ORIGINAL ARTICLE

RISK FACTORS AND OUTCOMES IN PATIENTS WITH SEVERE NECROTIZING FASCIITIS ADMITTED TO SURGICAL INTENSIVE CARE UNIT: A RETROSPECTIVE COHORT STUDY FROM PAKISTAN

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Background: Necrotizing fasciitis (NF) is a debilitating condition that has high mortality and morbidity even in specialized centres. This study aims to determine risk factors in our local population and identify variables that contribute to mortality in the necrotizing fasciitis patients treated in the surgical intensive care unit of a tertiary care hospital **Methods:** This retrospective cross-sectional study included 39 patients admitted to the surgical ICU from January 1, 2015 to June 30, 2019. They were analyzed for comorbidities, symptoms at presentation, predisposing factors, location of the infection, microbiological analysis and mortality. **Results:** There were 27 (69.2%) males and 12 (30.8%) females while the age was distributed as 47.44±15 years. Pain was the most frequently reported symptom (89.7%), followed by swelling (79.5%) and tenderness (77%). Significant predisposing factors included trauma in 14 (35.9%) and Intramuscular injections (IM) in 10 (25.6%) patients. On univariate and multiple logistic regression, patients with chronic kidney disease (AOR:1.27, 95% CI: 0-691.22) and ischemic heart (AOR: 1.55, 95% CI: 0.02-153.26) disease had higher odds of mortality than those with no comorbidity. The overall mortality was 12/39 (30.8%). **Conclusion:** Intramuscular injections without aseptic measures in our local population are a significant predisposing risk factor for severe necrotizing fasciitis. High laboratory risk Indicators for necrotizing fasciitis and acute physiology and chronic health evaluation II scores at admission were associated with increased mortality.

Keywords: Necrotizing fasciitis; Sepsis; Intramuscular injection; Mortality; LRINEC score

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INTRODUCTION

Necrotizing fasciitis (NF) is a progressive, fulminant bacterial infection of subcutaneous tissue.[1] It is the most severe kind of necrotizing soft tissue infection (NSTI) and can affect any portion of the body. Even with advanced medical treatment, the mortality rate is as high as 24–34%. The prognosis for this rare, potentially fatal condition depends on early, precise diagnosis and the prompt initiation of effective treatment.[2] In the United States, this accounts for about 0.4 in every 100,000 patients; in Europe, the incidence is 1 in every 100,000.[3] A higher risk of complications and mortality is linked to NF associated with streptococcal infection.[4] Age, diabetes, trauma, peripheral vascular disease, obesity, and chronic renal failure are some of the factors that increase the risk of developing NF. Intramuscular injections have emerged in recent years as one of the important causes of necrotizing fasciitis.[5]

Various studies in the literature have evaluated the prevalence of variables including predisposing factors, clinical findings, distribution of tissue involvement and mortality rates in necrotizing fasciitis. A study by Kwan et al was undertaken to determine its co-morbidity and risk factors affecting the outcome of its surgical treatment.[6] This investigation aimed to study risk factors and outcomes of necrotizing patients treated in the intensive care unit. The primary objective was to determine predisposing and prognostic factors associated with mortality in our patients admitted to the surgical intensive care unit.

MATERIAL AND METHODS

This retrospective study reviewed all medical records of patients admitted between January 1, 2015 to June 30, 2019 (fifty-four months) to the surgical intensive care unit of a tertiary centre. All data were obtained with the approval of the institutional ethics review committee and the hospital administration. Patients diagnosed with necrotizing fasciitis admitted to the intensive care unit (ICU) were included. Medical record numbers of patients with the diagnosis of necrotizing fasciitis (NF) were taken from the ICU data log. The hospital medical record directory was also used to find such cases using ICD-10 code M72.6 for "necrotizing fasciitis". A grid was maintained using Microsoft® Excel 2016 (Redmond, WA, USA) for serial numbers with their respective medical record numbers to maintain the privacy of patients' data. Detailed information on cultures was

extracted from an online hospital database. Discharge/death summaries were extracted from their medical records to get details regarding several procedures performed, ventilator days, ICU days, days of admission and reason for death if applicable. Laboratory risk indicator for necrotizing fasciitis (LRINEC) scores[7], which is a 13-point scoring system to predict the diagnosis of necrotizing fasciitis, was also calculated from the data available on the day of admission. The data collection form specially designed for this study was then used to compile and all analyses were conducted by using IBM® SPSS Statistics 19.0 (Armonk, NY, USA). As the missing data management plan, missing completely at random (MCAR) data was not included in the analysis. For a single variable, less than or equal to 5% missing data was acceptable while up to 20% missing at random (MAR) data was predicted by using mean-value imputation at the analysis phase. Therefore variables such as CRP which was missing for more than 50% of the patients, were not included in the final analysis.

Descriptive statistics were computed for independent variables such as demographic characteristics. Mean and standard deviation were calculated for continuous variables frequencies were calculated for categorical variables. Fisher's exact test was applied to explore any association between mortality (deceased/survived) and gender, predisposing factors, comorbidities, and microbiological assessment of the samples received for culture. Univariate and multiple logistic regression were also applied.

RESULTS

A total of 39 patients were admitted to the Surgical Intensive Care Unit with the diagnosis of necrotizing fasciitis. There were 27 (69.2%) male and 12 (30.8%) females while the age was distributed as 47.44±15 years. The patients were admitted with various comorbid conditions and symptoms. A total of 16 (41%) patients had no comorbidities and were of either young or middle age, while 9 patients (23.1%) had diabetes mellitus, 6 (15.0%) suffered from ischemic heart disease, and 3 (7.7%) had hypertension. Observed symptoms included swelling, fever, pain, and tenderness in all 39 patients. Pain was the most frequently reported symptom (89.7%), followed by swelling (79.5%) and tenderness (77%) More than half (51.3%) of the patients reported experiencing all symptoms. The frequency and percentages of other reported parameters and lab values on admission are given in Table 1.

The predisposing factors and conditions that rendered patients vulnerable to develop necrotizing fasciitis were trauma 14 (35.9%), intramuscular injections 10 (25.6%), surgical procedures 9 (23.1%), diabetic foot 4 (10.3%) and cellulitis in 2 (5.1%) cases. The location of necrotizing fasciitis varied among the patients with the maximum occurrence of lower limb in 17 patients followed by the gluteal area. The distribution of location is shown in Figure 1. The tissue cultures sent for analysis found that the majority of the wounds had polymicrobial infestation(41%) whereas MRSA was found to be the second most common(12.1%), as shown in Figure 2.

Overall mortality was calculated to be 12 (30.8%). The main cause is septic shock followed by multiorgan failure. One out of those 12 died in the general ward whereas 11 of them died in the ICU. A total of 35 patients out of 39 required vasopressor support during their hospital admission. No statistically significant association was found between gender, predisposing factors and comorbidities as evident from the p-values in Table 2.

On univariate and multiple logistic regression, no statistically significant relationship was noted between mortality and gender, comorbidities, predisposing factors, and tissue culture. Females had a higher adjusted odds ratio of mortality than males (AOR:35.92, 95% CI:1.02-1270.30). The patients with chronic kidney disease (AOR:1.27, 95% CI: 0-691.22) and ischemic heart (AOR: 1.55, 95% CI: 0.02-153.26) disease had higher odds of mortality than those with no comorbidity (Table 3).

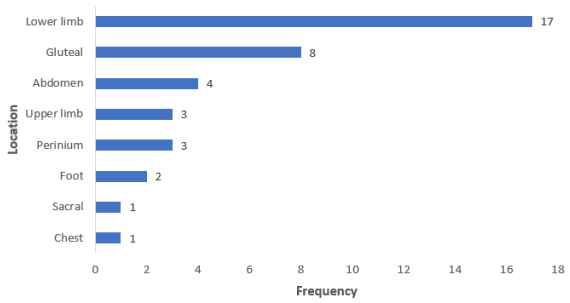

Figure-1: The location of necrotizing fasciitis from most to least

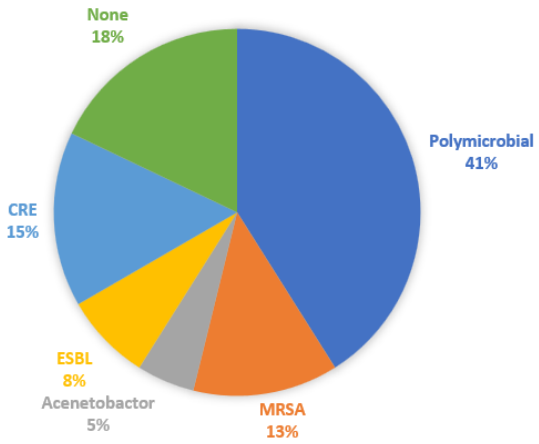

Figure-2: Tissue culture

Table-1: Baseline parameters on admission and length of stay (LOS)

	Minimum	Maximum	Median	IQR
Hemoglobin	5.30	16.40	10.50	14.8
White blood cell	2	88.90	16.70	18
Platelets	29	631	248	239
Sodium	123	143	135	9
Creatinine	0.30	6.60	1.40	1.8
Bilirubin	0.30	14.40	0.95	0.8
Glucose	64	285	124	82
pH	7.01	7.53	7.37	0.18
Bicarbonate	9.30	32.40	19.70	10.1
LRINEC score	1	12	6	4
Lactate level	0.50	15.60	2.45	3.50
CCI	0	7	2	4
APACHE II	8	48	22	19
Ventilator days	0	19	2	4
ICU days	1	19	4	4
Hospital Days	1	35	10	11

Table-2: Association of gender, predisposing factors, comorbidities and tissue culture between deceased and survived patients

Variables	Total subjects (n=39)	Deceased (n=12)	Survived (n=27)
Gender			
Male	27 (69.2%)	7(58.3%)	20 (74.1%)
Female	12 (30.8%)	5(41.7%)	7 (25.9%)
Predisposing factors			
Trauma	14 (35.9%)	4 (36.4%)	10 (37%)
Surgical procedure	9 (23.1%)	1 (9.1%)	8 (29.6%)
Diabetic foot	4 (10.5%)	0	4 (14.8%)
IM injection	10 (25.6%)	5 (45.5%)	5 (18.5%)
Cellulitis	2 (5.1%)	1 (9.1%)	0
Comorbidities			
None	16 (41%)	6 (50%)	10 (37%)
Hypertension	3 (7.7%)	0	3 (11.1%)
Diabetes mellitus	9 (23.1%)	2 (16.7%)	7 (25.9%)
Chronic kidney disease	2 (5.1%)	1 (8.3%)	1 (3.7%)
Ischemic heart disease	6 (15.4%)	2 (16.7%)	4 (14.8%)
Other	3 (7.7%)	1 (8.3%)	2 (7.4%)
Tissue culture			
Polymicrobial	16 (41.0%)	6(50.0%)	10 (37.0%)
MRSA	5 (12.8%)	1(8.3%)	4 (14.8%)
Acinetobacter	2 (5.1%)	0	2 (7.4%)
ESBL	3(7.7%)	0	3(11.1%)
CRE	6(15.4%)	4(33.3%)	2(7.4%)
None	7 (17.9%)	1(8.3%)	6 (22.2%)

Table-3: Univariate and multivariate analysis of factors associated with mortality

Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Gender				
Male (ref)				
Female	2.04 (0.49-8.57)	0.330	35.92 (1.02-1270.30)	0.049
Comorbidities				
None (ref)				
Hypertension	-	-	-	-
Diabetes mellitus	0.47 (0.07-3.09)	0.437	0.29 (0.01-8.87)	0.475
Chronic kidney disease	1.67 (0.09-31.87)	0.734	1.27 (0-691.22)	0.941
Ischemic heart disease	0.83 (0.12-6.01)	0.857	1.55 (0.02-153.26)	0.853
Other	0.83 (0.06-11.28)	0.891	0.18 (0-129.59)	0.608
Predisposing factor				
Trauma (ref)				
Surgical procedure	0.31 (0.03-3.38)	0.338	0.002 (0-0.91)	0.046
Diabetic foot	-	-	-	-
IM injection	2.5 (0.46-13.65)	0.29	0.17 (0.01-6.27)	0.334
Cellulitis	-	-	-	-
Tissue culture				
None (ref)				
Polymicrobial	3.6 (0.35-37.62)	0.285	45.92 (0.5-4223.57)	0.097
MRSA	1.5 (0.07-31.58)	0.794	4.16 (0.06-298.55)	0.514
Acinetobacter	-	-	-	-
ESBL	-	-	-	-
CRE	12 (0.8-180.97)	0.073	366.04 (1.16-115325.48)	0.046

DISCUSSION

Necrotizing fasciitis is a debilitating condition that carries a high morbidity and mortality. Although it can affect any part of the body, lower limbs and extremities are most commonly found to be affected.[8] Wilson first used the term 'necrotizing fasciitis' in 1952 when, in the presence of cutaneous gangrene, he noticed a rapidly progressing inflammation and necrosis of subcutaneous tissue, superficial fascia, and superficial portions of deep fascia.

Based on microbiological grading, necrotizing fascitis has two types. Type 1 infections are polymicrobial, commonly caused by non-group A *streptococcus*, as well as aerobic and anaerobic microorganisms. *Streptococcus pyogenes* alone or along with *Staphylococci* give rise to Type 2 infections.[9–11] The patients in our study had polymicrobial infections in their tissue which were sent for analysis during surgery (64.1%), whereas MRSA was the second most common bacteria found in the tissue culture (12.1%). The triad of pain, swelling, and fever is almost always present in all patients. Our investigation also revealed these three symptoms quite common with pain being the most prevalent. It is essential to identify NF before subcutaneous involvement. Immense pain at the time of presentation may raise a strong suspicion of necrotizing fasciitis. Cellulitis that worsens with adequate antibiotic coverage, formation of bullae, and conversion to gangrenous tissue may all lead to a strong suspicion of NF. Apart from the extremities, it can also develop in the head and neck, trunk, perineum and scrotum. NF in the upper torso especially head and neck carries a high mortality.[12]

LRINEC scoring system was first published in 2004 to develop an early diagnostic tool for necrotizing fasciitis. A systematic review conducted in 2017 showed a direct correlation between a high LRINEC score with the diagnosis of necrotizing fasciitis in a hospital setting.[13] Mean score from the 16 studies was 6.06 amongst confirmed cases and those who did not have NF had a mean score of 2.45. Our study showed a median score of 6, which also signifies the relevance of this scoring system.

Due to the presence of nonspecific signs, such as swelling, erythema, tenderness and pain at the affected site, necrotizing fasciitis can be difficult to distinguish from other soft tissue infections in the early stages.[14] Tachycardia (>100 beats/min) is typically seen (59%), whereas fever (>38°C) is frequently absent (44%). Hypotension (Systolic BP<90 mm Hg) (21%) and tachypnea (>25/min) (26%) can sometimes be present. The presence of these findings suggests that NF is opposed to NSTI with odds ratios (OR) of 3.4 (1.6-7.4), 4.5 (1.7-11.8), and 2.6 (1.1-6.0), respectively.[15] Any area of the body can develop NF, but the extremities (36–55%), trunk (18–64%), and perineum (up to 36%) are mostly affected. Erythema is seen in 80% of infected locations, along with induration (66%), pain (54%), fluctuation (35%), skin necrosis (23%), and bullae (11%).[15] The odds ratio of 3.5 indicates that there is a higher chance of bullae for NF than NSTI (1.0-11.9). In another study[16], the presence of tense oedema (23% vs. 3%, *p*-0.0002), purple skin discolouration (10% vs. 1%, *p*=0.02), and sensory or motor loss (13% vs. 3%, p=0.03) distinguished NF patients from NSTI. Skin necrosis was present among 6% of NF patients compared to 2% of those with NSTI. Certain variants of NF according to their site include Ludwig's angina (submandibular space) and Fournier's gangrene (scrotum and penis or vulva) and these can result in a high chance of mortality and prolonged hospital course. In our study, the highest incidence according to the location turned out to be lower limbs and the gluteal region. Out of the gluteal sites, most were those who had been administered intramuscular injections for various reasons.

Another cause for the development of NF is intramuscular injection. There was a case report involving a subject who developed severe pyelonephritis and NF after an intramuscular injection of diclofenac sodium in the thigh.[17,12] The subject developed sepsis and underwent drainage of the abscess. He was kept on piperacillin/tazobactam, vancomycin and amphotericin prophylactically, however, the blood cultures were ongoing negative. Due to non-resolving pyelonephritis, he underwent a unilateral nephrectomy. Delayed wound closure was performed after 4 months. Another case reported in the literature mentions the development of toxic shock syndrome after intramuscular injection.[18] Numerous cases are reported showing the development of NF after intramuscular diclofenac injections, but there are other medicines used as IM injection, which proves that it might not be the drug that is responsible for causing NF but the way it is administered and lack of proper sterility techniques in poorly developed parts of the world. A case of NF after intramuscular injection of paracetamol has also been reported.[19]

CONCLUSION

In conclusion, this study suggests that LRINEC score is a powerful tool in the diagnosis of necrotizing fasciitis in patients who are admitted with fever, pain and swelling. 25.5% of the individuals with NF had a history of intramuscular injection, which is a preventable cause. This study could also have been taken as a prospective trial since cases of necrotizing fasciitis of the maxillofacial region have increased

secondary to mucormycosis in patients with COVID-19 disease.

AUTHORS' CONTRIBUTION

Concept: MFK, FS. Design: AAM, FS. Data Collection: AAM, ASU. Writing Manuscript: AAM, FS. Critical Review: MFK, ASU

Research quality and ethics statement

This study was approved by the Institutional Review Board / Ethics Committee (Approval # 2019-1785-4709; Approval date: Aug 9, 2019). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE Guideline, during the conduct of this research project.

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