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Pyomyositis in the United States 2002–2014

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SUMMARY

Objectives: Primary pyomyositis is a bacterial infection of skeletal muscle first recognized in tropical regions of the world but needing characterization in temperate climates.
Methods: This population-based study used the Healthcare Utilization Project/Nationwide Inpatient Sample database to characterize the trends of pyomyositis admissions in the United States from 2002–2014 using ICD-9 diagnostic codes.
Results: We found a concerning more than three-fold increase in the incident pyomyositis admissions over our study period. The median length of stay was over twice as long compared to other hospitalized patients. Patients with pyomyositis were younger and more likely to be male and Black. There were more cases in the West and South compared to Midwest and Northeast. Age-adjusted odds ratios revealed significant association of pyomyositis with HIV, types 1 and 2 diabetes mellitus, hematologic malignancy, organ transplant, malnutrition, chronic kidney disease, obesity, and rheumatoid arthritis. The most commonly identified bacterial diagnosis was *Staphylococcus aureus*. *Pseudomonas* species were the most commonly identified gram-negative bacteria.
Conclusion: This nationwide review of pyomyositis in the United States suggests a concerning increase in incidence and provides information on the trends, demographics, risk factors, and causative organisms for pyomyositis in the United States.

Introduction

Primary or tropical pyomyositis is a bacterial infection of skeletal muscle that arises from hematogenous seeding rather than from contiguous infection of an adjacent site. It can lead to abscess formation, sepsis, and other infectious complications if not adequately treated [1]. Pyomyositis was first recognized in tropical regions of the world in otherwise healthy young men following physical exertion or non-penetrating trauma [2–4]. Primary pyomyositis must be suspected clinically based on history and physical examination suggesting muscle inflammation and symptoms of infection. Magnetic resonance imaging (MRI) is considered the most sensitive and specific imaging modality, but computed tomography (CT) can be used for speed and cost and ultrasound may be preferred for cost, lack of radiation, and portability [5–13]. Pyomyositis can be managed conservatively with intravenous antibiotics but may require surgical or radiological guided drainage of muscle abscess [14,15]. *Staphylococcus aureus* causes the majority of pyomyositis cases, at least 75% in both temperate and tropical areas in prior reported series [1,16]. There is paucity of data of the epidemiology and characteristics of primary pyomyositis outside the tropics.

Data about primary pyomyositis in the United States is limited to case reports and small studies, but these prior studies suggest that the incidence of pyomyositis is increasing in the United States [1,17]. This study was designed to provide more information about the trends, causes, and potential risk factors of pyomyositis throughout the United States.

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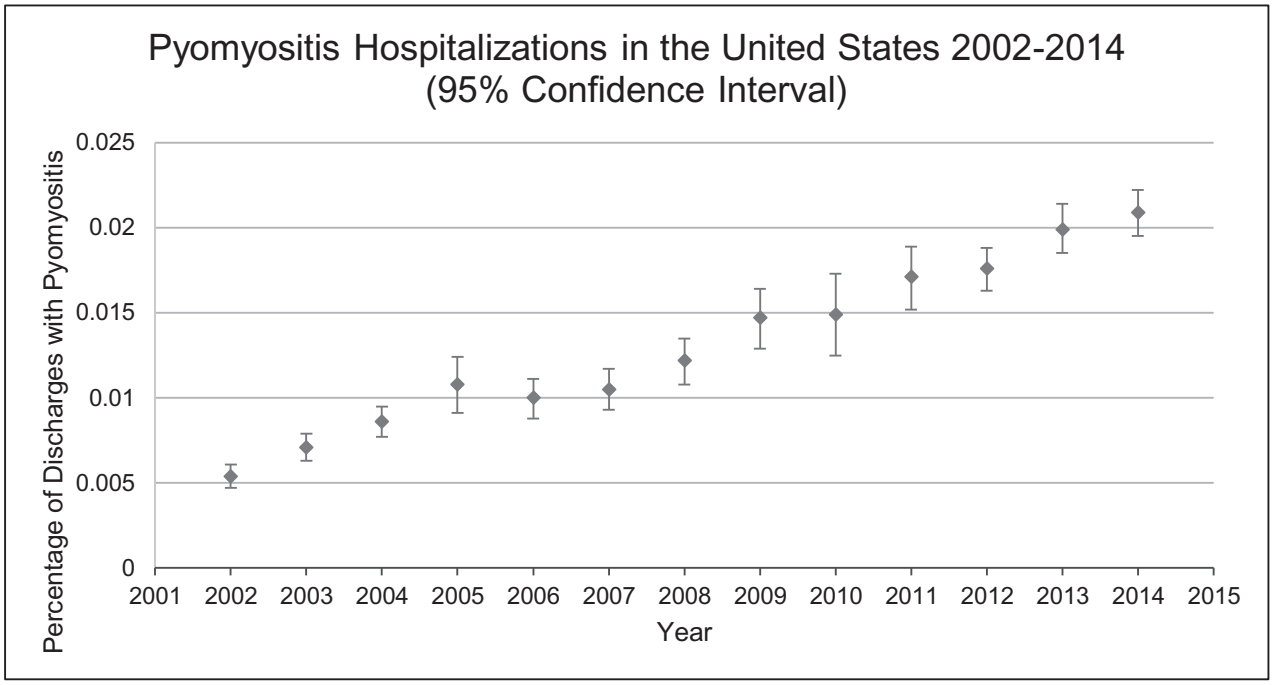


Fig. 1. Pyomyositis cases in the United States 2002–2014 by percentage of all hospital discharges.

Methods

This population-based study used the Healthcare Utilization Projects/Nationwide Inpatient Sample (HCUPS-NIS) database from 2002–2014 to describe the trends over time and region, demographics, candidate risk factors, and associated bacteria of primary pyomyositis in the United States. The National Inpatient Sample contains discharge data from the HCUP Data Partners [18] and is designed to represent hospital admissions and discharges at a national level using random sampling of hospital discharges stratified by US census region, urban or rural location, teaching status, ownership, and bed size. The data collected includes demographic information and diagnostic and procedural codes that were recorded during the patient's hospital stay. Our study was granted an exemption by our institutional review board as the database precludes any identifiable data by not reporting any results with less than 10 individuals.

We systematically searched all available ICD-9 codes for inclusion and exclusion criteria to identify cases of pyomyositis. Specifically, we designated infective myositis (7280) and tropical pyomyositis (04,081) as inclusion criteria, and designated progressive myositis ossificans (72,811) and traumatic myositis ossificans (72,812) as exclusion criteria. This established our group of pyomyositis cases to be compared to the remaining hospital discharge population. Subsequent analysis revealed that there was trivial overlap between diagnosed cases of pyomyositis and our exclusion criteria, so the exclusion did not significantly affect our results.

We compiled lists of codes for expected co-occurrences, risk factors, and specific bacterial diagnoses by searching the entire group of ICD-9 codes for key words and homonyms. Each specific association of interest was compiled into a single composite variable that represented multiple ICD-9 codes. Potential risk factors were chosen based on existing pyomyositis literature as well as our institutional experience. The complete list of codes analyzed under each group is available in supplementary data.

Demographic information from the group with pyomyositis was compared to patients in the database without pyomyositis. The frequency of candidate risk factors in patients with pyomyositis was compared to patients in the general hospital population both by comparing confidence intervals of the percentages and by using the data to generate odds ratios. Odds ratios for the co-occurrences were calculated while controlling for age to avoid confounding.

Categorical patient variables are reported as frequency in percent, and continuous patient variables are reported as mean with standard deviation and 95% confidence intervals or median with interquartile range (IQR) for skewed data. All frequencies reported are weighted frequencies, and all analyses were completed using weighted estimates in accordance with the NIS sampling methodology. SAS Studio was utilized for analysis.

Results

The database included a total of 100,790,900 discharges accounting for 482,872,274 weighted discharges with 13,011 pyomyositis cases accounting for 62,657 weighted cases over the study period from 2002–2014. The proportion of discharges with pyomyositis has steadily risen from 0.0054% (95% CI 0.0047, 0.0061) in 2002 to 0.0209% (95% CI 0.0195, 0.0222) in 2014. This trend is visible in Fig. 1 and represents over a three-fold increase in the hospitalizations for pyomyositis in the United States. Because pyomyositis is an acute rather than chronic condition and nearly universally requires hospital admission, it can be assumed that the number of hospital discharges with pyomyositis approximately estimates the incidence. The increasing trend was consistent across all regions of the country with slightly higher incidence in the South and West.

Less than 2% of the patients identified with pyomyositis had an open wound or traumatic amputation, suggesting that these potential causes of secondary pyomyositis were rare. Of the cases of pyomyositis, 16.67% also had osteomyelitis, 8.80% had septic arthritis, 1.51% had an open wound, and 0.162% had a traumatic amputation. Osteomyelitis and septic arthritis may either cause secondary pyomyositis or be a complication of primary pyomyositis, limiting our classification of primary or secondary in those patients. Over 80% of patients identified with pyomyositis did not have a diag-

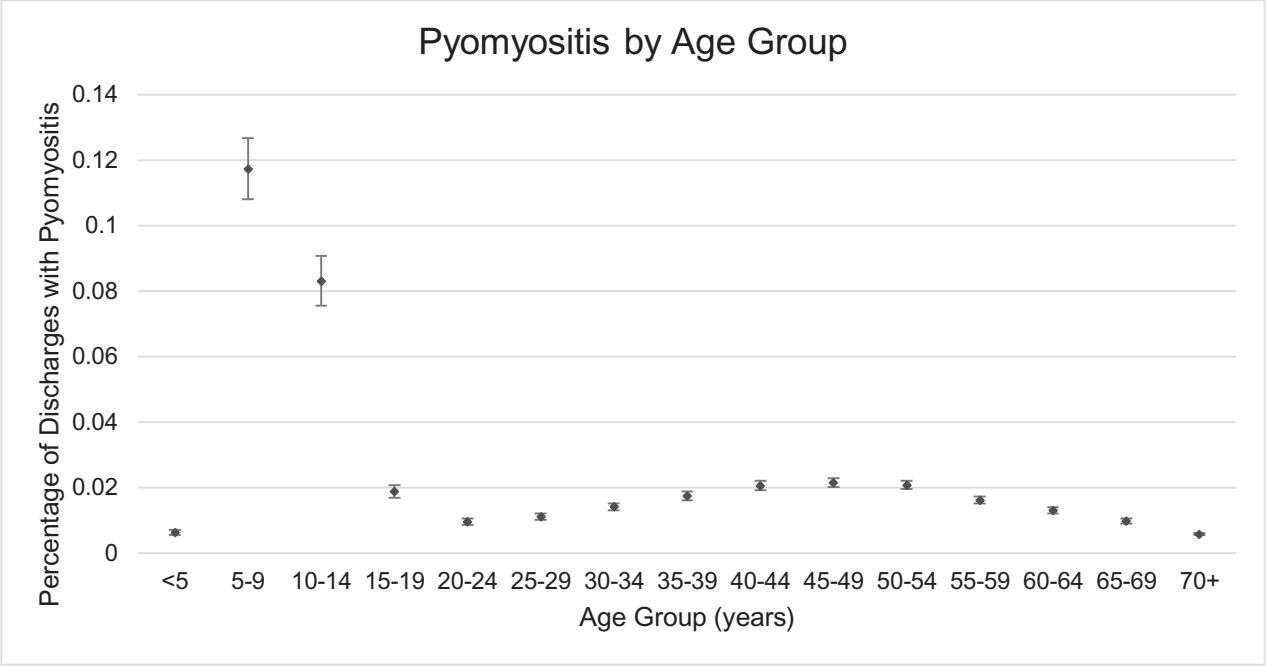


Fig. 2. Pyomyositis incidence by age as percentage of hospital discharges for each age group.

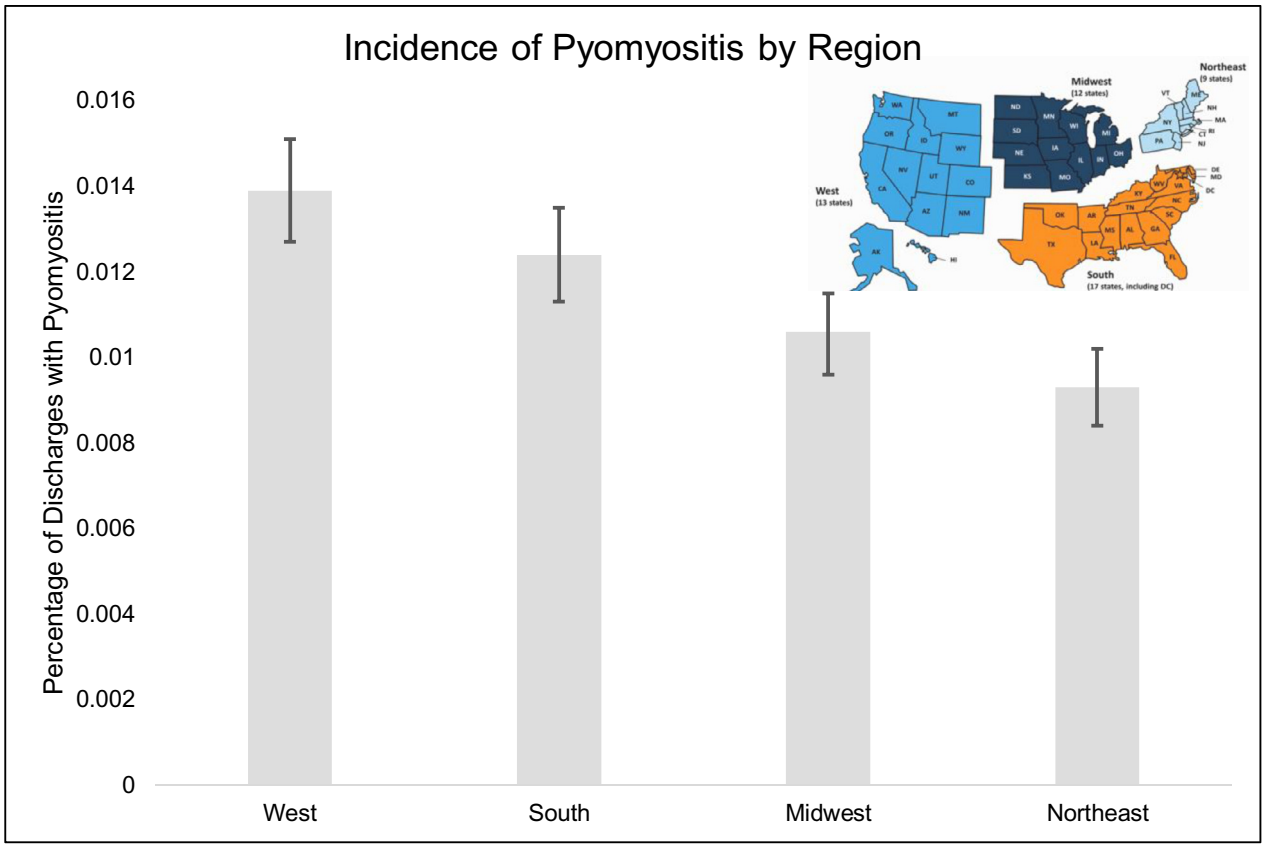


Fig. 3. Pyomyositis cases by region of the country as percentage of all hospital discharges.

nostic code for any of the above additional infections, suggesting that most of our sample represents primary pyomyositis. Nearly half (49.9%) of patients with pyomyositis also carried a diagnosis of muscle abscess, and 31% carried a diagnosis of bacteremia and/or septicemia.

The demographic information collected about the patients with pyomyositis included hospital length of stay, death during hospitalization, gender, race, income quartile, and insurance payer. Patients with pyomyositis had a significantly longer length of stay compared to patients without pyomyositis, 6.7 days (IQR 3.5, 12.2)

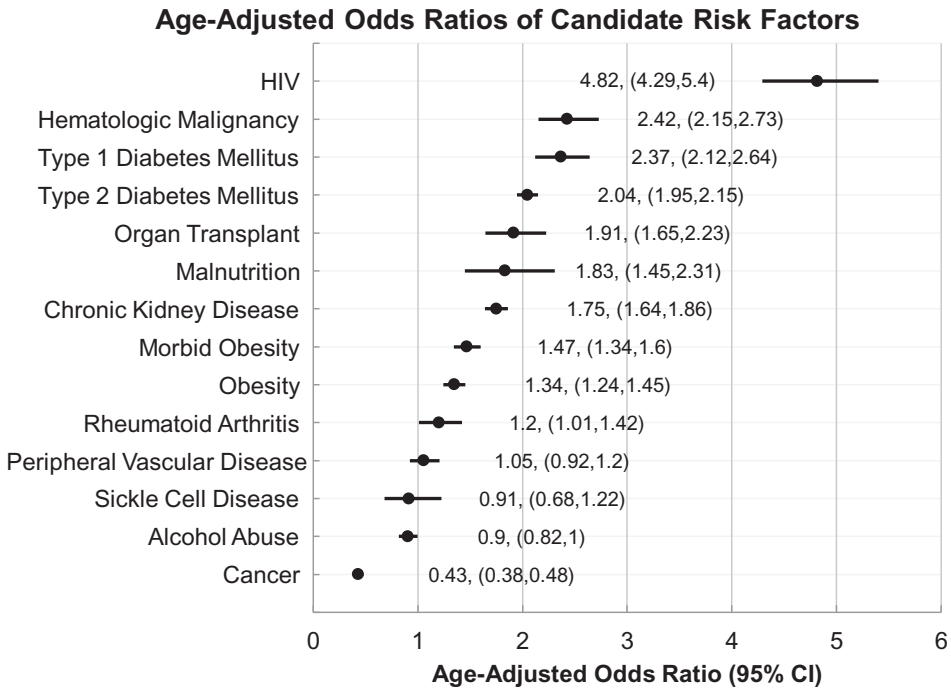


Fig. 4. Age-adjusted odds ratios of candidate risk factors for pyomyositis in the United States.

compared to 2.4 (IQR 1.3, 4.5). The proportion of primary pyomyositis cases that resulted in death during hospitalization is 1.82% (95% CI 1.59, 2.05) compared to 2.02% mortality in patients without pyomyositis. Most patients with primary pyomyositis were male at 63.16%, compared to 41.63% of patients discharged without pyomyositis. Reported race reveals that Black patients were somewhat overrepresented among the group with pyomyositis compared to White patients, but there were no other statistically significant racial differences. The primary pyomyositis weighted discharges is made up of 60.4% White patients (compared to 66.3% of patients without pyomyositis), 19.3% Black patients (compared to 14.3% of patients without pyomyositis), 13.5% Hispanic patients, 2.48% Asian or Pacific Islander, 0.94% Native American, and 3.41% other. Patients with pyomyositis were more likely to be in the lowest income quartile compared to all hospitalized patients, 30.8% compared to 29.0%. Expected primary payer of pyomyositis cases was 25% Medicare compared to 37% of all hospitalized patients, 24% Medicaid compared to 20%, 36% private insurance compared to 34%, 9% self-pay compared to 5%, 1% no charge compared to 0.5%, and 5% other compared to 3%.

The age of pyomyositis patients was significantly younger than that of the general hospitalized population. The median age of those with primary pyomyositis during the study period is 44 (IQR 21, 58) compared to those without primary pyomyositis, 52 (IQR 26, 71). The distribution of ages of cases of pyomyositis as a percentage of hospital discharges was bimodal with a peak incidence in the 5 to 9-year-old age group and another smaller peak in the fifth decade of life (Fig. 2).

Our study examined trends by region of the country as divided by the NIS-HCUPS database and month of the year. The trend for increasing incidence was observed in all regions of the country. There was a significantly higher incidence in the West and Southeast compared to the Northeast and Midwest (Fig. 3). The differences by month were not statistically significant.

The frequency of observing candidate risk factors in patients with pyomyositis was compared to the total hospital discharge population, and age-adjusted odds ratios were calculated to determine the strength of association. When controlling for age, significant odds ratios (95% confidence interval) were observed for the following risk factors, indicating a significant association with pyomyositis: HIV (OR 4.8; 95% CI 4.3, 5.4), type 1 diabetes mellitus (OR 2.4; 95% CI 2.1, 2.6), hematologic malignancy (OR 2.4; 95% CI 2.1, 2.7), type 2 diabetes mellitus (OR 2.0; 95% CI 1.9, 2.1), organ transplant (OR 1.9; 95% CI 1.6, 2.2), malnutrition (OR 1.8; 95% CI 1.4, 2.3), chronic kidney disease (OR 1.7; 95% CI 1.6, 1.9), morbid obesity (OR 1.5; 95% CI 1.3, 1.6), rheumatoid arthritis (OR 1.197, 95% CI 1.008, 1.422), and obesity (OR 1.3; 95% CI 1.2, 1.5). Sickle cell disease and peripheral vascular disease were not significantly associated with pyomyositis. Indications of a solid tumor malignancy and alcohol abuse were associated with a lower likelihood of pyomyositis. See the age-adjusted odds ratios in **Fig. 4**.

The database was able to reveal if a patient had a specific microbiological diagnosis for the hospital stay in which they were treated for pyomyositis, based on ICD-9 codes. At least one bacterial diagnosis was identified in 46% of patients hospitalized for pyomyositis, and it is likely that this often represents the causative pathogen. The total number of identified bacterial diagnoses adds up to a total of 51%, indicating that approximately 5% of the identified bacterial diagnoses were likely multiple bacterial diagnoses in a single patient. The most commonly identified pathogen was methicillin-sensitive *Staphylococcus aureus* (MSSA), identified in 46% of patients with pyomyositis in whom a bacterial association was observed. The next most frequent bacterial diagnoses were methicillin-resistant *Staphylococcus aureus* (MRSA) at 20% of those with bacterial association, streptococcal species 11%, *Group A streptococcus* 4.8%, *Group B streptococcus* 3.6%, *Pseudomonas species* 3.6%, enterococcus 2.7%, and *Escherichia coli* 2.7%. Associations with *Haemophilus influenzae*, mycobacterial species, *Serratia* species, and *Clostridium* species were very rare and there is no guarantee of causality. There were no observed associations with *Bacteroides* species, understanding that there must be at least 10 instances to be reportable by the database. Bacterial diagnoses that account for at least 1% of all bacterial co-occurrences can be seen in **Fig. 5**.

We additionally analyzed bacterial diagnoses in the subsets of patients with pyomyositis and HIV as well as pyomyositis and hematologic malignancy. *Staphylococcus aureus* was still the most

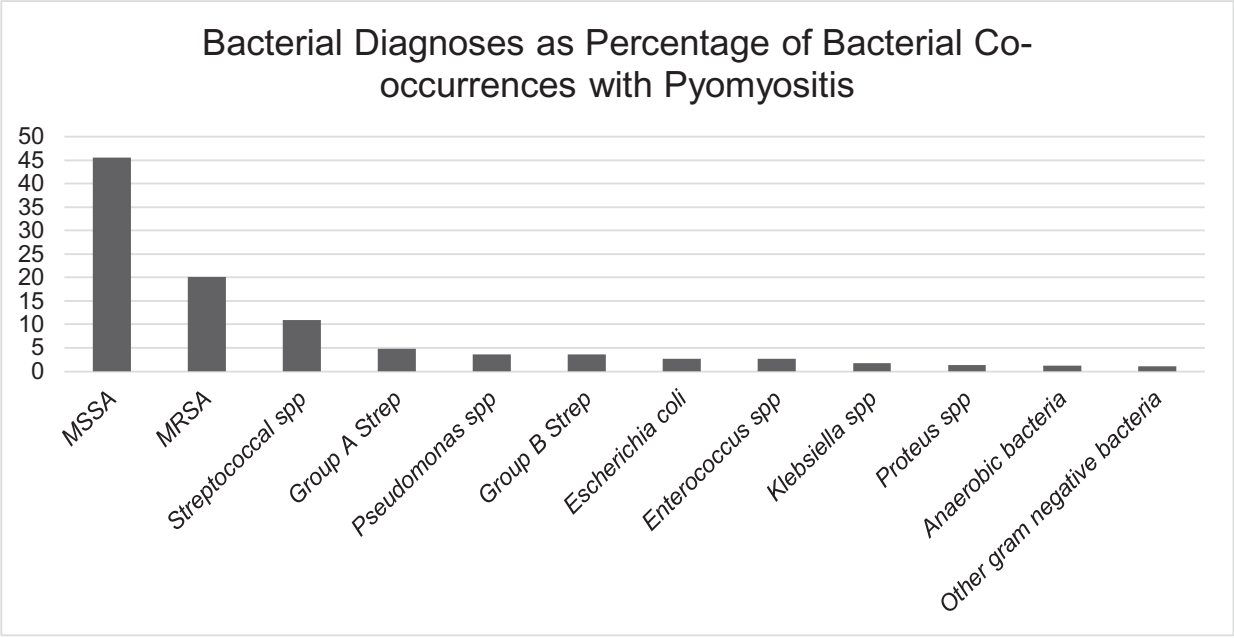


Fig. 5. Bacterial Diagnoses Co-occurring with Pyomyositis.

commonly associated bacterial diagnosis in pyomyositis patients with HIV or a hematologic malignancy. However, patients with pyomyositis and HIV were more likely to have a mycobacterial diagnosis (1.49%; CI 0.34, 2.71) compared to patients with pyomyositis without HIV (0.046%; CI 0.009, 0.083). Patients with pyomyositis and hematologic malignancy were more likely than other patients with pyomyositis to have diagnoses of *E coli* and *Pseudomonas spp.* *E coli* was diagnosed in 5.0% (CI 2.5, 7.1) of patients with pyomyositis and hematologic malignancy compared to 1.3% (CI 1.1, 1.5). *Pseudomonas* spp. were diagnosed in 4.8% (CI 2.5, 7.1) of patients with pyomyositis and hematologic malignancy compared to 1.8% (CI 1.6, 2.0). See **Fig. 6**. Only bacterial co-occurrences observed in at least 1% of patients with pyomyositis and each HIV and hematologic malignancy respectively were reported in this section.

Discussion

This study is the largest existing review of pyomyositis in the United States. Our results demonstrated a significant linear trend of increasing diagnosis of pyomyositis in hospitalized patients in the United States between 2002 and 2014. This represents a three- to four-fold increase over our 12-year study period. Increasing prevalence of significant risk factors may play a role in explaining this trend. Risk factors including HIV infection, diabetes mellitus, and obesity are increasing in the United States [19–21]. Changing bacterial characteristics including Panton-Valentine Leucocidin may also be playing a role [22].

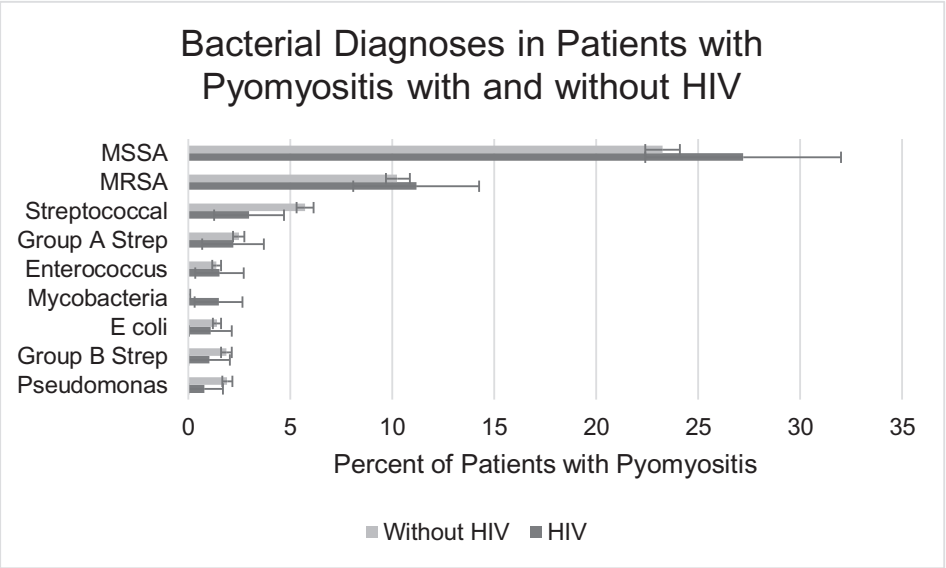
Our study confirmed the recognized male-predominance and younger age in pyomyositis patients. A total of 24% of pyomyositis cases were in patients less than 20 years of age with the greatest incidence between age 5–9 years and another peak near age 40. The number of hospital admissions (denominator) is low in the 5–9-year-old age group, which influences the percentage of hospital discharges in that age group with pyomyositis. However, the peak persisted even when compared to US Census population data[23]. Because primary pyomyositis is classically associated with tropical regions, we hypothesize that warmer seasons and warmer regions of the country would have a higher incidence. Our study showed that there was a slightly higher incidence in the Southeastern and Western states relative to the Northeast or Midwest. However, our study showed no statistically significant differences between months of the year. Due to significant variability in climate data, we were unable to directly correlate to climate trends over time. However, this remains a very interesting area for future investigation.

HIV/AIDS has been identified as a risk factor for pyomyositis in many different studies [3,16,17,24–26]. Our study was not able to differentiate AIDS from uncomplicated HIV, but it did show a significant co-occurrence between HIV and pyomyositis. The age-adjusted odds ratio was 4.8 (95% CI 4.3,5.4), the strongest identified in our study. This suggests that HIV infection is an important risk factor for pyomyositis in the United States. Our data also suggest that mycobacteria may be a more common cause of pyomyositis in patients with HIV compared to those without, although the absolute number remains low at around 1.5%. The observed co-occurrence also cannot establish causality, and patients with advanced HIV/AIDS may have had more than one infection or opportunistic infections.

Diabetes mellitus has been previously recognized as a risk factor for pyomyositis and our study confirms this association [17]. The strength of association between type 2 diabetes mellitus and pyomyositis decreased when controlled for BMI but remained significant, suggesting that diabetes and obesity independently contribute to the risk of pyomyositis in the United States.

Our study showed significant positive odds ratios for obesity and morbid obesity with pyomyositis, of 1.3 (95% CI 1.2, 1.5) and 1.5 (95% CI 1.3, 1.6) respectively. Obesity has steadily risen in the United States since the 1970s, including over our study period and may be contributing to the increasing incidence of pyomyositis [21]. The percentage of all patients carrying a diagnosis of obesity in their discharge diagnostic codes is dramatically lower than the known prevalence of obesity in the United States. However, we found no reason to believe that act of documenting obesity status would be correlated to a diagnosis of pyomyositis, so the association remains plausible.

Malnutrition has been noted as a risk factor for pyomyositis in numerous studies [24,26,27]. Our study showed a modest odds ratio of 1.8 (95% CI 1.4, 2.3) for malnutrition when controlling for age, but the overall incidence of malnutrition in the patients with pyomyositis was similar to the general hospitalized population



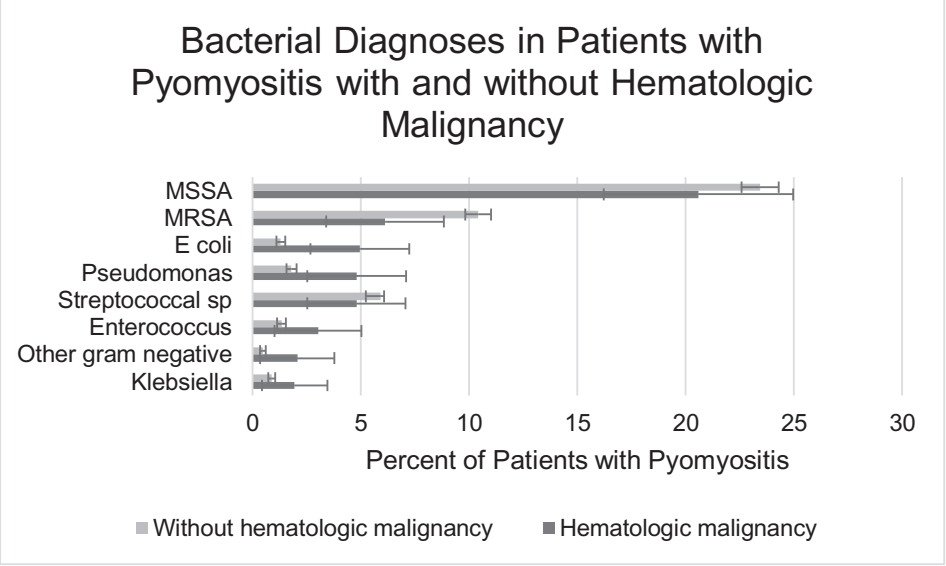


Fig. 6. Bacterial diagnoses in patients with pyomyositis and HIV, pyomyositis and hematologic malignancy.

(approximately 0.9%). Notably, the low percentage of patients identified as malnourished may represent under-coding of this condition among hospitalized patients.

Malignancy has been noted as a risk factor in several previous studies [16,17]. The authors' institutional experience suggests a correlation between pyomyositis and hematologic malignancies in specific, so this was examined in this study. Hematologic malignancies had an odds ratio of 2.2, consistent with our institutional observations and suggesting that this may be a relevant risk factor. Interestingly, our study revealed an odds ratio of less than one for solid tumors, suggesting that patients with non-hematologic malignancies were less likely than the general hospitalized population to be diagnosed with pyomyositis. This trend diminished but persisted when controlling for age (odds ratio increased from 0.38 to 0.48). Possible reasons may be that patients with solid tumors have more hospital admissions in general for treatment and complications or that they are more likely to get other infections rather than pyomyositis.

Prior literature has implicated alcohol abuse, hepatitis, IV drug use, steroid use, immunosuppressing medications, and rheumatologic conditions as potential risk factors for pyomyositis [17,24]. Our study provided large epidemiologic evidence that rheumatoid arthritis, organ transplant, and chronic kidney disease are associated with an increased risk of pyomyositis in the United States. We did not find evidence of association with alcohol abuse.

The literature firmly establishes *Staphylococcus aureus* as the most common bacterial pathogen responsible for primary pyomyositis in both tropical and temperate countries [3,5,6,28–34]. More recent studies show increasing concern about the proportion of these that represent methicillin-resistant *Staphylococcus aureus* [6,29]. *Staphylococcus aureus* has several virulence factors that predispose to abscess formation and pyomyositis and Panton-Valentine leucocidin (PVL) has been shown to be an important virulence factor [22]. Our study similarly showed *Staphylococcus aureus* as the predominant causative pathogen.

A bacterial diagnosis was identified in 46% of the patients with pyomyositis in our study. While it would certainly be desirable to have bacterial diagnoses in a higher percentage of patients, this is likely explained by the fact that approximately half (49.9%) had a diagnosis of muscle abscess, 26.8% had a recorded incision

and drainage procedure, and 31.3% (CI 30.4–32.2) had a diagnosis of bacteremia and/or septicemia. Without either a positive blood culture or cultures collected by prompt incision and drainage, empirical antimicrobial treatment can proceed without positive identification of the causative organism. Prior case series from single institutions not reliant on a database have had roughly similar yields of bacterial diagnoses [29,31].

The magnitude of the database, including information about millions of patients each year, is a significant strength of our study. Limitations include the inability to assess temporal or causative relationship between different diagnoses and dependence on the coding during the hospitalization. The assessment of co-occurring infection with osteomyelitis or septic arthritis or trauma provided evidence that a large percentage of the cases represent primary pyomyositis, but due to the nature of the retrospective review we were not able to verify this directly.

The reliance on diagnostic coding poses limitations because only diagnoses that were coded during the incident hospitalization were included. This leaves the possibility that chronic diagnoses may have been overlooked or that co-occurring diagnoses or identified pathogens were not entered in the billing data. While odds ratios and correlation cannot identify a direction of causation, the candidate risk factors we chose to investigate are generally longer-term diagnoses and therefore significantly likely to have pre-existed the development of pyomyositis. Therefore, we reach the conclusion that the long-term diagnosis is more likely a risk factor for developing pyomyositis compared to the reverse, although the observed co-occurrence alone cannot prove this.

This study demonstrates a concerning rise in the incidence of pyomyositis in the United States, provides additional information about the typical demographics of patients with pyomyositis in the United States, and confirms that most cases occur without an adjacent known source of infection. It substantiates known risk factors related to immune suppression and raises concern about diabetes mellitus and obesity as potential risk factors that are increasing in prevalence. Empiric antibiotic therapy needs to include anti-staphylococcal antibiotic which may be targeted once microbiological information is known. In immunocompromised patients such as those with hematological malignancy, the addition of an antimicrobial with gram-negative activity together with anti-staphylococcal antibiotic should also be considered. It is important that clinicians be aware of this emerging diagnosis that must be recognized and treated in temperate as well as tropical regions of the world.

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Declaration of Competing Interest

The authors have no competing interests to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.02.005.

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