Mortality from necrotizing fasciitis: a cross-sectional study

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ABSTRACT

Background: Necrotizing fasciitis refers to the rapidly progressive inflammation of the fascia, with secondary necrosis of subcutaneous tissues. Due to the high mortality, it is considered a surgical emergency, needing timely diagnosis and appropriate treatment with early debridement. The aim of the study was to analyse the clinical profile of patients with necrotizing fasciitis so as to determine the mortality and the risk factors associated with mortality and other poor outcomes.

Methods: This retrospective cross-sectional study was conducted in a tertiary hospital in Kerala, from January 2016 through January 2018. 175 cases were identified through the ICD codes for necrotizing fasciitis and Fournier’s gangrene in the discharge and death registers; and data were obtained about these patients. The data were analyzed to assess the study objectives.

Results: In this study mortality was found to be 22.7%. Diabetes mellitus was found to be the most common comorbid disease and had a significant association with increased risk of amputation. Mixed growth (type I NF) was the most common microbiological isolate and Pseudomonas was the most common gram-negative isolate. 4 cases of MRSA were recorded. Klebsiella infection was found to have increased risk of undergoing limb amputation. 7.4% of the patients required amputation during hospital stay for infection control.

Conclusions: Necrotizing fasciitis has a high mortality. Diabetes mellitus was found to be the most common comorbid disease. Increased blood glucose and low serum albumin had a significant association with an increased risk of amputation. Proper control of these factors is essential to reduce mortality from this condition.

Keywords: Diabetes mellitus, Fournier’s gangrene, Mortality, Morbidity, Necrotizing fasciitis

INTRODUCTION

Necrotizing fasciitis (NF) is a rapidly progressive inflammatory infection of the fascia, with secondary necrosis of the subcutaneous tissues. The term ‘Necrotizing fasciitis’ was first described in 1952 by Wilson.¹ The speed of spread is directly proportional to the thickness of the subcutaneous layer, wherein the infection moves along the fascial planes. It is a surgical emergency which needs to be diagnosed timely and treated with early debridement. Delayed intervention could result in extremely high mortality rate (~80 to 100%), and even with modern aggressive treatment modalities, mortality remains high, approaching as high as 36-40%.² Of late, the incidence of NF is seen to be on the rise because of an increase in immuno-compromised patients like those with diabetes mellitus, cancers, vascular insufficiencies, organ transplants and HIV infection.

NF may be classified based on per the anatomical site, depth of invasion or microbiological profile.³ The commonly accepted classification is based on the microbiology, which was first proposed by Giuliano et al originally.⁴ Initially there were two described types, with two more being added subsequently to the classification.⁵
Type I NF- polymicrobial- synergistic: Type I infections are poly-microbial with various species of gram-positive cocci, gram negative rods and anaerobes causing synergistic gangrene. *Clostridial* infections usually termed as gas gangrene are represented as a subtype of type I NF. *Clostridial* infection, even though relatively rare now, remain relevant because of the rapid deterioration and high mortality. NF involving the genitalia and perineum (a type I variant) is described as Fournier’s gangrene, in honour of the French Venereologist, Jean Alfred Fournier.

Type II NF- Mono-microbial- gram positive: Type II infections are mono microbial involving group A β-hemolytic streptococci or *staphylococci* species. Of special mention is the increasing trend in prevalence of community acquired MRSA:CA-MRSA). They have a significant potential for aggressive local spread and systemic toxicity. Compared to type I NFs, patients with type II infections are younger, healthier, and often have a history of trauma, surgery, or even parenteral drug abuse.

Type III NF- Mono-microbial- gram negative including marine organisms: Mono-microbial and caused by other gram-negative organisms, also including a variant involving *Vibrio vulnificus*. Infection can occur via exposure through open wounds or breaks in the skin or rarely via ingestion of colonized oysters by patients with immune compromise. *Pasteurella multocida, Haemophilus influenzae, Acinetobacter, Pseudomonas, Enterobacter, Klebsiella spp.* and *Aeromonas* are other organisms involved.

Type IV NF- fungal: Further NF may be caused by fungi including *Candida* or Zygomycetes, *Cryptococcus gattii*. *Candida* mainly affect the immuno-compromised and *zygomycotic necrotising* infections (Mucor and Rhizopus spp.) affect immuno-competent patients. Fungal invasion is seen to be commonly following traumatic wounds or burns.

Patients with NF need prompt recognition and admission as they require aggressive debridement, intravenous antibiotics and local wound care. Pathognomonic features that should prompt immediate surgical exploration in NF include presence of bullae, skin ecchymosis that precedes skin necrosis, presence of gas in the tissues by examination or radiographic evaluation, and cutaneous anesthesia. Less specific signs include pain out of proportion, edema extending beyond the cutaneous erythema, features of systemic toxicity and progression of infection despite antibiotic therapy. One clinical finding classically given impetus to, but rarely seen is subcutaneous emphysema. The gold standard for diagnosis of NF is by surgical exploration: by placing a small skin incision down to the fascia and assessment of adherence of the fascia to soft tissue. In NF the thrombosed and necrosed fascia can be easily separated from other layers by sliding a finger along the fascial plane, the so-called positive ‘sweep sign’. Also seen are other findings including the ‘dishwater’ pus fluid, absence of bleeding and absence of the typical sheen over the fascia. Previous studies have identified factors like advanced age (>60 years), *Aeromonas* and *vibrio* infection, cirrhosis of liver, cancers, presence of hypotension, band polymorphonuclear neutrophils (PMN) >10%, and serum creatinine >2 mg/dl to be independent predictors of mortality in cases with NF.

For improving the outcome of patients with NF, high risk patients who may go into sepsis and have high mortality risk need to be determined so that aggressive treatment may be started. This would allow for better allocation of resources as well as in improvement in overall outcome. Authors is a tertiary level teaching institution which caters to a large number of patients from the southern districts of Kerala and Tamil Nadu. Authors encounter patients with clinically diagnosed NF on a regular basis. With this background, the aim of this study was to analyze the clinical profile of patients presenting to us with NF so as to determine the mortality, the risk factors associated with mortality and morbidity (amputation, sepsis and prolonged hospital stay). Authors also analyzed the pattern of microbial flora in NF and the predisposing co-morbid conditions of prognostic significance.

**METHODS**

The study was designed as a hospital based Retrospective Cross-sectional study. The study setting was at the General Surgical wards of Government Medical College Trivandrum. The study population included diagnosed cases of NF admitted in Surgery wards of institution during the time period from January 2016 to January 2018. The primary objective of the study was to assess the mortality in patients admitted with NF in wards during the study period. Secondary objectives were to assess the co-morbid conditions and laboratory values of prognostic significance in these patients.

Sample size was estimated from the reference study available, where overall mortality rate was 36%. Authors used the formula: \(n = (\frac{Za/2}{d})^2pq/d^2\), where, \(n\) = sample size, \(Za/2\) is confidence interval=1.96 at an error of 5%, \(p\) = estimated proportion, taken as 36 here; \(d\) = desired precision taken 20% of \(p\), i.e. 7.2. As per the formula value of \(n\) = 171 (sample size required). Consecutive Sampling method was used to achieve the sample size. Authors fixed the sample size at 175.

Patients were included by searching for the ICD codes (ICD 10) M72.6 (NF), N49.3 (Fournier’s gangrene) from the case records and death registers. Structured Questionnaire was used to collect data including demographic details, history, clinical features and laboratory values. Recording of data was done in the proforma after getting clearance from the Institutional Ethical committee and permission from the hospital.
Authors via proper channel. Data was entered in excel sheets. All quantitative variables were expressed as mean and standard deviation and quantitative variables were expressed as proportion. Appropriate statistical tests of significance were used, where a p value less than 0.05 was considered significant. Association was assessed by means of odds ratio by constructing suitable 2×2 tables. All analysis was done in the Student version of SPSS software by IBM.

RESULTS

Here, 175 patient records were studied, among whom 124 were male and 51 females. Mean age was calculated as 58.27 (SD 13.795). Mean duration of symptoms before admission was 8.61 days (SD 7.77). The lower limbs were affected in 92% of cases. Upper limb (2.9%), abdomen (1.7%), perineum (2.8%) and neck (0.6%) were the other affected sites. The mortality was found to be 22.7% (40 out of 175). Mortality rate among females was 25.49% and that among males was 21.77%. No significant association was found between sex and mortality. 24.4% patients developed multiple organ dysfunction syndrome (MODS) during their hospital stay. 41 cases of acute kidney injury (13 requiring hemodialysis) and 2 cases of acute respiratory distress syndrome (both cases requiring ventilator care) were detected. 9 patients required ICU admission. The mean period of hospital stay was 16.53 days (SD 14.565). 13 patients (7.4%) required amputation during the hospital stay for infection control.

The mean hemoglobin value was 10.686 g% (SD 2.106), total leukocyte count 19200 cells/µl (SD 8284.94), neutrophil count 10843 cells/µl (SD 5143.72), lymphocyte count 7290.99 cells/µl (SD 3019.88), platelet count 2.60 lakh cells/µl (SD 1.45 lakh), serum sodium 130.7 mEq/l (SD 6.09), random blood sugar 181.89 mg% (SD 115.64), blood urea 78.79 mg% (SD 62.76), serum creatinine 2.20 mg% (SD 2.07), total bilirubin 1.28 mg% (SD1.36) and serum albumin 2.5 mg% (SD 0.48) (Table 1).

The mean platelet lymphocyte ratio of 46.237 (SD 46.269) and neutrophil: lymphocyte ratio 1.497 (SD 0.325) were ascertained. Anemia [OR 2.59; 95% CI 1.23-5.46; p=0.01], high blood urea [OR 4.17; 95% CI 1.84-9.44; p=0.006], high serum creatinine [OR 2.66; 95% CI 1.2-5.77; p=0.01] and low serum albumin [OR 2.51; 95% CI 1.11-5.69; p=0.02] were related with increased mortality. High blood glucose [OR 6.66; 95% CI 1.76-25.23; p=0.005] and low serum albumin [OR 8.04; 95% CI 1.02-63.34; p=0.04] were associated with increased risk of amputation.

70% of the patients had one or more co-morbidity. The commonest co-morbidities in decreasing order were diabetes mellitus (53.4% of the study population), systemic hypertension (25%), coronary arterial disease (11.4%), chronic kidney disease (10.2%), chronic liver disease (4.5%), and hypothyroidism (2.8%). Among the co-morbidities, only a positive history of Diabetes mellitus [OR 11.7; 95% CI 1.48-92.14; p=0.01] was found to have an increased risk with poor outcomes while no other co-morbidity had any bearing on the outcome. No significant association was found between the various co-morbidities with mortality in these patients.

Table 1: Descriptive statistics of laboratory parameters.

<table>
<thead>
<tr>
<th>Lab parameter (unit)</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g%)</td>
<td>175</td>
<td>4.8</td>
<td>16.8</td>
<td>10.686</td>
<td>2.106</td>
</tr>
<tr>
<td>Total leucocyte count (cells/µl)</td>
<td>175</td>
<td>2600</td>
<td>54,000</td>
<td>19200</td>
<td>8284.946</td>
</tr>
<tr>
<td>Neutrophil count (cells/µl)</td>
<td>175</td>
<td>1482</td>
<td>35640</td>
<td>10843.86</td>
<td>5143.721</td>
</tr>
<tr>
<td>Lymphocyte count (cells/µl)</td>
<td>175</td>
<td>988</td>
<td>16,200</td>
<td>7290.998</td>
<td>3019.885</td>
</tr>
<tr>
<td>Platelet count (cells/µl)</td>
<td>175</td>
<td>30,000</td>
<td>7.70,000</td>
<td>2,60,285.7</td>
<td>1,45,906.55</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>175</td>
<td>110.0</td>
<td>153.0</td>
<td>130.703</td>
<td>6.094</td>
</tr>
<tr>
<td>RBS (mg%)</td>
<td>175</td>
<td>38</td>
<td>574</td>
<td>181.89</td>
<td>115.647</td>
</tr>
<tr>
<td>Blood urea (mg%)</td>
<td>175</td>
<td>3.8</td>
<td>393</td>
<td>78.792</td>
<td>62.766</td>
</tr>
<tr>
<td>Blood creatinine (mg%)</td>
<td>175</td>
<td>0.46</td>
<td>14.62</td>
<td>2.208</td>
<td>2.074</td>
</tr>
<tr>
<td>Total bilirubin (mg%)</td>
<td>175</td>
<td>0.2</td>
<td>11.7</td>
<td>1.282</td>
<td>1.365</td>
</tr>
<tr>
<td>Serum albumin (mg%)</td>
<td>175</td>
<td>1.3</td>
<td>3.8</td>
<td>2.506</td>
<td>0.488</td>
</tr>
<tr>
<td>PLR</td>
<td>175</td>
<td>2.89</td>
<td>309.72</td>
<td>46.237</td>
<td>46.269</td>
</tr>
<tr>
<td>NLR</td>
<td>175</td>
<td>1.04</td>
<td>2.68</td>
<td>1.497</td>
<td>0.325</td>
</tr>
</tbody>
</table>

PLR: platelet lymphocyte ratio, NLR: neutrophil lymphocyte ratio.

Positive cultures were recorded in 89 cases (Table 2). Commonest isolates were poly-microbial (Mixed growth - 28% of the positive isolates). The other common positive isolates in decreasing order of frequency were Pseudomonas, Klebsiella, Escherichia coli, Enterococcus, Acinetobacter, and Proteus vugaris. Gram negative organisms together formed 51.68% of the positive isolates, while gram positive organisms (Staphylococcus including MRSA and Streptococcus) combined formed 16% of the positive isolates. Thus, authors found that type III NF followed by type I NF were the most common microbiological types of NF in setting. Klebsiella was the only infection found to have
increased risk of undergoing amputation of limb [OR 5.77; 95% CI 1.32-25.19; p=0.01]. None of the studied parameters showed significant association with increased risk for ICU admission or MODS or other adverse events.

Kwan et al studied the co-morbidity and risk factors affecting the outcome of surgical treatment in NF between 1998 and 2002 and found the mortality rate to be 36%. Diabetes mellitus was the most common associated co-morbidity, Pseudomonas, Staphylococcus, Streptococcus and Enterobactericeae were the common pathogens isolated. 27.8% underwent major amputation. High serum urea and creatinine and low hemoglobin levels were predictors for higher mortality. A study by Wang and Lim found male gender, increased length of hospital stays and low albumin level as significant risk factors for mortality.10 Liver cirrhosis and diabetes mellitus were the most common co-morbidities associated with the disease in their study, where the mortality was 20.9%. A retrospective study by Golger et al showed a mortality rate of 20%. In that study 16% required amputation and diabetes was the most common associated co-morbidity. Advanced age had a significant association with mortality.

Singh et al did a study on the clinical profile of NF and found a mortality of 27%. Jaundice and serum albumin were the only factors to have a significant influence on mortality. Another retrospective study by Elliot et al showed a mortality rate of 25.3%, and the same in a retrospective study by Kulasegharan et al was 20.3%.17,18 Gupta et al found the mortality to be 26.2% in a tertiary care centre with 4.2% requiring amputation for infection control. Alcoholism and diabetes were the most common associated conditions in that study.19 In a cohort of 350 patients, Anaya et al found six admission parameters to independently predict death namely, age >50 years, heart rate >110 beats/min, temperature <36 degrees C, white blood cell count >40,000 cells/cc, serum creatinine concentration >1.5 mg/dl, and hematocrit >50%. A similar prospective study by Ramin et al concluded that hypotension, hyperkalemia and increased leucocyte cell counts are useful parameters in distinguishing life-threatening NF. The mortality rate in that study was 20.8%, while the amputation rate was 29%.

In a study by Yu et al, Diabetes was the most common co-morbidity (45.8%) followed by chronic liver disease and chronic kidney disease. Mono-microbial infections were predominant in the culture positive cases. Escherichia coli was the most frequently identified pathogen (14.4%), followed by Staphylococcus aureus (13.3%; out of which methicillin-resistant S. aureus [MRSA] formed 41.6%) and Streptococcus pyogenes (12%). None of the Streptococcus pyogenes infections cases were community acquired. Salvador VB et al found the most frequent isolates to be E. coli (44%), Acinetobacter baumannii (19%), S. aureus (15%) and Enterococcus faecium (15%).23 The mortality rate was 36% in their study. Risk factors significantly associated with mortality included leukocytosis, acidosis, hypoalbuminemia and hypernatremia, wherein logistic regression analysis revealed hypoalbuminemia as significant independent risk factor for mortality. Yim et al did a multivariable regression analysis in a

**DISCUSSION**

This study retrospectively evaluated 175 cases of NF admitted in surgical wards of Trivandrum Medical College in a cross-sectional design. The mortality due to the disease was found to be 22.7% which is less than that of the parent study and is matching the newer studies about NF. 24.4% patients had MODS during their hospital stay. 7.4% of the patients required amputation. Diabetes mellitus was found to be the most common co-morbid disease. Anemia, high blood urea, high serum creatinine and low serum albumin were related with increased mortality. Diabetes mellitus, increased blood glucose and low serum albumin had a significant association with an increased risk of amputation. In this study mixed growth (type I NF) was the most common microbiological isolate. Pseudomonas was the most common gram-negative isolate. Klebsiella infection was found to have increased risk of undergoing amputation of limb.

**Table 2: Frequency distribution of isolated cultures.**

<table>
<thead>
<tr>
<th>Organisms isolated</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recorded culture positive</td>
<td>89</td>
<td>50.6</td>
</tr>
<tr>
<td>Mixed growth</td>
<td>25</td>
<td>14.2</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16</td>
<td>9.1</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>11</td>
<td>6.2</td>
</tr>
<tr>
<td>E. coli</td>
<td>7</td>
<td>4.0</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>7</td>
<td>4.0</td>
</tr>
<tr>
<td>MRSA</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Figure 1: Outcome in NF.**

**Outcome in necrotizing fasciitis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>80</td>
</tr>
<tr>
<td>Dead</td>
<td>20</td>
</tr>
</tbody>
</table>
retrospective study and found that high NLR and high PLR were independent prognostic factors for poor prognosis from Fournier’s gangrene.24

Wong et al developed the laboratory risk indicator for NF (LRINEC) score in 2004, which is widely accepted for risk stratification in NF.25 Using white blood cell count, hemoglobin, sodium, glucose, serum creatinine and serum C-reactive protein they developed a scoring system for the likelihood of NF on admission in the emergency department. A total score of ≥6 yielded a positive predictive value of 92% and negative predictive value of 96% for a diagnosis of NF. Bozkurt et al studied patients with Fournier’s gangrene and found that patients with higher Fournier’s gangrene severity index scores, LRINEC scores and NLR were more likely to require mechanical ventilation in intensive care unit, have a longer hospitalization duration as well as have a higher mortality.26 Another study suggested that clinical findings together with significantly elevated CRP greater than 150 mg/litre as well as decreased hemoglobin and erythrocyte count would be able to identify a large share of the NF patients.27

CONCLUSION

Authors analyzed the clinical profile and risk factors among patients admitted with NF in our institution. The clinicians should do their utmost to secure an early diagnosis in NF, as any undue delay in diagnosis can be fatal, and septic shock is almost inevitable if the disease remains untreated. This study is not without its own share of limitations. The retrospective design does affect the significance of the inferences. Also, the single centre setting might affect the external validity of the results. Nevertheless, strengths of the study include the completeness of reporting of data in the institution, and documentation with ICD coding to capture cases of NF. Also, authors did obtain significantly strong results and infer that further prospective studies can strengthen the usefulness of these results.

To conclude, necrotising fasciitis is associated with low mortality and high morbidity including longer hospital stay. A high index of clinical suspicion is necessary to accurately diagnose NF. Diabetes mellitus remains the most common co-morbid disease in patients with necrotising fasciitis. Increased blood glucose and low serum albumin have significant association with an increased risk of amputation among these patients. To reiterate, appropriate control of these risk factors can be helpful in reducing the mortality and morbidity from this serious condition. Authors recommend further research to validate this research findings and to ascertain the correlation between the risk factors and clinical outcome. Accurate assessment and timely interventions remain the critical steps in treatment of patients affected with necrotising fasciitis so as to ensure best possible outcome.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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