impact of COVID-19 on case identification and investigations, as well as transmission rates and isolation measures, and other changes in behavior during the pandemic period.

Figure 4. Ixodes Scapularis reference sizing

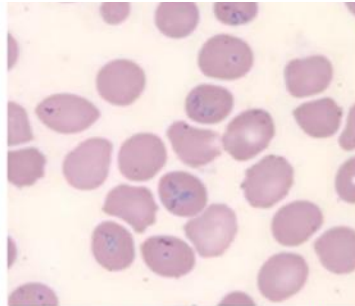


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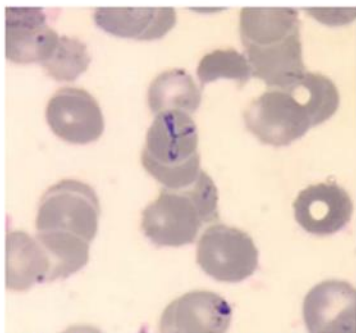
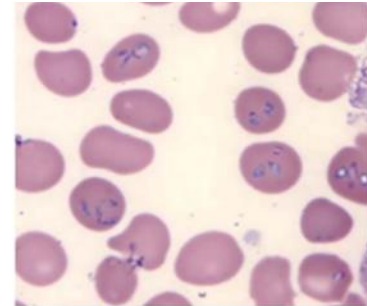
Figure 5. Babesia Blood Smears



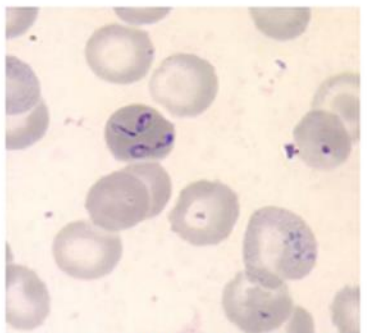
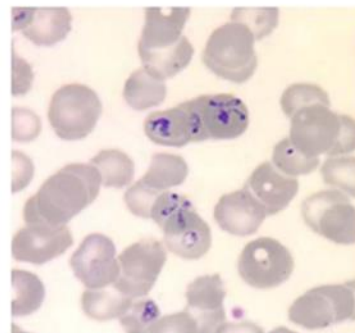
Babesia microti in a thin blood smear. Note the classic "Maltese Cross" tetrad-form in the infected rbc in the lower part of the image.



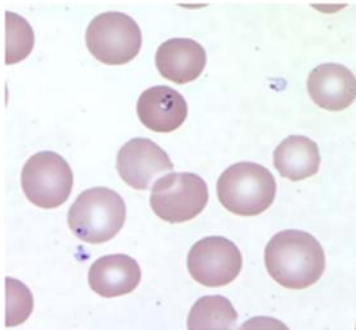
Babesia microti in thin blood smears. Notice the vacuolated and pleomorphic rings and multiply-infected rbcs. Notice also there is no pigment present in any of the parasites.



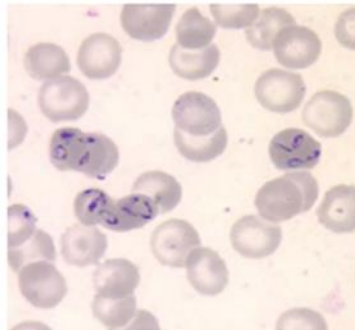
Babesia sp. in a thin blood smear stained with Giemsa, showing pleomorphic rings and tetrad forms.



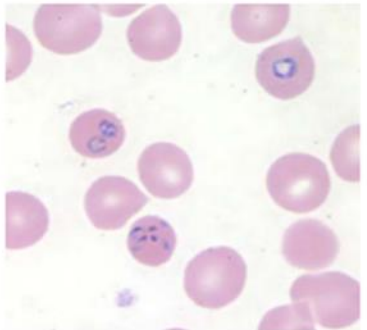
Babesia sp. in a thin blood smear. Notice the pyriform rings.



Babesia sp. in a thin blood smear. Notice two extracellular forms.



Babesia sp. in a thin blood smear, showing pleomorphic and pyriform rings and multiply-infected rbcs.



Babesia duncani (formerly WA1) in a thin blood smear. Notice the tetrad-form.

Reprinted from Laboratory Diagnosis of Babesiosis. Centers for Disease Control and Prevention, 2024. Public-use data file and documentation.

https://www.cdc.gov/dpdx/resources/pdf/benchAids/Babesia_benchaid.pdf, 2024.

Antimicrobial therapy is the treatment of choice for this disease, though the exact combination of therapies can vary depending on the severity of infection. Historically, the clinical guidelines recommended a combination of clindamycin and quinine for treatment of moderate to severe symptoms (Renard, 2021). This combination had been the standard since the successful treatment of a newborn with transfusion induced *Babesia* (Wittner, 1982), and remained that way until, in 2000, a randomized clinical trial was conducted in 58 patients with mild babesiosis on Nantucket, MA, Block Island, RI, and Southern Connecticut. Patients in this double-blind clinical trial were randomly assigned to treatment with either a combination of atovaquone and azithromycin or clindamycin and quinine. Researchers found that eradication of infection and improvement in clinical symptoms was as effective in the atovaquone and azithromycin groups when compared to the clindamycin and quinine group. Additionally, when receiving the combination of atovaquone and azithromycin, side-effects were reduced from 72% to 15% when compared to the control group of clindamycin and quinine (Krause, 2000). Thus, atovaquone and azithromycin became, and have continued to be, the gold standard treatment for babesiosis. The most recent Clinical Practice Guidelines were published in 2020 by the Infectious Diseases Society of America (IDSA) detailing the proper approach to a patient with suspected or confirmed babesiosis (Krause).

Acute Kidney Injury

Acute kidney injury (AKI) describes what happens when your kidneys are unable to properly filter your blood, thus leaving waste products to build-up. It will typically

occur as a secondary complication of another illness and can range from a transient decrease in function to a progression of chronic kidney disease (CKD). A meta-analysis of nearly 50 million cases found that, globally, AKI has a mortality rate of 20% in hospitalized patients and up to 50% in ICU patients (Susantitaphong, 2013). The complication has become increasingly prevalent, with the percentage of hospitalizations with AKI diagnoses increasing from 15.5% in 2011 to 26.8% in 2021 (Johansen, 2024). The need for continued research to identify incidence, risk factors, and complications of AKI in emerging diseases becomes increasingly evident.

Acute Tubular Necrosis

Acute Tubular Necrosis (ATN) is well-known to be the most common cause of AKI. There are many pathways that can cause ATN, including ischemia, sepsis, and use of certain nephrotoxic medications. In an analysis of renal biopsies, patients with active ATN were found to have significant necrosis of tubular epithelial cells and reduction of the apical brush border membrane present in proximal tubules when compared to control patients (Solez, 1979). Thus, these two lesions became the central players behind ATN-induced AKI. Studies in canines have shown a tendency of *Babesia* pathogens to accumulate and alter the structure and function of the renal tubules, restrict blood flow, and cause degenerative changes that can lead to necrosis of the kidneys (Máthé, 2007; Kelly, 2015).

Pre-Renal Azotemia

Parasitic infections, such as *Babesia*, signal the body's immune system to trigger an inflammatory response. In addition to the release of cytokines and inflammatory markers, this response also results in vasoconstriction of blood vessels and hypotension, resulting in hypoperfusion of organs, including the kidneys. This disruption is known as azotemia, which characterizes a build-up of nitrogenous products in the blood. Pre-renal azotemia attributes an increase in waste products to a decrease in blood reaching the kidneys, the site of normal filtration for these nitrogenous products (Tyagi, 2019). There is strong evidence that the inflammatory host response to *Babesia* is a major cause of poor kidney outcomes in Canines infected with *Babesia rossi* (Goddard, 2016). Another consequence of impaired blood transport is hypoxia, which is a well-known trigger of injury to the kidneys (see above discussion regarding ATN) (Eckardt, 2005). A study by Thai physicians in 1988 attributed AKI from malaria, another intraerythrocytic parasitic infection, to renal ischemia and intravascular hemolysis (Sitprija, 1988; Barsoum, 2013).

Hemolysis

Hemolysis can injure the kidney in major ways. Initially, the destruction of RBCs causes the release of free hemoglobin, which acts as a reactive oxygen species and accumulates in the renal tubules, leading to necrosis and subsequent injury. When the destruction of RBCs is occurring faster than the production of new RBCs, it is known as hemolytic anemia, which causes less oxygen to be carried to your tissues and organs and subsequently results in damage to the kidneys. Case studies have theorized that hemolytic

anemia make be a leading mechanism driving adverse outcomes in Babesiosis (Blum, 2011). In the case of malaria, which is a well-studied parasitic disease with pathological similarities to *Babesia*, hemolysis is known to occur directly as a result of parasite-induced destruction of RBCs. Destruction may occur as a result of RBC rupture, removal via phagocytosis, or other intracellular chemical changes (Phillips, 1992).

Prior Publications on Babesiosis and AKI

So far little has been published on the connection between babesiosis and AKI, with the majority of reports being small case studies. In 1992, a researcher in Europe conducted a cohort study in 19 patients, which, at that time, included every patient with babesiosis in Europe. He found that 16 of the 19 patients (84%) developed “renal failure”, though the exact parameters for the definition remain unclear (Brasseur, 1992). In 1998, a similar cohort study was conducted in New York with 139 hospitalized patients. This study found 6 patients (4%) who developed renal failure, which was defined as any diagnosis per chart review (White, 1998). 40% of patients in that study developed a serious complication, with the most common being congestive heart failure (CHF) and ARDS at 11% and 8% incidence, respectively. In 2001, a cohort study of 34 patients on Long Island found the incidence of renal failure to be 6%, though the paper lacked specifications regarding definition guidelines for renal failure (Hatcher). In 2021, 11 patients out of a study with 128 developed AKI requiring dialysis (Mareedu). The most recent cohort study on babesiosis in 2022 reviewed cases from 2010 through 2016, which totaled 7818 patients with *Babesia* infections, and found over 20% of the cases to

have developed acute renal failure (Bloch). Interestingly, there have not been any cohort studies published that have included patients who contracted *Babesia* more recently than 2016. Thus, while some studies have investigated the incidence of AKI-requiring dialysis, there has been no research on AKI more generally, including on its incidence and risk factors. With the exception of the study in 2022 which had 7818 patients, all prior research in the area has had very small samples sizes. In addition, that study had certain limitations, including the restrictive use of data from administrative databases and procedural billing codes, rather than detailed, granular data extracted at the patient-level from manual chart review.

SPECIFIC AIMS

The primary goal of this research is to provide a stronger understanding of *Babesia*-induced AKI. The large cohort size and detailed data being collected in this study will allow for better understanding of its incidence, risk factors, complications, treatments, and outcomes. The findings from this study will be used to supplement prior research and will be built upon in future research to improve management of the disease as it becomes an increasingly large public health threat to the Northeast and Midwest regions of the United States. In addition, this study aims to understand the mechanisms driving AKI, with particular attention paid to the hemolytic nature of the parasitic infection. We aim to produce the largest-to-date, epidemiological review of every case of babesiosis from 2015 onward admitted to our medical center using detailed data extraction, rather than billing and diagnostic codes automated from databases.

METHODS

Study Population and Setting

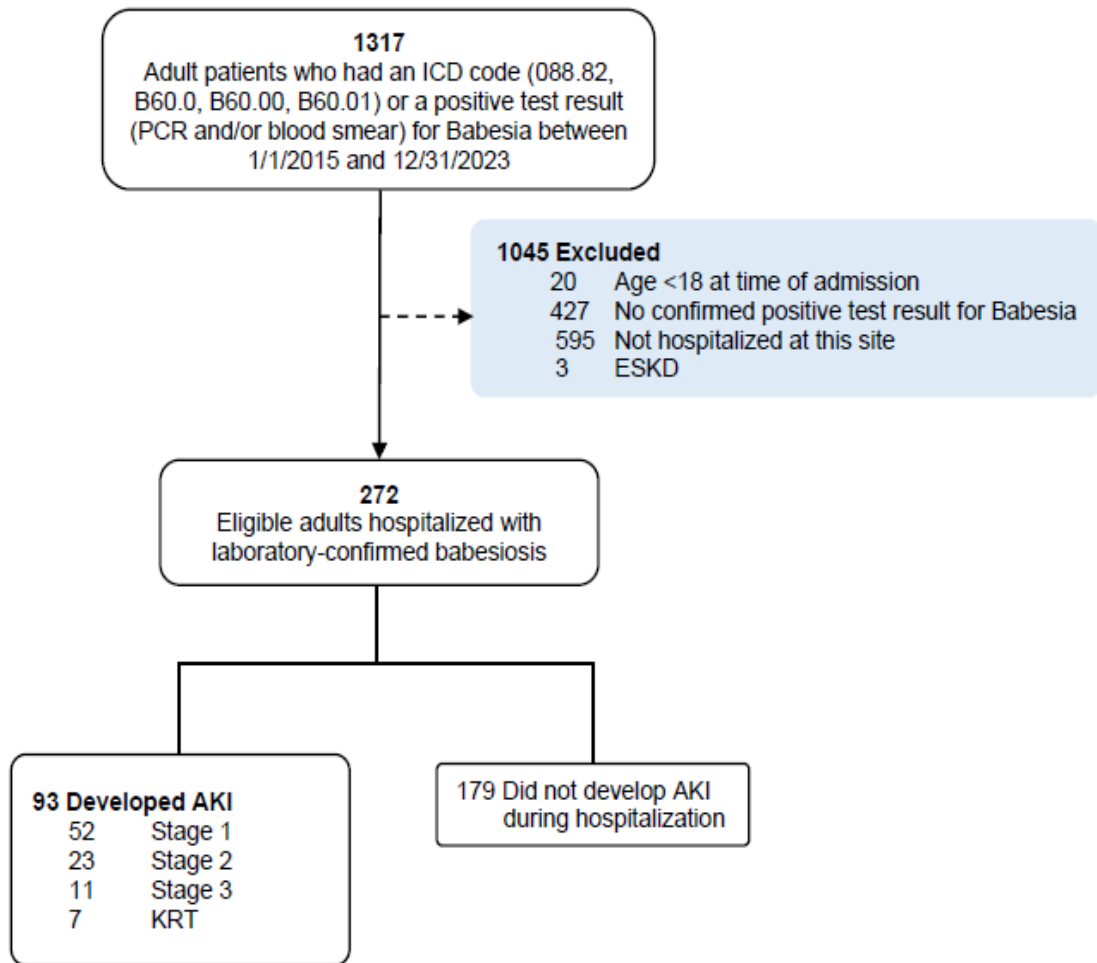
While Nantucket Island garnered the disease nickname, *Babesia* is pervasive throughout the entirety of New England. Brigham and Women's Hospital is located centrally in Boston, MA and sits only 3-miles from Massachusetts General Hospital. Together these two sites acted as the founding members of the Mass General Brigham (MGB) healthcare network, which also incorporates community hospitals in and around Massachusetts, with 9 inpatient locations within the state. Given the significant incidence of babesiosis cases in New England, we were able to garner a notable cohort of patients within the MGB system. We initially requested data on the records of every patient with either an ICD-9/10 code for babesiosis or a positive laboratory result (PCR or blood smear) for *Babesia* between January 2015 and June 2023. Given that babesiosis is known to have reoccurring infections, and that latent infections can trigger a positive result without clinical presentation, we chose to work exclusively with the initial index infection. Within these constraints, our search resulted in 1317 unique identification codes for patients whose initial encounters were at a hospital within the MGB system, each of whom was then manually chart reviewed for confirmation of meeting all eligibility criteria.

From the initial cohort of 1317 patients, 272 were included in the analyzable study cohort. Of the 1045 who did meet exclusion criteria, 20 were excluded for being

younger than 18 years old at the time of admission, 595 for a lack of admission to an MGB hospital during the index infection, and 427 were excluded for absence of a positive test result diagnosing *Babesia*. Three patients were excluded due to a past medical history of end-stage kidney disease (ESKD) at presentation (Figure 4). We further separated our cohort of 272 patients based on the development of AKI during admission, which was defined as a $\geq 50\%$ increase in serum creatinine (SCr) from a baseline value during their admission and/or receipt of KRT.

AKI staging was defined according to KDIGO consensus criteria (Khwaja, 2012) by assessing the relative difference between the highest serum creatinine (SCr) value within the first 10 days following the index admission versus the baseline SCr value. The latter was defined as the lowest SCr value within 7 to 365 prior to admission. If no baseline data were available, the trough value during hospitalization was used in its place. Stage 1 AKI was defined as a 50-99% increase in SCr. Stage 2 AKI was defined as a 100-199% increase in SCr. Stage 3 AKI was defined as $\geq 200\%$ increase in SCr, a SCr value $\geq 4\text{mg/dL}$, or receipt of kidney replacement therapy (KRT). KRT includes either continuous kidney replacement therapy (CKRT) or intermittent hemodialysis (HD).

Figure 6. Flow Diagram for Inclusion and Exclusion Criteria



From our manual chart review of each patient, we were able to record a wide range of variables, including demographics, past medical histories, comorbidities, hospital admission characteristics, treatments administered, complications, and outcomes. In addition, we extracted data on various hemolytic lab values (e.g., LDH) and longitudinal data on SCr to assess incidence and severity of AKI. All data were entered and stored in REDCap, a secure, HIPAA-compliant, web-based application. Patients were entered using a unique study identifier, with a separate password-protected key linking the study ID to the patient's name and medical record number (MRN).

Study Outcomes

The primary outcome of this study was development of AKI during hospitalization. AKI was defined using modifications of the accepted KDIGO staging guidelines (Table 1). This study sought to determine independent risk factors for AKI. As such, results are presented as stratified comparisons between two patient groups: those who developed AKI (according to the KDIGO definition) versus those who did not.

Table 1. Staging of AKI

Stage	Serum Creatinine
1	50-99% increase in SCr
2	100-199% increase in SCr
3	≥200% increase in SCr, a SCr value ≥4mg/dL, or receipt of kidney replacement therapy (KRT)

Data Collection

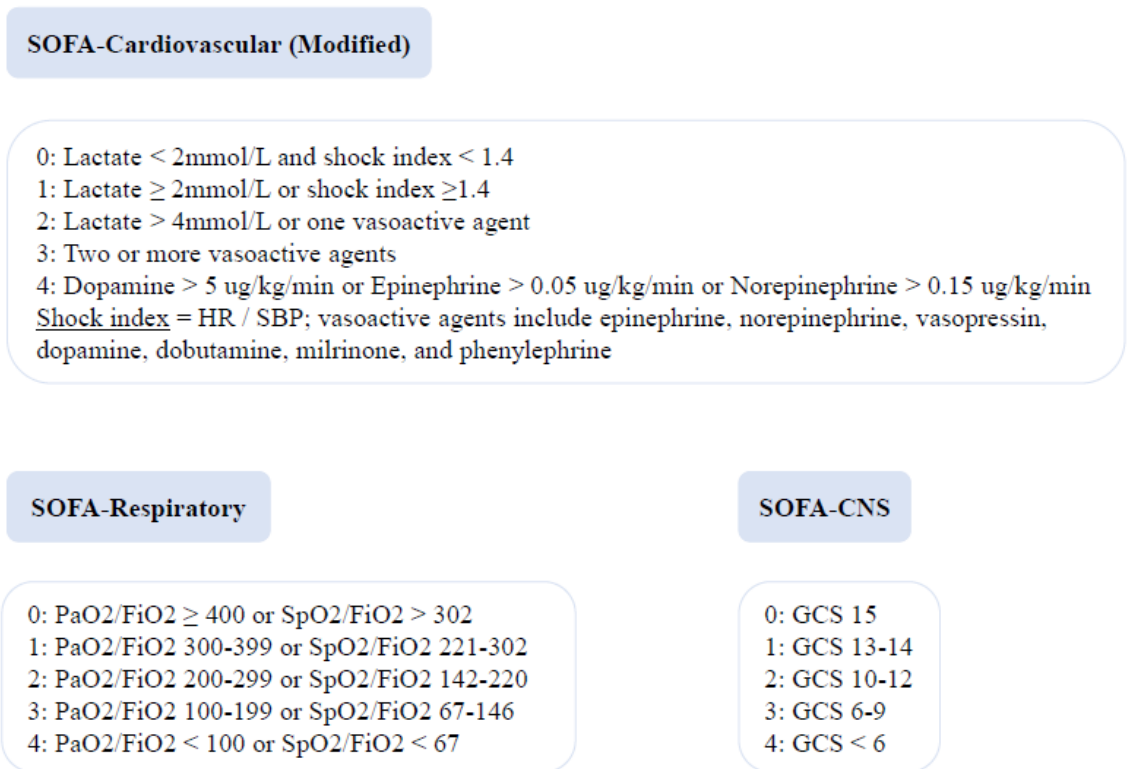
Presence of all included pre-existing conditions were recorded, as defined by diagnostic criteria and guidelines from prior publications (Waked, 2022; Spichler-Moffarah, 2022; Locke, 2023). Inclusion of prior comorbidities included atrial fibrillation, chronic liver disease, coronary artery disease, congestive heart failure, smoking status, COPD, CVA, diabetes mellitus, hypertension, PAD/PVD, recurrent infection, and asplenia (Table 2). Details were collected on immune status, active malignancy, solid organ transplant, allogenic bone marrow transplant, immunotherapy, use of immunosuppressive medications, and autoimmune disease. Preexisting conditions were determined from physician notes and documentation.

Details of hospital admission pertaining to infection with *Babesia* were also documented, which included dates of admission, laboratory results, dates of adverse events and outcomes, antimicrobial therapies, red-cell exchange, length of hospital stay, admission to the ICU, and death, including its cause(s) (Table 3).

The SOFA score is a well-validated instrument that uses various clinical data and lab results as predictive measures for mortality in critically ill patients. While this study was not limited to patients admitted to the ICU, SOFA scores were collected for each of the first 10 days following hospital admission. Variables pertaining to SOFA score were obtained from vital signs, infusion medications, oxygenation and ventilation settings, and neurological reports. SOFA values for respiratory, CNS, and CV (modified) were

collected separately using standard guidelines, whereas we collected the liver, renal, and hematologic SOFA scores by collecting the raw data from longitudinal lab values (Figure 5).

Figure 7. SOFA Score Calculation Guidelines



Statistical Analysis

Continuous and categorical data were compared using Wilcoxon rank-sum and Fisher's exact tests, respectively. Multivariable logistic regression was used to identify risk factors for AKI. For each of the multivariable analyses above, covariate selection was based on univariate associations, biologic plausibility, prior knowledge, and parsimony. Analyses were performed using SAS version 9.5 (SAS Institute), R version 3.6.3 (R Foundation), and GraphPad PRISM version 9.1.0 (GraphPad Software). All comparisons were two-tailed, with $P < 0.05$ considered significant.

RESULTS

Study Population

A total of 272 patients met eligibility criteria and were included in the study (Figure 7). Their demographics are shown in Table 2. A majority of the patients were male (68.0%), White, (85.3%), and non-Hispanic (94.5%). The median age was 68.0 years (interquartile range [IQR], 58-76 years). Patients were further analyzed according to their AKI status (presence vs. absence in the first 10 days following hospitalization). The AKI group was predominantly male (68.8%) and white (86.0%), though did have a higher number of Hispanic patients (8.6%). The non-AKI group was also predominantly male (67.6%), white (84.9%), and non-Hispanic (96.1%). There were no significant differences between groups with respect to sex, race, and ethnicity; however, there were differences in the median ages between the two groups. The median age in the AKI group

was 73.0 years (IQR, 63-79 years), while the non-AKI group had a median age of 67.0 years (IQR, 56-72 years).

Table 2. Patient Demographics Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
Demographics			
Age (yrs.) – median (IQR)	68 (58-76)	67 (56-72)	73 (63-79)
Male sex – no. (%)	185 (68.0)	121 (67.6)	64 (68.8)
White Race – no. (%)	232 (85.3)	152 (84.9)	80 (86.0)
Hispanic – no. (%)	15 (5.5)	7 (3.9)	8 (8.6)

Co-morbidities

Detailed data on pre-existing conditions was collected for all 272 patients within the study cohort. Over half of the patients, a count of 146 (53.7%), were found to have hypertension prior to their index hospitalization. 89 patients (32.7%) had a history of smoking, including both current and former use. 42 patients (15.4%) were found to have diabetes mellitus, either type 1 or type 2, and 34 (12.5%) were found to have coronary artery disease (CAD) prior to the index hospitalization. 31 patients (11.4%) had an active malignancy, defined by any treatment in the 30 days prior to date of admission. 27 patients (9.9%) had an autoimmune disease, and 21 (7.7%) were on immunosuppressive medications. Asplenia, either functional or anatomical, was present in 24 patients (8.8%).

Table 3. Patient Comorbidities Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
Comorbidities – no. (%)			
Atrial Fibrillation/Flutter	31 (11.4)	20 (11.2)	11 (11.8)
Chronic Liver Disease	7 (2.6)	3 (1.7)	4 (4.3)
Coronary Artery Disease	34 (12.5)	21 (11.7)	13 (14.0)
Congestive Heart Failure	14 (5.1)	7 (3.9)	7 (7.5)
Current or Former Smoker	89 (32.7)	50 (27.9)	39 (41.9)
COPD	15 (5.5)	7 (3.9)	8 (8.6)
Cerebral Vascular Accident	6 (2.2)	3 (1.7)	3 (3.2)
Diabetes Mellitus	42 (15.4)	27 (15.1)	15 (16.1)
Hypertension	146 (53.7)	96 (53.6)	50 (53.8)
PAD/PVD	9 (3.3)	4 (2.2)	5 (5.4)
Recurrent Infection	3 (1.1)	2 (1.1)	1 (1.1)
<i>Immune Status</i>			
Active Malignancy	31 (11.4)	16 (8.9)	15 (16.1)
Asplenia	24 (8.8)	9 (5.0)	15 (16.1)
Solid Organ Transplant	2 (0.7)	1 (0.6)	1 (1.1)
Allogenic Bone Marrow Transplant	2 (0.7)	1 (0.6)	1 (1.1)
Immunotherapy	7 (2.6)	4 (2.2)	3 (3.2)
Immunosuppressive Medications	21 (7.7)	13 (7.3)	8 (8.6)
Autoimmune Disease	27 (9.9)	16 (8.9)	11 (11.8)

Admission Variables

The frequencies of clinical symptoms, as well as other admission variables, are described in Table 4. The most common symptoms on presentation were fever and fatigue, at 68.4% and 63.2% respectively. There were 102 patients (37.5%) who reported symptoms of anorexia on arrival. Symptomatic chills were common to 95 patients (34.9%) and myalgias to 75 patients (27.6%). A total of 106 out of 272 patients (39.0%) were coinfecting with Lyme disease. Co-infection with Lyme disease required either positive IgG antibodies, positive IgM antibodies, a positive PCR result, or clinical features consistent with the infection, such as an Erythema Migrans rash. Interestingly,

there was only 1 patient who was concurrently diagnosed with COVID-19 during the index admission.

The reason for admission to the hospital was found to be overwhelmingly due to confirmed or suspected Babesiosis at 86.8%. There were 87, 22, and 13 patients who were admitted due to confirmed or suspected Lyme Disease, Anaplasmosis, and Ehrlichiosis, respectively. There were 73 patients (26.8%) who were admitted to the hospital and were incidentally found to have babesiosis. 51 patients were admitted to the ICU at some point during their hospitalization. Within this group, the reason for admission to the ICU was well-balanced between hypotension/shock (19.6%), respiratory failure (21.6%), and need for exchange transfusion (23.5%). 9 of the 10 patients who were admitted to the ICU for hypotension or shock were part of the AKI group, accounting for a 25% incidence rate within that group.

Table 4. Admission Variables Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
Admission Variables – no. (%)			
<i>Clinical Symptoms</i>			
Abdominal Pain	53 (19.5)	43 (24.0)	10 (10.8)
Altered Mental Status	23 (8.5)	10 (5.6)	13 (14.0)
Anorexia	102 (37.5)	57 (31.8)	45 (48.4)
Arthralgias	32 (11.8)	24 (13.4)	8 (8.6)
Chest Pain	9 (3.3)	6 (3.4)	3 (3.2)
Chills	95 (34.9)	64 (35.8)	31 (33.3)
Choluria	28 (10.3)	13 (7.3)	15 (16.1)
Conjunctivitis	1 (0.4)	0 (0.0)	1 (1.1)
Cough	54 (19.9)	30 (16.8)	24 (25.8)
Diarrhea	44 (16.2)	22 (12.3)	22 (23.7)

Lightheadedness/Dizziness	42 (15.4)	25 (14.0)	17 (18.3)
Emotional Lability	1 (0.4)	1 (0.6)	0 (0.0)
Erythema Migrans Rash	19 (7.0)	12 (6.7)	7 (7.5)
Fever	186 (68.4)	128 (71.5)	58 (62.4)
Fatigue	172 (63.2)	107 (59.8)	65 (69.9)
Headache	59 (21.7)	43 (24.0)	16 (17.2)
Jaundice	13 (4.8)	4 (2.2)	9 (9.7)
Myalgias	75 (27.6)	52 (29.1)	23 (24.7)
Nausea	55 (20.2)	33 (18.4)	22 (23.7)
Neck Stiffness	13 (4.8)	10 (5.6)	3 (3.2)
Shortness of Breath/Dyspnea	54 (19.9)	31 (17.3)	23 (24.7)
Sore Throat	8 (2.9)	6 (3.4)	2 (2.2)
Sweats/Diaphoresis	62 (22.8)	43 (24.0)	19 (20.4)
Vomiting	29 (10.7)	13 (7.3)	16 (17.2)
<i>Co-Infection</i>			
Lyme Disease	106 (39.0)	73 (40.8)	33 (35.5)
Ehrlichiosis	0 (0.0)	0 (0.0)	0 (0.0)
Anaplasmosis	11 (4.0)	8 (4.5)	3 (3.2)
Other Tick-Borne Disease	1 (0.4)	1 (0.6)	0 (0.0)
COVID-19	1 (0.4)	0 (0.0)	1 (1.1)
<i>Reason for Admission*</i>			
Confirmed or suspected Babesiosis	236 (86.8)	156 (87.2)	80 (86.0)
Confirmed or suspected Lyme Disease	87 (32.0)	61 (34.1)	26 (28.0)
Confirmed or suspected Anaplasmosis	22 (8.1)	12 (6.7)	10 (10.8)
Confirmed or suspected Ehrlichiosis	13 (4.8)	6 (3.4)	7 (7.5)
Other Reason	73 (26.8)	49 (27.4)	24 (25.8)
<i>Reason for ICU Admission</i>			
Respiratory Failure	11/51 (21.6)	4/7 (26.7)	7/36 (19.4)
Hypotension / Shock	10/51 (19.6)	1/15 (6.7)	9/36 (25.0)
Exchange Transfusion	12/51 (23.5)	3/15 (20.0)	9/36 (25.0)
Other	18/51 (35.3)	7/15 (46.7)	11/36 (30.6)

*Note that percentages sum over 100 because patients could have more than one reason for admission selected during data collection.

Laboratory Values

Basic lab values were compiled from each of the 272 patients within the study cohort, with the earliest available result being the recorded value. When comparing the median values for the CMP results, the AKI group had a higher potassium, lower chloride, lower bicarbonate, higher BUN, higher SCr, higher glucose, higher anion gap,

lower calcium, and higher phosphate when compared to the non-AKI group. The median values for sodium and magnesium were equal for the two. Median values for AST, total bilirubin, and direct bilirubin were higher for the AKI group than the non-AKI group, while median values for ALT, ALP, and Albumin were higher in the non-AKI groups. When looking at the median values for the CBC labs, Hgb, HCT, and PLT were all lower in the AKI group. WBC, MCV, RDW, and MPV were higher in the AKI group. The median value for parasitemia doubled from the non-AKI group to the AKI group.

Table 5. Laboratory Values Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
Admission Laboratory values – median (IQR)			
Sodium – mmol/L	133 (130-137)	133 (130-137)	133 (130-136)
Potassium – mmol/L	4.1 (3.9-4.5)	4.1 (3.9-4.3)	4.3 (3.9-4.7)
Chloride – mmol/L	98 (94-101)	98 (94-101)	97 (95-101)
Bicarbonate – mEq/L	23 (21-25)	24 (22-25)	22 (20-25)
Blood Urea Nitrogen – mmol/L	20 (15-28)	17 (14-23)	29 (21-45)
Serum Creatinine – mg/dL	1.0 (0.9-1.3)	0.9 (0.8-1.1)	1.4 (1.1-1.7)
Glucose – mg/dL	120 (106-145.3)	117 (105-140)	127 (107-147)
Anion Gap – mmol/L	12 (10-14)	12 (10-14)	13 (10-15)
Calcium – mg/dL	8.6 (8.2-8.9)	8.6 (8.2-8.9)	8.5 (8.0-8.8)
Magnesium – mg/dL	2.0 (1.8-2.2)	2.0 (1.8-2.2)	2.0 (1.8-2.2)
Phosphate – mg/dL	3.1 (2.6-3.5)	2.9 (2.5-3.4)	3.2 (2.7-4.0)
AST – U/L	58 (37-100)	53 (35-81)	88 (47-162)
ALT – U/L	45 (31-72)	46 (31-78)	43 (32-63)
ALP – U/L	85 (66-130)	85 (68-130)	81 (63-129)
Total Bilirubin – mg/dL	1.2 (0.9-1.9)	1.1 (0.8-1.7)	1.5 (1.0-2.7)
Direct Bilirubin – mg/dL	0.4 (0.2-0.6)	0.3 (0.2-0.5)	0.5 (0.3-1.0)
Albumin – g/dL	3.3 (2.8-3.6)	3.4 (3.0-3.7)	3.0 (2.5-3.4)
White Blood Cell Count – K/uL	5.3 (4.1-6.9)	4.8 (3.9-6.4)	6.2 (5.1-8.3)
Hemoglobin – g/dL	11.0 (9.3-12.5)	11.0 (9.5-12.5)	10.4 (9.0-12.5)
Hematocrit - %	32.2 (27.0-36.2)	32.5 (27.3-36.3)	31.1 (26.4-36.1)
Platelets – K/uL	80 (54-131)	81 (57-121)	75 (53-132)
MCV – fL	87.8 (84.9-91.5)	87.4 (84.8-91.2)	88.7 (86.2-92.0)
RDW - %	14.6 (13.7-15.7)	14.3 (13.5-15.2)	15.2 (14.2-16.4)
MPV – fL	11.3 (10.4-12.4)	11.0 (10.3-12.3)	12.0 (11.0-12.9)
Arterial Blood pH	7.38 (7.36-7.45)	7.44 (7.36-7.48)	7.38 (7.35-7.44)

Lactate – mmol/L	1.5 (1.0-2.0)	1.2 (1.0-1.7)	1.8 (1.4-2.6)
Haptoglobin – mg/dL	5 (0-10)	5 (0-10)	0 (0-10)
INR	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.2 (1.1-1.3)
LDH – U/L [earliest within first 2 days]	529 (373-752)	490 (367-656)	752 (419-1193)
Reticulocyte Count - %	3.3 (2.1-5.8)	2.8 (2.0-4.8)	4.3 (2.7-7.1)
Parasitemia - % [earliest within first 2 days]	1.1 (0.5-2.8)	1.0 (0.5-1.9)	2.0 (0.7-8.77)
Urine pH	5.5 (5.0-6.0)	6.0 (5.0-6.0)	5.5 (5.0-6.0)
Urine Specific Gravity	1.016 (1.011-1.023)	1.016 (1.010-1.024)	1.016 (1.012-1.021)
UA Blood – no. (%)			
None/Trace	93/242 (38.4)	67/155 (43.2)	26/86 (30.2)
1+	61/242 (25.2)	42/155 (27.1)	19/86 (22.1)
2+	45/242 (18.6)	34/155 (21.9)	11/86 (12.8)
3+	42/242 (17.4)	12/155 (7.7)	30/86 (34.9)
UA Glucose – no. (%)			
None/Trace	216/242 (89.3)	139/155 (89.7)	77/87 (88.5)
1+	8/242 (3.3)	3/155 (1.9)	5/87 (5.7)
2+	3/242 (1.2)	3/155 (1.9)	0/87 (0.0)
3+	15/242 (6.2)	10/155 (6.5)	5/87 (5.7)
UA Protein – no. (%)			
None/Trace	116/242 (47.9)	86/154 (55.8)	30/81 (37.0)
1+	71/242 (29.3)	45/154 (29.2)	26/81 (32.1)
2+	39/242 (16.1)	22/154 (14.3)	17/81 (21.0)
3+	9/242 (3.7)	1/154 (0.6)	8/81 (9.9)
UA Sediment - #RBCs/hpf	1 (1-4)	1 (1-4)	1 (1-4)
UA Sediment - #WBCs/hpf	2 (1-5)	2 (1-5)	3 (1-7)
Urine Sodium – mEq/L	23 (0-54)	21 (0-49)	36 (5-63)

Babesia-Induced AKI

We further separated our cohort of 272 patients based on the development of AKI during admission, which was defined as a $\geq 50\%$ increase in serum creatinine (SCr) from a baseline value during their admission and/or receipt of KRT. 93 patients (34.2%) developed AKI according to these definitions. Of the patients who developed AKI, 52 (55.9%) were classified into stage 1, 23 (24.7%) were stage 2, and 18 (19.4%) were stage

3, 7 of whom (7.5%) received KRT (Figure 6). The most common etiologies of AKI were ATN, pre-renal azotemia, and hemolysis (Figure 7).

Independent risk factors for AKI included older age, smoking, higher LDH, higher parasitemia load, and hematuria (Figure 8). When compared both to all patients and non-AKI patients, the AKI patient group had a significant increase in proportion of current or former smokers in the group. Smoking status was found to be one of the five independent risk factors associated with development of AKI following infection with Babesia. Altered mental status occurred in 14% of the AKI patients compared to 5.6% in non-AKI patients and 8.5% for the population as a whole. AMS as a symptom on presentation may be another risk factor associated with development of AKI. LDH was found to have an elevated increase in patients with AKI, a difference that was statistically significant, and indicated the lab result is an independent marker of AKI. Interestingly, Urinalysis (UA) Heme was found to be a strong risk factor for AKI, with a nearly 5-fold increase in the incidence of a 3+ result from 7.7% in the non-AKI group to 34.9% in the AKI group. The total population had a 17.4% incidence rate of 3+ hematuria.

Figure 8. Maximum AKI Stage

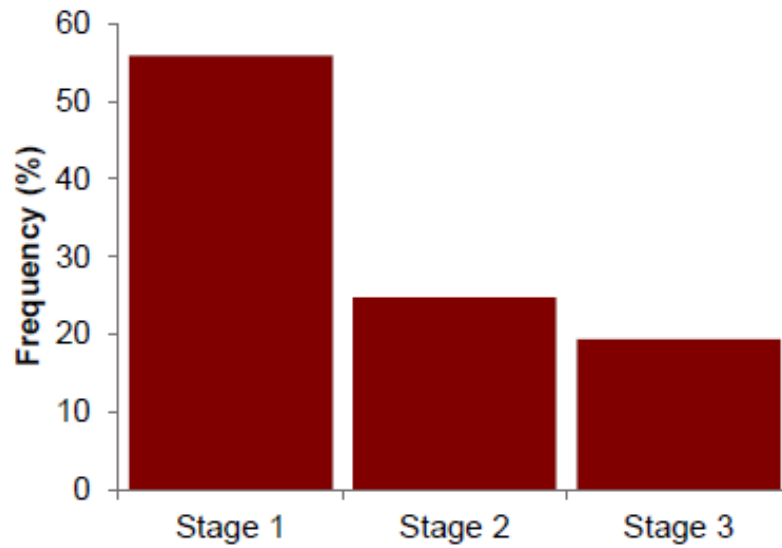


Figure 9. AKI Etiology

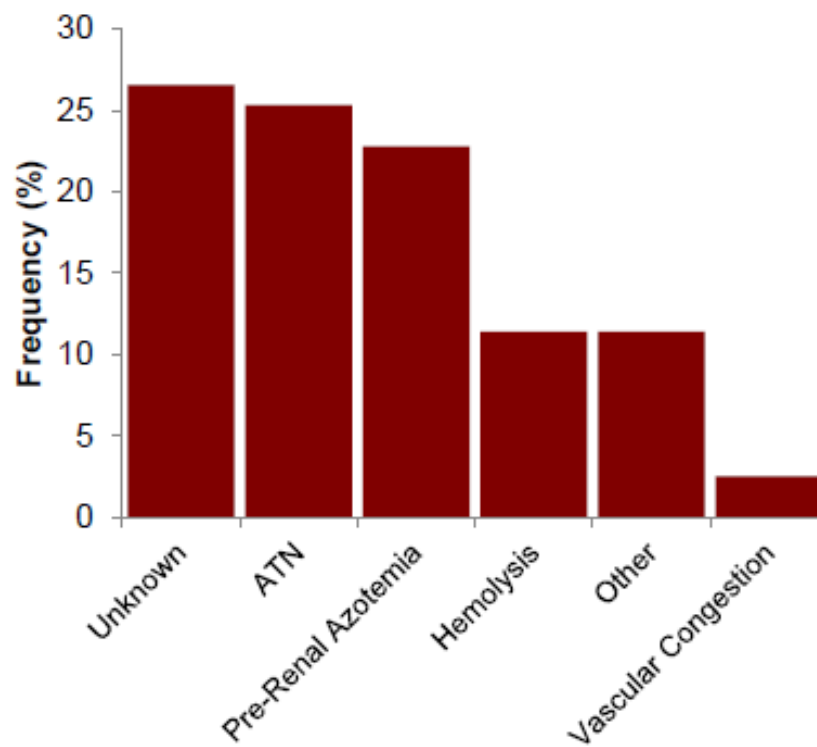
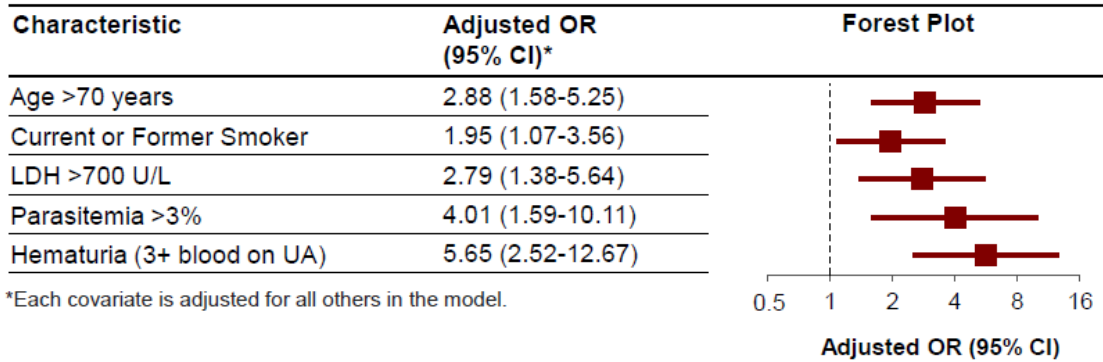


Figure 10. Risk Factors for AKI



Outcomes of Babesia-induced AKI

Eight of 50 patients (16%) with data available had persistent kidney dysfunction at day 90. Persistent kidney dysfunction was defined as SCr \geq 50% above baseline and included patients who died during their index hospitalization. We also analyzed data on readmission and relapse status, but found no significant difference in rates of incidence between the AKI group and the non-AKI group when compared to the cohort as a whole. A rare, but important, complication of babesiosis is Warm Autoimmune Hemolytic Anemia (wAIHA), which can often times be seen developing months following the initial *Babesia* infection (Woolley, 2017). As such, we collected longitudinal data on wAIHA, which was confirmed with either a C3-positive or an IgG-positive direct antiglobulin test (DAT) result, at 90-days following hospitalization.

There was a difference in the incidence of receipt simple transfusion between the AKI and non-AKI groups, with a 44.1% and 17.9% incidence, respectively. However, the median value for number of packed red blood cells (pRBCs) transfused was 2 units for all 3 sub-groups. Exchange transfusion was much more likely in the AKI group, with an incidence of 22.6% compared to 2.2% in the non-AKI group (Table 8). However, given the complexity of AKI and significant likelihood of various confounders, the treatment cannot be considered to be an independent risk factor for development of AKI. We also analyzed data on the rationale behind the need for exchange transfusion, with the most likely being parasitemia levels over 10%, presence of acute organ injury, and severe hemolysis at 68%, 64%, and 38% for each reason, respectively.

Extrarenal Outcomes

The frequencies of well-known outcomes of babesiosis were calculated for all patients (Table 6). Splenomegaly was the most common outcome, with 49 patients (18.0%) experiencing the event, confirmed by a radiologist read. The maximum length of the spleen in these cases was measured, with a median size of 15-cm. 30 patients (11.0%) developed acute liver injury, defined by an ALT value that is more than 3-fold greater than the upper-normal limit (ULN) of the reference range. Shock, defined by the receipt of vasopressors and/or inotropes, was displayed in 27 patients (9.9%). Acute cardiac injury occurred in 25 patients (9.2%), using a definition of a value for Troponin T or Troponin I that was greater than the 99th percentile of the ULN.

Table 6. Transfusion Characteristics Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
Simple Transfusion – no. (%)	73 (26.8)	32 (17.9)	41 (44.1)
pRBCs transfused – median (IQR)	2 (1-3)	2 (1-2)	2 (1-3)
Exchange Transfusion – no. (%)	25 (9.2)	4 (2.2)	21 (22.6)
<i>Reason for Exchange Transfusion – no. (%)</i>			
Parasitemia >10%	17/25 (68.0)	1/4 (25.0)	16/21 (76.2)
Severe Hemolysis	9/25 (36.0)	2/4 (50.0)	7/21 (33.3)
Acute Organ Injury	16/25 (64.0)	2/4 (50.0)	14/21 (66.7)
Other	1/25 (4.0)	0/4 (0.0)	1/21 (4.8)

Table 7. Patient Outcomes Stratified by AKI

Characteristic	All Patients (N=272)	No AKI (N=188)	AKI (N=93)
<i>Cardiovascular</i>			
Acute Decompensated Heart Failure	19 (7.0)	5 (2.8)	14 (15.1)
Acute Cardiac Injury	25 (9.2)	12 (6.7)	13 (14.0)
Atrial Fibrillation/Flutter	14 (5.1)	5 (2.8)	9 (9.7)
Shock	27 (9.9)	4 (2.2)	23 (24.7)
<i>Pulmonary</i>			
Respiratory Failure	18 (6.6)	3 (1.7)	15 (16.1)
ARDS	12 (4.4)	3 (1.7)	9 (9.7)
<i>Liver</i>			
Acute Liver Injury	30 (11.0)	11 (6.1)	19 (20.4)
Acute Liver Failure	9 (3.3)	1 (0.6)	8 (8.6)
<i>Neurologic</i>			
AMS/Encephalopathy	20 (7.4)	4 (2.2)	16 (17.2)
Ataxia/Gait Disorder	5 (1.8)	4 (2.2)	1 (1.1)
Transient Vision Impairment	1 (0.4)	0 (0.0)	1 (1.1)
Secondary Infection	18 (6.6)	7 (3.9)	11 (11.8)
<i>Heme</i>			
DIC	9 (3.3)	1 (0.6)	8 (8.6)
Warm Autoimmune Hemolytic Anemia	7 (2.6)	2 (1.1)	5 (5.4)
<i>Thrombosis</i>			
DVT	3 (1.1)	0 (0.0)	3 (3.2)
Pulmonary Embolism	1 (0.4)	0 (0.0)	1 (1.1)
Stroke	1 (0.4)	0 (0.0)	1 (1.1)
<i>Radiographic Findings</i>			
Splenic Infarct	24 (8.8)	19 (10.6)	5 (5.4)
Splenic Rupture	7 (2.6)	4 (2.2)	3 (3.2)
Splenomegaly	49 (18.0)	32 (17.9)	17 (18.3)
Splenomegaly (cm) – median (IQR)	15 (13.9-16.1)	15 (14.1-16.6)	14.5 (13.3-15.7)
Pulmonary Edema	26 (9.6)	8 (4.5)	18 (19.4)

DISCUSSION

Acute kidney injury occurred in over a third of patients who were admitted to a hospital within the Mass General Brigham system between 2015 and 2023 with a positive test result for *Babesia*. Of the 93 patients who developed AKI, 52 (55.9%) developed stage 1, 23 (24.7%) developed stage 2, and 18 (19.4%) were stage 3. Of the 18 patients who developed stage 3, 7 (7.5%) received KRT during the index hospitalization.

Our study revises prior estimates of the incidence of AKI in *Babesia* patients. For example, studies in 1998 and 2001 found incidence of *Babesia*-induced AKI to be 4% and 6% in hospitalized patients, compared with an over 8-fold and nearly 6-fold increase, respectively, in our study (White; Hatcher). Even the most recently published study, in 2022, underestimates incidence at 20% (Bloch), compared to 34.2% in our study. The variation between rates of AKI may be attributed to the use of granular data in replacement of diagnostic codes to review each patient. Similarly, previous studies on co-infection with Lyme Disease and *Babesia* found the incidence to be only 11% for patients in southern New England (Krause, 1996). Our research, which captured a similar cohort in the same location, found a 40% incidence of co-infection. While there is a 28-year difference in these two studies, and significant increased prevalence of the disease in that time, our methods allow for a more specific, accurate capture of each patient's hospital course and review of complications.

There was no association between previously known risk factors for AKI, including hypertension, diabetes, CHF, and chronic liver disease (Thongprayoon, 2020), and the development of AKI in our cohort. Rates of these preexisting conditions were consistent between the AKI group, non-AKI group, and the cohort as a whole, indicating that there was no association with these comorbidities and the development of AKI.

There were 5 characteristics associated with the index hospitalization that were found to be independent risk factors for the development of AKI following infection with *Babesia microti*. Risk of AKI increases for patients over the age of 70, patients who are active or former smokers, those with an elevated LDH (>700U/L) or elevated parasitemia (>3%), and for those with 3+ heme noted on their urinalysis.

Both age and smoking status have been well-proven to be risk factors for AKI. Prior studies found, in a study with over 25,000 patients, that nearly 70% of the patients who developed AKI were aged 55 years and older (Kane-Gill, 2015). Similarly, a study in North China determined that, for patients aged 75 and older, the risk and incidence of AKI began to increase in an age-dependent manner (Xu, 2021). Cigarette smoking has also been well-established as a risk factor for AKI, as evidenced by the ARIC study, which found a significant increase in risk of AKI for smokers when compared to non-smokers. However, this study also noted the risk of AKI decreased in the same population following smoking cessation (Chen, 2023).

Babesiosis and malaria are often compared to one another, due to the strong morphological similarities between the two parasites. Many times, due to these similarities as well as common features in symptoms and treatment protocols, the two can be confused in the literature (Clark, 1998). Research on malaria has been racing against the increasing rate of transmission to produce data on clinical features and risk factors. Several recent studies have published correlations between high levels of parasitemia in patients with malaria as a risk factor for the onset of AKI (Katsoulis, 2021; Igiraneza 2018; Sacomboio, 2020). These results are corroborated by our findings of the relation between higher parasitemia levels and development of AKI in patients with babesiosis.

We looked specifically at hemolysis as a mechanism of *Babesia*-induced AKI. Our finding of elevated LDH as an independent risk factor for the development of AKI is supported by previous studies; however, the significant result of 3+ hematuria, with a nearly 5-fold difference, is novel to our study. A 2021 publication reviewed 14 articles – four randomized clinical trials, seven cross-sectional studies, and three case-control studies – and determined that elevated LDH was a valuable indicator for acute kidney failure due to rhabdomyolysis (Heidari). Another study found elevated LDH to be almost linearly correlated to increased hospital mortality among patients with AKI (Zhang, 2021). Moreover, a reported 60% of critically ill patients admitted to the ICU develop AKI during their hospitalization, with 12% requiring RRT (Chawla, 2014). These studies corroborate our findings of elevated LDH as an important biomarker in predicting *Babesia*-induced AKI, as well as emphasize the importance of the results by quantifying

the risk of AKI in critically ill patients, as many of those with babesiosis are. Our findings of LDH, in conjunction with the significance of hematuria in our patient cohort, provide strong evidence in support of our proposed theory of hemolysis as a mechanism of *Babesia*-induced AKI.

One case study noted a patient with Babesiosis who had several signs of hemolysis, including LDH elevated to 2235 U/L, Hemoglobin of 7.2 mg/dL, decreased haptoglobin, hyperbilirubinemia, elevated reticulocyte count elevated to 8.9%, and RBC smear with a normocytic normochromic anemia. A urine dipstick test was positive for heme, but “very few RBCs” were noted on the urine sediment, findings suggestive of hemoglobinuria, and the patient developed AKI (Blum, 2011). Importantly, this case study did not note hematuria. 3+ hematuria, which we found to have a 5-fold higher incidence rate among patients with AKI when compared with those who did not develop AKI, could be the link between the hemolytic nature of *Babesia* and the development of AKI. A 2012 study reviewed the pathophysiology of hematuria-induced AKI and found an association in patients with IgA nephropathy, which may offer some appealing insight into inflammation as a trigger for hematuria resulting in AKI (Moreno).

CONCLUSION

Babesiosis continues to grow as a national epidemiological concern throughout the Northeastern U.S., prompting the need for continued progression in research on the tickborne illness to improve the understanding of and treatment for severe complications. This research is significant in providing evidence for five independent risk factors of *Babesia*-induced AKI, an area that had previously been unexplored. We found that age over 70 years old, current or former history of smoking, an LDH value above 700 U/L, a parasitemia level above 3%, and presence of large amounts of hematuria (3+) were each independently associated with a higher risk of developing AKI in those infected with *Babesia microti*. These results illustrate the high frequency of AKI as a complication of babesiosis, as is consistent with our findings that over 34% of patients in our analyzable cohort were diagnosed with AKI during the index hospitalization.

There are certain limitations inherent to this research, as is the case with any retrospective study. First, there was a significant component of missing data for some variables, for which little can be done, as laboratory tests were ordered at the discretion of the providers. We chose to include patients who were transferred to an MGB facility from an outside hospital, which prompted certain obstacles in obtaining data from those sites. Patients are sent with physical copies of their hospitalization reports when transferred, but only a portion of these notes are scanned in and available to physicians and researchers at a later point, contributing to the issue of missing data. A second

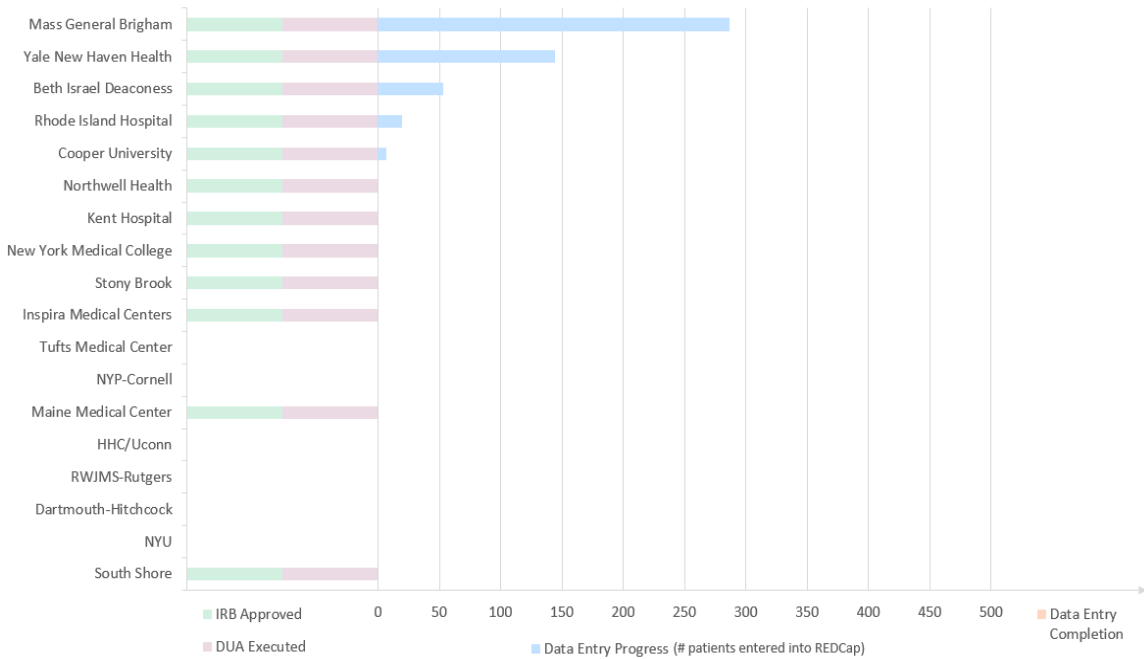
limitation appears when we consider that both Brigham and Women's Hospital and Massachusetts General Hospital, two of the largest academic centers in the Northeast, act as regional referral centers for critically ill patients throughout New England. As such, there is a lack of generalizability in our study population in the constraint of the MGB hospital system. It is possible that our study cohort included a disproportionate number of critically ill patients. Thus, the primary outcome, the incidence of AKI following Babesia infection, could have been skewed by the referral of the most acute patients to Mass General Brigham hospitals. In the same vein, the sites included in this analysis do not include community hospitals and are not based in any small, rural regions. Again, this threatens to skew the data. Additionally, our study population resulted in a disproportionate number of White, non-Hispanic patients, who do not accurately represent the demographic makeup of New England.

Future Directions

While our study cohort of 272 patients is a significant increase in sample size compared to previous studies in the area, the resulting evidence would benefit from a large sample size inclusive of hospitals outside of the MGB system. Future research should broaden primary outcomes to include all disciplines of medicine and provide a larger and more geographically diverse study cohort. As such, our team has grown this project into a large multicenter consortium, with 18 major medical centers contributing detailed data on >2,000 adults hospitalized with babesiosis (Figure 9). With the inclusion of locations outside of Massachusetts, we plan to conduct the largest and most

comprehensive study on babesiosis to date, with patients admitted between 2010 and 2023 included in our analyzable cohort and broadening our interests outside of acute kidney injury to investigate all outcomes of babesiosis. We already have 12 sites who have IRB approval and fully executed DUA agreements, of which 5 have already begun data entry. We hope to have all data entry from all sites completed by the Fall of 2024, so that we can analyze and publish the results quickly.

Figure 11. STOP-BABESIOSIS Site Progression



This research will be paramount in uncovering the risk factors and outcomes of babesiosis and providing conclusive evidence on the tickborne disease, with hopes of bringing attention to this area of research. Further studies that validate experimental knowledge are needed to produce indisputable links between onset of babesiosis and various complications and outcomes of the disease. Additionally, prospective studies that explore longitudinal outcomes of patients would be a novel area of study that would allow for continued research on suspected risk factors related to *Babesia*-induced AKI. An ideal resolution to this project, though much research is likely needed prior to onset of this advancement, would be the realization of a potential mechanism for the development of a vaccination against *Babesia microti* and other sub-species of the tickborne disease.

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CURRICULUM VITAE

