Risk of DVT, ICU Admission, and Mortality in Pediatric Lower Extremity Musculoskeletal Infections

Impact of MRSA and Elevated CRP

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Background: Musculoskeletal infections (MSKIs), including osteomyelitis and pyogenic arthritis, present significant health risks in pediatric populations. This study evaluates the risks of septic deep vein thrombosis (DVT), intensive care unit (ICU) admission, and mortality in children diagnosed with lower extremity MSKIs, with a focus on methicillin-resistant Staphylococcus aureus (MRSA) infections.

Methods: This retrospective cohort study from a multi-institutional database included 38,023 pediatric patients diagnosed with lower extremity MSKIs. Incidence and risk factors for DVT, ICU admission, and mortality were collected. Comparisons were made between age groups and MRSA versus non-MRSA infections. The association between CRP levels and outcomes was also examined. Multivariable logistic regression models were utilized.

Results: The mean age of the cohort was 8.49 years. Overall, 1.52% of patients developed septic DVT, 0.49% required ICU admission, and 0.48% died. Patients with MRSA had significantly higher risks of DVT (RR 4.89, $P < 0.001$) and mortality (RR 3.57, $P < 0.001$) compared with those without MRSA. CRP levels were also markedly higher in MRSA patients ($P < 0.001$). When comparing age groups, those < 12 years had a higher risk of ICU admission (RR 2.03, $P < 0.001$), whereas the 12 to 18 age group had a higher risk of DVT (RR 0.71, $P < 0.001$). Among patients with DVT, the mortality risk was significantly increased (RR 5.18, $P < 0.001$). MRSA patients with DVT had the highest mortality risk (RR 5.38, $P < 0.001$) and elevated CRP levels ($P < 0.001$).

Conclusions: Reporting the largest series of children with lower extremity MSKI, our study found increased risk of DVT, ICU admission, and mortality in pediatric patients with MRSA. MRSA patients with septic DVT had significantly higher level of CRP than those without DVT (100.95 mg/L vs. 61.59 mg/L, $P < 0.001$). MRSA infections with septic DVT had the highest rate of mortality (7.24%). Clinicians should consider proactive screening and aggressive management strategies for septic DVT in the at-risk population, especially in patients with high CRP.

Level of Evidence: Prognostic level III.

Key Words: pediatric, musculoskeletal infections, osteomyelitis, pyogenic arthritis, MRSA, deep vein thrombosis, ICU admission, mortality, C-reactive protein

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Musculoskeletal infections (MSKIs), including osteomyelitis and septic arthritis, pose significant health risks for children[1] and have only increased in incidence over the last 2 decades.[2] MSKIs can lead to a multitude of short- and long-term complications, including growth plate damage, osteonecrosis, and pathologic fractures.[3,4] More severe potential outcomes include hematogenous spread of infectious organisms leading to sepsis or a procoagulant state with subsequent deep venous thrombosis (DVT).[1,5] Critical MSKIs may require intensive care unit (ICU) admission and carry a risk of mortality, particularly in the presence of complications or underlying comorbidities.[6–8]

MSKIs are often caused by bacterial pathogens, with Staphylococcus aureus being the most common causative organism. Specifically, methicillin-resistant Staphylococcus aureus (MRSA) infections have emerged as a significant concern, accounting for a substantial proportion of pediatric MSKIs.[2,8] In fact, recent studies have shown community-acquired MRSA to be an increasingly prominent cause of the most severe MSKI in the pediatric population, with Sarkissian et al finding longer inpatient stays, more frequent ICU admissions, and increased incidence of DVT and disseminated disease.[9,10]

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As MSKIs pose the threat of severe and potentially fatal outcomes in the pediatric population, it is of great interest to identify patients who are most at risk . Prior studies have shown that elevated C-reactive protein (CRP) levels, a marker of inflammation, are strongly associated with an increased risk of venous thromboembolism (VTE), including DVT, in children with MSKIs.[6,11] Additional studies have reported increased likelihood of ICU admission with concurrent infections, infection with MRSA, and/or severe onset of illness as evidenced by CRP $\geq$ 100 mg/L.[12,13] Other inflammatory markers, such as IL-6 and procalcitonin, have potential for predicting severity of MSKI's, but research is currently limited due to the lower utilization of these labs in clinical practice.[1]

While the majority of MSKIs in children are promptly treated and ultimately inconsequential,[8] the potential for devastating complications underscores the necessity for screening guidelines to identify those at highest risk. The provided context highlights the importance of understanding the risks associated with these infections, such as septic DVT, ICU admission, and mortality. In addition, the role of CRP as a potential marker for infection severity and the development of complications, such as DVT, warrants further investigation. This study aims to assess the risks of septic DVT, ICU admission, and mortality among children diagnosed with lower extremity MSKIs, with a focus on those with MRSA infections. Furthermore, we explore these risks across different age groups ($<$12 and 12 to 18 y) and analyze the relationship between CRP levels, MRSA infection, and DVT occurrence.

METHODS

Study Design and Data Source

We conducted a cohort study using the TriNetX research network, which provides access to global de-identified electronic medical records (diagnoses, procedures, medications, lab values, and genomic data).[14] The study used data from the TriNetX Research United States Platform, adhering to STROBE guidelines. TriNetX's reliability and sustainability in research have been validated by multiple sources.[14,15]

Codes and Data Integrity

Data were derived from electronic health records used in clinical practice. Aggregated data allowed tracking of patient outcomes, such as mortality, beyond hospital boundaries. Concurrent use of CPT, ICD-9, and ICD-10 codes with GEMS2 mapping enhanced search sensitivity. Regarding infection types, the TriNetX database provides diagnostic codes that distinguish between septic arthritis (ICD-10 M00 series) and osteomyelitis (ICD-10 M86 series). For example, pyogenic arthritis subtypes include M00.0 (staphylococcal), M00.1 (pneumococcal), and M00.9 (unspecified). Similarly, osteomyelitis codes include M86.0 (acute hematogenous), M86.4 (chronic with draining sinus), and M86.9 (unspecified).

Study Population and Outcome Variables

We identified patients diagnosed with lower extremity MSK infections from 2003 to 2023, examining outcomes such as DVT, ICU admissions, and mortality. We focused solely on lower extremity infections because they are more common in the pediatric population compared with upper extremity infections and present with relatively consistent clinical features, aiding in more reliable identification and stratification.[2] MSKIs were defined as lower extremity cases of osteomyelitis, septic arthritis, or pyomyositis, identified via ICD-9/10 diagnostic codes. Cases were not restricted to culture-positive infections, as culture data were inconsistently available and many pediatric MSKIs are treated empirically. Among available laboratory values, CRP was the single inflammatory marker selected for analysis based on its clinical ubiquity in pediatric MSKI management and its consistent availability in the TriNetX electronic health record dataset. Other inflammatory markers such as ESR, WBC count, and procalcitonin were sporadically recorded and therefore excluded from primary analyses. Vital signs and physiological data (eg, temperature, hemodynamic status) were not uniformly available across institutions and could not be reliably incorporated. CRP levels included in the present study were obtained on the day of diagnosis of MSKI. If multiple CRP levels were reported on the day of diagnosis, the earliest CRP level was utilized.

Cohorts

A total of 38,023 pediatric patients diagnosed with lower extremity MSKIs were included. Cohorts were stratified by age ($<$12 vs. 12 to 18), MRSA as source of infection, and presence of DVT (Fig. 1). Age was stratified as $<$12 vs. 12 to 18 years based on developmental and clinical distinctions in pediatric care. The general cohort was assessed for the 3 primary outcomes mentioned, while the subanalysis groups underwent a similar analysis with the added inclusion of CRP levels on the day of diagnosis. 26,168 (69%) patients had a reported CRP level. Full demographics, with counts and proportions, can be seen in Table 1.

Statistical Analysis

We first calculated the percentage of patients within each defined group (eg, MRSA vs. non-MRSA) who experienced each of the outcomes assessed—namely, DVT, ICU admission, or mortality. Risk ratios were then derived from the absolute risks. Categorical variables were tested using Fisher exact test or χ^2, and continuous variables using ANOVA or t Test. Risk ratios include 95% CIs; P values $<$ 0.05 were significant. Data analysis ensured statistical integrity.

IRB and Data Security

TriNetX, LLC complies with HIPAA, ISO 27001:2013, and applicable privacy regulations to safeguard health care data. Datasets generated by the TriNetX Platform are deidentified as per the de-identification standard defined in Section 164.514(a) of the HIPAA

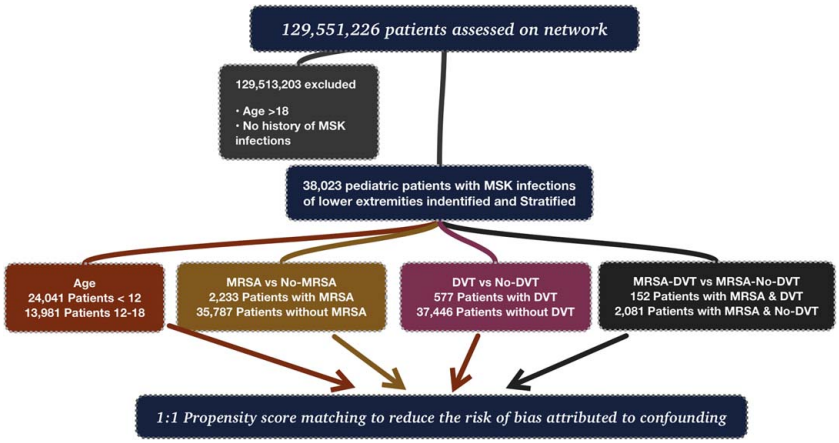

FIGURE 1. Flow chart of patient inclusion. Inclusion and stratification of 38,023 pediatric patients with lower extremity MSKIs from an initial assessment of 129,551,226 patients. Patients were stratified by age (< 12 vs. 12 to 18 y), presence of MRSA infection, and occurrence of DVT, with 1:1 propensity score matching used to reduce confounding bias.

Privacy Rule. As such, this study was exempt from full institutional review board approval (Authorization of Action: IRBHSC20230367NHR).

Software and Validation

Data analysis and visualization were performed on the TriNetX Live platform and further analyzed using Python 3.11.3 (Fredericksburg, Virginia) and STATA 18 MP24 (College Station, Texas). Visualizations were created by the in-house team using Adobe Creative Suite, BioRender (San Jose, California), and STATA. Analytical procedures were independently validated by 2 statisticians and confirmed by a senior author at key stages.

RESULTS

Patient Characteristics

A total of 38,023 pediatric patients diagnosed with lower extremity MSKIs were included. The mean age of our cohort was 8.49 (SD 5.16), and 22,173 (58.31%) of our patients were male. The mean BMI percentile was 59.13 (SD 31.69). 185 patients (0.49%) were admitted to the ICU, and 182 cases (0.48%) were fatal. Full demographics with counts and proportions can be seen in Table 1.

TABLE 1. Patient Characteristics

Lower extremity MSKI (38,023)	
Characteristics	**N or mean (SD or %)**
Age	8.49 (5.16)
BMI percentile	59.13 (31.69)
CRP mg/L (N = 23,123)	66 (44.91)
DVT	577 (1.52)
Male	22,173 (58.31)
White	20,258 (53.28)
Female	15,849 (41.68)
Black or African American	5332 (14.02)
Hispanic or Latino	5981 (15.73)
Unknown race	11,388 (29.95)
Asian	1045 (2.75)
Mortality	182 (0.48)
ICU	185 (0.49)

Demographic and clinical characteristics of pediatric patients diagnosed with lower extremity musculoskeletal infections (MSKIs) (N = 38,023).

Age Comparisons

Patients under the age of 12 had a higher chance of being admitted to the ICU [Risk Ratio (RR) 2.03; $P < 0.001$] than patients aged 12 to 18 (Incidence 0.60% vs. 0.30%) (Fig. 2). On the other hand, patients under the age of 12 had a lower risk of being diagnosed with a DVT than those aged 12 to 18 (RR 0.71; $P < 0.001$) (incidence 1.30% in < 12 age group vs. 1.82% in 12 to 18 age group). We found no significant difference concerning the mortality of the 2 cohorts ($P = 0.48$). The full results of our multivariate analysis can be found in Table 2.

MRSA Versus Non-MRSA Infections

Pediatric patients with diagnosed MRSA infections had a significantly higher risk of mortality (1.75%) when compared with the non-MRSA cohort (0.49%) (RR 3.57; $P < 0.001$). They also had higher risk of deep venous thrombosis (6.81%) compared with the non-MRSA group (1.39%) (RR 4.89; $P < 0.001$). Patients with MRSA infections had markedly higher CRP levels (100.95 mg/L) than the non-MRSA cohort (61.59 mg/L) ($P < 0.001$). There was no significant difference in the risk of ICU admission ($P = 0.30$).

DVT Versus No DVT

Overall, patients with a diagnosed DVT had a 5 times higher risk of mortality (2.60%) than those without a DVT (0.50%) (RR 5.18; $P < 0.001$). Looking at only patients with MRSA infection, those with a diagnosed DVT also had a higher risk of mortality (7.24%) compared with those with no DVT (1.35%) (RR 5.38; $P < 0.001$). In that same cohort, patients with MRSA and a DVT had a significantly higher CRP (143.82 mg/L) than those with MRSA but no DVT (94.98) ($P < 0.001$) (Fig. 2).

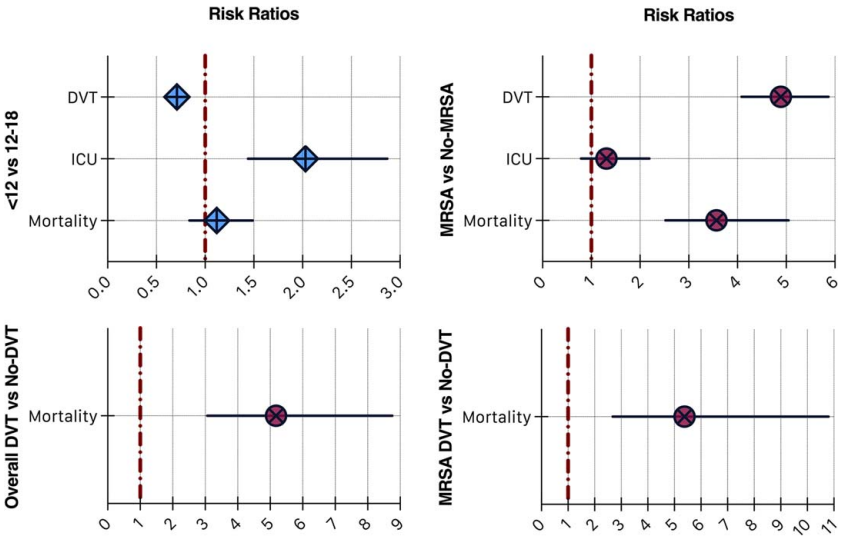

FIGURE 2. Risk ratios for DVT, ICU admission, and mortality in pediatric lower extremity MSKIs, stratified by age (< 12 vs. 12 to 18 y), MRSA infection, and DVT occurrence.

In this pediatric cohort, patients with MRSA and DVT (n = 178) were slightly older (mean age 16.5 vs. 15.3 y) and more likely to be male (66.3% vs. 62.2%) compared with those with MRSA without DVT (n = 2694). The DVT group had a higher proportion of non-Hispanic (78.1% vs. 68.3%) and White patients (64.6% vs. 56.5%), with fewer unknown entries for race and ethnicity. Overall, MRSA+DVT patients showed demographic differences suggesting older, predominantly non-Hispanic White males are more affected.

DISCUSSION

This study sought to determine the incidence of ICU admission, DVT, and mortality in a large cohort of children diagnosed with lower extremity MSKI based on CRP levels and the presence of MRSA infection. In our investigation, pediatric patients under the age of 12 had a higher risk of being admitted to the ICU, but a lower risk for DVT. Furthermore, patients with diagnosed MRSA infections had a higher risk of DVT and mortality compared with the non-MRSA cohort. Development of a DVT was also associated with a 5 times higher risk of mortality. Patients with MRSA infections or a diagnosis of DVT had markedly higher CRP levels on day of diagnosis, which may be useful in predicting outcomes in pediatric patients with MSKI and developing risk-management protocols.

The literature is limited and equivocal regarding the impact of age on pediatric patients with MSKI.[12,16] A retrospective case review of 299 children by Martin et al[17] found that the odds of complicated acute hematogenous osteomyelitis increased by 1.13 for every year increase in age. A cross-sectional study of 77 pediatric patients with either septic arthritis or osteomyelitis determined that older age was associated with higher odds of chronic disability.[18] Alternatively, a retrospective chart review study of 44 children with septic arthritis found that children younger than 2 years had significantly higher complication rates than those older than 2.[19] Despite the association between age and negative sequelae following MSKI not being well defined, this study aligns with our results, which suggest that younger children may have more severe initial presentations, which would warrant more intensive care regimens.

Several studies have investigated the impact of MRSA infections on the clinical course of pediatric osteomyelitis and septic arthritis.[20,21] Our study reinforces the current consensus that MRSA infections are associated with more severe illness and poorer outcomes compared with non-MRSA infections.[22,23] Hawkshead et al[24] found that MRSA osteomyelitis was associated with increased fever duration, acute-phase reactant levels, length of hospital stay, and surgical interventions compared with methicillin-susceptible Staphylococcus aureus (MSSA) or other bacterial infections. A study by Saavedra-Lozano had very similar results; they found that children with MRSA osteomyelitis had increased CRP levels, length of hospital stay, and prescribed antibiotic therapy.[25] They also found that MRSA was becoming more frequently isolated over a 4-year period.[25] Similarly, we found that MRSA infections not only were associated with more severe illness, but also significantly heightened the mortality risk in pediatric patients with MSKI.

DVT can be a devastating complication in children with MSKI. Chronic sequelae of DVT in children includes postthrombotic syndrome with swelling, stasis ulcers, and limb pain.[26] Identifying specific risk factors of DVT development is necessary for prediction and prevention of these potentially lifelong complications. Multiple studies have found that MRSA is more frequently associated with developing a DVT than other bacterial infections.[22,23] Likewise, we found that patients with MRSA had a sig-

TABLE 2. Risk Ratios

Age < 12 vs. 12-18								
Variable	**< 12 (24,041)**	**12-18 (13,981)**	**< 12 Risk, %**	**12-18 risk, %**	**Risk ratio**	**LB**	**UB**	***P***
Mortality	141	73	0.59	0.52	1.12	0.84	1.49	0.48
ICU	145	41	0.60	0.30	2.03	1.44	2.87	0.00
DVT	313	255	1.30	1.82	0.71	0.61	0.84	0.00
MRSA vs. No MRSA								
Variable	MRSA (2233)	No MRSA (35,787)	MRSA risk, %	No MRSA risk, %	Risk ratio	LB	UB	*P*
Mortality	39	175	1.75	0.49	3.57	2.52	5.05	0.00
ICU	16	195	0.72	0.54	1.31	0.79	2.19	0.30
DVT	152	498	6.81	1.39	4.89	4.08	5.87	0.00
CRP (mean)	100.95	61.59						0.00
Overall DVT vs. No DVT								
Variable	DVT (577)	No DVT (37,446)	DVT risk, %	No DVT risk, %	Risk ratio	LB	UB	*P*
Mortality	15	188	2.60	0.50	5.18	3.06	8.76	0.00
MRSA DVT vs. No DVT								
Variable	DVT (152)	No DVT (2081)	DVT risk, %	No DVT risk, %	Risk ratio	LB	UB	*P*
Mortality	11	28	7.24	1.35	5.38	2.68	10.80	0.00
CRP (mean)	143.82	94.98						0.00

Risk ratios for mortality, ICU admission, and DVT in pediatric lower extremity MSKIs, stratified by age (< 12 vs. 12 to 18 y), presence of MRSA infection, and DVT occurrence.

nificantly higher risk of both developing a DVT and mortality, evidenced by a RR of 4.89 and 3.57, respectively. Our findings are consistent with other studies investigating these outcomes,[27,28] which underscores the importance of vigilant monitoring and aggressive management strategies to lower the risk of DVT and mortality in pediatric MSKI patients.

We found that children with a MRSA MSKI were nearly 5x more likely to develop a DVT than those with a non-MRSA MSKI (6.81% vs. 1.39%, respectively). Notably, our results also show a much higher rate of mortality in MRSA patients with DVT (7.24%) compared with those without concurrent DVT (1.35%). Our findings indicate that prophylactic anticoagulation may be a viable preventive measure for reducing the risk of DVT and subsequent complications in children with MRSA MSKIs. In line with other studies, we found that MRSA infections are closely associated with increased CRP levels, which ultimately contribute to a heightened risk of DVT.[29] Therefore, elevated CRP levels may be useful for distinguishing between a likely complicated or uncomplicated progression of illness. CRP levels are already valuable in the management of MSKIs; due to the short half-life of CRP, it is the most sensitive test for monitoring ongoing therapeutic response and dictating treatment recommendations.[30] Our study is limited by lack of an exact timeline for when CRP levels were initially taken, which makes it difficult to determine an appropriate cutoff value based on this information alone. Therefore, future research should focus on developing an algorithm using finely tuned CRP cutoffs, in combination with other prognostic markers such as age, MRSA status, and the aforementioned inflammatory markers, to predict the likely illness course and identify patients that may benefit from prophylactic anticoagulation. With anticoagulation comes its own risks, of course. Stem and colleagues conducted a study to assess the impact of prophylactic anticoagulation on high-risk children and young adults. They found no bleeding events (major or minor) in nonsurgical patients, while the incidence of major bleeding events in orthopaedic surgery patients was 4%. However, these patients were undergoing major orthopaedic surgery.[31] Further research is necessary to both establish the best CRP cutoffs and elucidate the efficacy of prophylactic anticoagulation in children with MSKIs.

The predominant strength of this investigation is the large number of patients included for analysis, while previous reports are limited to several hundred patients. However, our study does possess several limitations. The present study did not account for a variety of comorbid conditions that may influence a patient's overall morbidity and mortality after a MSKI. This study also did not further analyze outcomes based on anatomic location of MSKI. Although we identified infection subtypes (eg, osteomyelitis vs. septic arthritis) and multifocal cases via diagnostic codes, stratified analysis by infection subtype or location was not feasible due to small sample sizes in rare-outcome subgroups, which we acknowledge as a limitation and potential area for future research. In addition, the patient population included in the present study may not accurately reflect the general population, as patients were utilized from primarily large academic medical centers. Also, as this is a database study, we cannot be certain that every case was appropriately coded. While procedure codes may indicate that imaging was performed, the platform does not provide the actual imaging findings or values, which limits our ability to assess the diagnostic accuracy or correlation with clinical outcomes. As well, longitudinal follow-up in TriNetX is limited, as patients may relocate or receive care at a non-TriNetX-affiliated facility, limiting our ability to assess more long-term outcomes, such as chronic osteomyelitis. Finally, ICU admission was defined according to billing and ICD codes, but we were not able to assess why patients were admitted

to the ICU, despite its important and clinical utility. Despite the aforementioned limitations, this study is the largest study to date reporting on risk factors for poor outcomes in pediatric patients with MSKI. In spite of the aforementioned limitations, this study is the largest to date reporting on the risk factors surrounding poor outcomes in pediatric patients with MSKI, and specifically elucidates the significant impact of both MRSA infections and elevated CRP levels on patient outcomes.

CONCLUSION

In conclusion, the present study is the largest to date exhibiting that pediatric patients diagnosed with lower extremity MRSA MSKIs have increased risk of DVT and death when compared with non-MRSA MSKIs. Specifically, the presence of MRSA increases the rate of DVT to 6.81% from 1.39% and mortality to 1.34% from 0.49%. MRSA patients with DVT have a markedly higher mortality rate (7.24%) compared with MRSA patients without DVT (1.35%). Elevated CRP levels were related to more severe infections and related complications, including DVT. We also demonstrated that pediatric patients under the age of 12 experience an increased risk of ICU admission but a lower risk for DVT compared with older children. Ultimately, these findings underscore the necessity for identifying high-risk pediatric patients with lower extremity MSKIs, such as those with an elevated CRP and the presence of MRSA, as these factors are associated with a higher risk of DVT and mortality. Additional investigations are necessary to determine the best CRP cutoff values and other inflammatory markers for creation of an algorithm that could guide clinical understanding and management. Further, future research should consider the risks and benefits of prophylactic anticoagulation in identified high-risk patients.

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